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论文摘要



目录

大会报告（Plenary Lecture, PL）……1

大会报告 PL 1：血液与慢病 ……1

大会报告 PL 2：Glucose sensing and physiological functions ……1

S1：“新时代”和“新医科”背景下的《生理学》教学问题 ……2

S1-1 “新时代”整合课程体系《生理学》的教学创新与实践 ……2

S1-2 教育部《生理学》课程思政示范课建设与实践 ……2

S1-3 激越四段式教学+IPE 在跨地域跨校际教学中的应用 ……3

S1-4 智能+背景下虚拟教研室建设与实践 ……3

S1-5 运用数字技术赋能《生理学》课程 ……3

S2：神经细胞再生与修复 ……4

S2-1 Feeling force with PIEZOs ……4

S2-2 死亡与新生：关于小胶质细胞的哲学 ……4

S2-3 Positive emotions, regeneration strengthens ……5

S2-4 Functional regeneration of spiral ganglion neurons and their synapses ……5

S2-5 Genetic and functional hearing and balance restoration in mice by *in vivo* template independent gene editing and repairing (TIGER) technique ……6

S3：呼吸生理基础与转化研究专题研讨会 ……6

S3-1 以临床问题为导向的肺纤维化基础研究 ……6

S3-2 嗜酸性粒细胞病理生理功能新认识 ……7

S3-3 固有免疫在肺动脉高压发病机制的研究进展 ……8

S3-4 突触-线粒体与中枢呼吸可塑性调控 ……8

S3-5 呼吸系统感染、炎症与免疫缺陷 ……8

S3-6 MRGPRX2——过敏性哮喘潜在药物靶标 ……9

S3-7 环氧二十碳三烯酸调节肺上皮稳态在肺纤维化中的作用研究 ……10

S4：脑病的脑-外周稳态失衡及中医药干预机制与前景 ……10

S4-1 从系统角度探索阿尔茨海默病 ……10

S4-2 非人灵长类抑郁猴肠-脑机制探索 ……11

S4-3 越鞠丸抗抑郁研究：抑郁症的新致病菌株及其代谢-炎症机制 ……11
S4-4 The crosstalk between nervous and immune system ……11
S4-5 逍遥散通过肠脑互作途径缓解抑郁症药效机制研究 ……11

S5：运动生理学专题 ……11

S5-1 运动与代谢健康-多组学队列与干预研究 ……11
S5-2 The role of PGC-1α in the antidepressant effects of exercise preconditioning in SATD mice ……13
S5-3 青少年持续训练和冲刺间歇训练的生理学适应特征 ……14
S5-4 有氧运动调控脑内 DA 改善遗传性 PD 行为障碍的研究 ……15
S5-5 Smyd1 介导抗阻训练改善衰老心脏功能的机制研究 ……16

S6：应激生理学专题讨论会 ……16

S6-1 从应激致抑郁的炎症机制到精神医学的挑战 ……16
S6-2 A liver-brain axis responds to environmental stress and induces anxiety-like behaviors …17
S6-3 氨基酸代谢与运动应激 ……17
S6-4 细胞对环境毒物亚硝胺的应激反应研究 ……17

S7：极端环境与脑认知 ……18

S7-1 潜水作业对人体认知功能影响及其机制研究 ……18
S7-2 空间脑科学研究进展与规划 ……18
S7-3 低氧适应改善极端环境脑缺血损伤的作用机制研究 ……18
S7-4 脑血管病内源性保护机制的研究进展 ……18
S7-5 低温应激致脑认知损伤的防护研究 ……18
S7-6 西藏高原环境对脑认知的影响 ……19

《生理学报》编委会会议 ……20

“泰盟杯全国高等学校人体生理学教师教学大赛”作品展示和交流会 ……20

《生理学报》专题论坛：受体信号与生理调控及疾病发生 ……20

胰岛细胞环路中的 GPCR ……20
核受体与血压的节律调控 ……20
脑-肠多巴胺与帕金森病胃轻瘫机制探讨 ……20
核受体与肾脏功能调控 ……20

S8：心血管研究新进展专题研讨会 ……20

S8-1 天然免疫与血管损伤 ……20
S8-2 下丘脑室旁核参与高血压中枢机制的研究进展 ……21
S8-3 孤束核 PNMT 神经元在血压调控中的作用及其环路基础 ……22
S8-4 固有免疫细胞在腹主动脉瘤发病机制中的作用 ……22
S8-5 孕期氨基酸失调致子代先天性心脏病的分子机制 ……23
S8-6 ncRNA Gpr137b-ps 调节巨噬细胞的自噬促进晚期动脉粥样硬化 ……24

S9：神经干细胞与抑郁障碍 ……25

S9-1 神经干细胞调控机制研究 ……25
S9-2 心理韧性的生物学机制 ……25
S9-3 Plasma proteomic profiling of major depressive disorder versus schizophrenia and healthy control and its association with clinical outcomes ……26
S9-4 双相障碍的发病机制研究 ……27
S9-5 人脑类器官与重性抑郁症研究 ……28

S10：中医院校生理专业委员会专题研讨会 ……28

S10-1 唤醒沉睡的中医古方-百合地黄汤治疗抑郁症的物质基础及分子机制 ……28
S10-2 补阳还五汤及其有效组分抗脑缺血炎性神经损伤的机制研究 ……29
S10-3 中医药改善 AD 样小鼠突触功能异常：聚集小胶质细胞和神经炎症 ……29
S10-4 非靶代谢组学筛选特应性皮炎分子标记及其致痒机制研究 ……30
S10-5 “肚腹三里留”的神经生物学基础 ……30

S11：体适能与健康促进 ……31

S11-1 不同运动方式对肥胖女大学生血管内皮功能的影响研究 ……31
S11-2 身体活动能量消耗与代谢综合征及其组分的量效关系研究 ……32
S11-3 “体医融合”干预糖尿病促进社区居民健康新模式研究 ……34
S11-4 长期运动干预对 ADHD 儿童核心症状和执行功能的影响：基于随机对照试验的 meta 分析 ……34
S11-5 基于心肺运动试验的中国部分居民心肺耐力等级标准研究 ……35

S12：RNA 生理与病理 ……36

S12-1 Ctnnb1 enhancers mediates neocortical neurogenesis and intestinal homeostasis ……36
S12-2 长链非编码 RNA 的功能与机制研究：打开基因组宝库的一把密匙 ……37

S12-3 新 microRNA novel-m009C 调控冰毒的奖赏效应 ……37
S12-4 Characterizing physiological roles of RNA modifications ……37
S12-5 ADRAM is an experience-dependent long noncoding RNA that drives fear extinction through a direct interaction with the chaperone protein 14-3-3 ……38

泰盟 ·人工智能与生理学 Satellite Symposium ……38

SS-1 人工智能与医学虚拟仿真 ……38
SS-2 智能医学与神经科学 ……38
SS-3 人工智能原理及其在生理学实验中的应用 ……39

大会报告（Plenary Lecture, PL) ……39

大会报告 PL 3：脑科学与脑损伤 ……39
大会报告 PL 4：类精子干细胞介导半克隆技术的建立与应用 ……39

张锡钧基金第十七届全国青年优秀生理学学术论文交流会议 ……40

C1 The peripheral-central crosstalk underlying exercise training and brain health ……40
C2 细胞铁死亡的代谢调控机制 ……41
C3 精神活性物质调控调控脑功能的神经机制 ……42
C4 Neurotransmitter sensors elucidate the mechanism of memory coding and coincidence detection in the olfactory learning of *Drosophila* ……43
C5 丘脑-初级听觉皮层环路介导慢性压力模型中心理韧性的产生 ……46
C6 PHB2 maintains the contractile phenotype of VSMCs by counteracting PKM2 splicing ……47
C7 2 型糖尿病心肌损伤的机制以及分型研究 ……48
C8 心肌重构的表观修饰机制 ……49
C9 运动锻炼促进心脏健康的 RNA 表观遗传分子机制研究 ……53
C10 DNA 修复定量报告系统的开发及其在衰老相关研究中的应用 ……54
C11 炎性疾病代谢调控及药理学干预 ……55
C12 血管稳态转录因子对肺动脉高压血管功能调控机制的研究 ……57
C13 突触发育及小胶质细胞功能研究 ……58
C14 系列微生理系统的构建及生理活性物质的纳米酶电化学传感测定 ……60
C15 Convergent adaptations counteracting aging and cancer in subterranean mammals ……64
C16 小胶质细胞乳酸代谢紊乱在阿尔茨海默病中的作用与机制 ……66
C17 星形胶质细胞在记忆维持中的生理病理作用及替代干预机制 ……68
C18 胃肠稳态与机体糖脂代谢紊乱及相关疾病 ……69
C19 前列腺素 E_2 系统与血管结构和功能稳态调控 ……70

C20 脂滴蛋白 17β-HSD13：肝脏脂代谢稳态的重要调控因子 ……71
C21 代谢手术改善机体代谢内分泌及生殖内分泌紊乱的相关研究 ……72
C22 TIP60 在急慢性应激反应中的调节作用 ……75

第十五届全国青年生理学工作者学术会议 ……76

Y1 心肌细胞特异性的体内基因递送 ……76
Y2 A putative loop connection between VTA dopamine neurons and nucleus accumbens encodes positive valence to compensate for hunger ……77
Y3 内皮细胞 BRD4 参与狼疮性肾炎的机制研究 ……79
Y4 Inner nuclear membrane protein LEMD3 stabilizes 3D chromatin architecture and controls vascular smooth muscle cell identity ……80
Y5 Gastrodin acts on presynaptic $GABA_B$ receptors to ameliorate vestibular disorders ……82
Y6 精子核周层蛋白的生理功能及其与男性不育的关联 ……83
Y7 孕期糖皮质激素暴露通过抑制 FTO/GLUT3 影响小鼠胎盘发育的机制研究 ……84
Y8 The specific roles of renal macrophages in monitoring and cleaning off intratubular particles ……85
Y9 Role of dopamine receptor D1/D2 neurons in mPFC in mediating CSDS-induced anxiety-like behavior and chronicity of postoperative pain ……86
Y10 SERCA2 is an essential regulator of cardiomyocyte maturation ……87
Y11 胆固醇调控溶酶体稳态在模拟失重大鼠脑动脉重塑中的机制研究 ……88
Y12 Activating a collaborative innate-adaptive immune response to enhance anti-tumor activity of human pluripotent stem cell-derived CAR-macrophages ……89

S13：比较生理学新进展——基因、行为、环境 ……90

S13-1 从 SARS 到 COVID-19：传统中草药是否是对抗新兴病毒的解方？ ……90
S13-2 Genetic and epigenetic evidence for non-estrogenic disruption of otolith development by bisphenol A in zebrafish ……91
S13-3 裸鼹鼠 cGAS 调控基因组稳定性的机制研究 ……92
S13-4 基于 CRISPR/Cas9 技术构建基因编辑动物疾病模型 ……92
S13-5 高原视觉皮层损伤和适应的环境和基因机制 ……93
S13-6 Dissecting aging and disease from non-model subterranean mammals ……93
S13-7 青藏高原上的蛙类对紫外辐射的适应机制 ……94
S13-8 White and brown adipose tissues: the fuel for hibernation ……95

S14：认识衰老-机制探索与应对策略 ……96

特邀嘉宾报告 ……96

S14-1 衰老的编程和重编程（Programming and reprogramming of aging） ……96

S14-2 线粒体表观遗传学与衰老及代谢综合征（Mitoepigenetics in aging and metabolic syndrome） ……96

S14-3 衰老导致血管平滑肌表型转化的作用和机制 ……96

S14-4 器官对话与系统衰老（Organ cross-talks and systemic aging） ……96

衰老与健康专业委员会专题报告 ……96

S14-5 血管衰老与认知障碍的队列研究 ……96

S14-6 幼年期运动促进小鼠中老年期脂肪酸代谢及健康 ……97

S14-7 组蛋白去乙酰化酶 SIRT2 在老年心血管疾病中的保护作用 ……97

S14-8 琥珀酸脱氢酶组装异常对肝脏胰岛素敏感性的影响及其在扩张型心肌病中的作用 ……97

S14-9 衰老肝脏的内皮分区 ……97

S14-10 酮体代谢与老年肌少症 ……97

S15：神经免疫内稳态与疾病 ……97

S15-1 Neuroimmune regulation in tumor microenvironment ……97

S15-2 骨髓免疫与神经炎症 ……98

S15-3 Diverse roles of microglia in the brain ……99

S15-4 Hypertension and microglia, a sensor bridges the CNS and periphery ……99

S15-5 Vessel-mediated immune surveillance at the boundary of central nervous system ……99

S15-6 Enteric GABAergic neuron-intestinal muscle unit promotes gut defense ……100

S16：细胞微环境在生理与病理中的功能与机制 ……100

S16-1 肝脏内皮细胞微环境与肝脏疾病 ……100

S16-2 细胞感应微环境配体分布的机制 ……101

S16-3 力学微环境与动脉硬化 ……101

S16-4 温度微环境与免疫监视 ……102

S17：生殖科学与生殖健康 ……102

S17-1 双胎生长不一致的分子机制探讨 ……102

S17-2 RNF17-ADAD2 复合物介导 P-body 生成调控 piRNA 通路及精子发生 ……103

S17-3 Redox homeostasis in the uterine epithelium is critical to embryo implantation ……103

S17-4 子痫前期发生中的“矛”与“盾” ……104
S17-5 内源性逆转录病毒衍生增强子调控滋养层细胞谱系分化的机制 ……104
S17-6 Haploid-genetic screening of trophectoderm specification identifies ……105

S18：神经退行性疾病：从发病机制到实验治疗 ……105

S18-1 Integration of stress by transcriptional factors in aging and aging-related diseases ……105
S18-2 小胶质细胞代谢紊乱在阿尔茨海默病发生中的作用机理 ……106
S18-3 神经退行性疾病大脑中一种新的小胶质细胞亚型的鉴别 ……107
S18-4 神经退行性疾病的感知觉机制 ……107
S18-5 阿尔茨海默病非人灵长类动物模型的建立及干细胞治疗探索 ……108

S19：神经调控能量代谢和平衡 ……108

S19-1 中枢神经调控代谢的机制研究 ……108
S19-2 摄食行为的神经机制及免疫调控 ……109
S19-3 Diet-induced inflammation in the paraventricular thalamus controls compulsive sucrose-seeking ……109
S19-4 能量稳态的神经调控机制 ……110
S19-5 雌激素调节体温与代谢的神经机制 ……110

S20：教育信息化专业委员会专题研讨会 ……111

S20-1 基于 ESP 可穿戴设备的早临床教学设计与实践 ……111
S20-2 医学实践课程数字化转型的探索与实践 ……112
S20-3 基于临床前构架的基础医学虚拟仿真综合实验建设成效 ……112
S20-4 基于“三位一体”理念的生理学线上线下课程教学探索 ……113

S21：感觉与情感障碍交互作用 ……113

S21-1 Brain control of gastric motility induced by stress ……113
S21-2 Regulation of chronic pain by orphan G protein-coupled receptor ……114
S21-3 初探光的非成像视觉功能 ……114
S21-4 Calcitonin gene-related peptide promotes inflammatory responses of $CD8^+$T cells ……115

S22：血液生态与疾病专题 ……115

S22-1 Engineering a soft bone marrow organoid for hematopoietic stem cell rejuvenation ……115
S22-2 Bone marrow granulopoiesis in neuromyelitis optica spectrum disorder ……116
S22-3 肿瘤髓外红系造血调控抗瘤免疫反应 ……116

S22-4 多组学联合解析 AML 耐药机制 ……117
S22-5 造血干细胞移植重建规律解析及临床应用 ……117
S22-6 显微镜下的骨髓造血：从多能干细胞到成熟血细胞 ……118

S23：内分泌学和代谢分会专题 ……118

S23-1 A new role of MDM2-p53 axis in metabolic diseases ……118
S23-2 代谢手术调控代谢内分泌及生殖内分泌 ……118
S23-3 Increased angiocrine factor R-spondin3 contributes to aerobic exercise-induced protection against acute kidney injury ……119
S23-4 白细胞介素 17 家族在胰岛发育和糖尿病中的作用及其机制研究 ……119
S23-5 生长激素促进脂肪细胞线粒体生物形成及改变其代谢的研究 ……120
S23-6 Effects of peptidoglycan on the development of lean NAFLD ……120

S24：肠道微生态与神经相关疾病 ……121

S24-1 肠道微生物组学在帕金森病中的研究进展 ……121
S24-2 Ghrelin 合成调控及其在机体糖脂代谢中的作用 ……121
S24-3 肠道微生物菌与“脑-肠轴”：探索基于作用机制的因果关系 ……122
S24-4 高原低氧诱导肠道激惹综合症 IBS 的 CRF 机制 ……122
S24-5 The central regulatory mechanisms of GI dysfunction in Parkinson's disease ……123

S25：脂滴蛋白和生物活性脂质在代谢性疾病中的作用 ……124

S25-1 Alox15/15-HpETE 通过促进心肌细胞的铁死亡加重心肌缺血再灌注损伤 ……124
S25-2 亚油酸代谢产物 13-HODE 在年龄相关肝脏脂质沉积中的作用 ……125
S25-3 脂滴蛋白 17β-HSD13 及其磷酸化在 NAFLD 中的作用及机制 ……125
S25-4 前列腺素合酶 mPGES-2 在 NAFLD 中的作用及机制 ……126
S25-5 用于监测脂滴和脂滴-溶酶体自噬的小分子荧光探针 ……127

S26：理论整合生理学专题研讨会 ……127

S26-1 主动健康：从理念到模式 ……127
S26-2 占比时中守恒的一元多次方程基础 ……127
S26-3 能量消耗占比时中守恒 ……128
S26-4 钙促进分泌亲脂蛋白的清除与其在生殖道中的作用 ……128
S26-5 体成分占比时中守恒 ……128
S26-6 健康预期寿命 ……129

S27：消化与营养专题 ……129

S27-1 The multifaceted GPER signaling in brain and gut ……129
S27-2 干细胞调控肠道稳态的机制研究 ……129
S27-3 营养行为干预研究探索 ……129
S27-4 肠道巨噬细胞在稳态维持和免疫反应中的作用 ……130
S27-5 The intestinal immune, microbiota, and therapy ……130
S27-6 神经元-肌肉信号轴调控肠道固有免疫的机制 ……130

青年组专题报告 ……130

S27-7 固有淋巴样细胞谱系建立与活化调控机制研究 ……130
S27-8 Chronic stress leads to the dysfunction of intestinal stem cells ……130
S27-9 Novel opioid-based therapies to manage visceral pain devoid of side effects ……130
S27-10 多巴胺调节肠胶质细胞释放胶质源性神经营养因子的机制研究 ……131
S27-11 苏糖酸镁对肠易激综合征大鼠的内脏痛和情绪的作用及其机制 ……131
S27-12 肝细胞 KLK8 通过促使巨噬细胞 M2 极化和 TGFβ1 分泌而参与肝纤维化的发生发展 ……131

S28：微生态交叉前沿与产业发展 ……131

S28-1 阴道微生态与中医药 ……131
S28-2 见“微”知著—慢性阻塞性肺疾病的气道微生态 ……132
S28-3 微生态与代谢性疾病 ……132
S28-4 口腔微生态前沿 ……132
S28-5 全球肠道微生态研究与转化前沿进展 ……133

S29：大脑与机体多系统功能交互 ……133

S29-1 神经-免疫-内分泌-代谢网络相互调控 ……133
S29-2 自身免疫性脑炎的神经环路机制 ……133
S29-3 神经调控技术的进展和思考 ……133
S29-4 体温的神经调控 ……133
S29-5 脂肪组织的神经支配和调控 ……134
S29-6 骨代谢的神经内分泌调控 ……134

S30：肾脏基础研究与疾病机制专场——代谢与高血压 ……134

S30-1 血脂与血压交互调节的分子机制 ……134

S30-2 Dahl 盐敏感大鼠高血压形成的肾脏代谢机制 ……134
S30-3 肾小管糖脂代谢异常促进 AKI-CKD 的机制 ……134
S30-4 肾脏细胞命运和功能的基因组精准调控 ……134
S30-5 肾小管上皮细胞可塑性的表观调控机制 ……135
S30-6 Pex11a 激活过氧化物酶体增殖与代谢抑制高血压肾损伤 ……135
S30-7 前列环素及其受体在肾脏纤维化中的作用及机制 ……135
S30-8 朊蛋白激活 TBK1-IRF 通路促进肾脏纤维化 ……135
S30-9 线粒体内铜过载在肾脏纤维化中的作用及机制研究 ……135
S30-10 PRDM16 deficiency triggered by TGF-β signaling aggravated renal fibrosis by promoting tubular mitochondrial dysfunction ……135

壁报展示（Poster Sessions） ……136

张锡钧基金第 17 届全国青年优秀生理学学术论文交流会议 ……136

CP-1 远曲小管钾通道参与糖尿病盐敏感性高血压的机制研究 ……136
CP-2 Series of studies on neurological diseases: Acute ischemic stroke, Alzheimer's disease, and glioma ……137
CP-3 The involvement of NLRP3 inflammasome in CUMS-induced depressive-like behaviours and related cognitive decline in mice ……139
CP-4 转录相关蛋白 BRD4 和 Fli-1 在炎症及肾脏疾病中的作用及机制研究 ……141
CP-5 孕期暴露 AT1 受体自身抗体对子代远期健康的影响及机制 ……142
CP-6 环境介质中碳纳米材料的细胞毒理学研究 ……143
CP-7 延髓头端腹外侧区 miR-335 和 LncRNA Inpp5f 以及 CircRNA Galntl6 调控应激性高血压机制研究 ……144
CP-8 Development of multifunctional and orally active cyclic peptide agonists of opioid/neuropeptide FF receptors that produce potent, long-lasting peripherally restricted antinociception with diminished side effects ……145
CP-9 帕金森病早期诊断和治疗的靶点探究 ……147
CP-10 肿瘤分子标记物的筛选及发病机制 ……148
CP-11 HBV 相关肝纤维化及慢加急性肝衰竭的作用机制研究 ……151
CP-12 KLF2 通过抑制 BMP/SMAD1/5 信号介导层流对血管钙化的保护作用 ……152
CP-13 The mechanism of rhubarb promoting ER stress in goblet cell to relieve constipation ……153
CP-14 Curcumol’s antitumor effect study and its target protein identification in nasopharyngeal carcinoma cell ……156

CP-15 A homotetrameric hemoglobin expressed in alveolar epithelial cells increases blood oxygenation in highaltitude plateau pika (*Ochotona curzoniae*) ……158
CP-16 电针足三里调控荷瘤小鼠免疫-炎性反应减缓肿瘤进展的效应及机制研究 ……159
CP-17 Association analysis of gut microbiota-metabolites-neuroendocrine changes in male rats acute exposure to simulated altitude of 5500m ……160
CP-18 针刺调节皮质-臂旁核-孤束核环路对中风后吞咽障碍模型动物干预作用的研究 ……161
YP 第 15 届全国青年生理学工作者学术会议 ……164
YP-1 Differential regulation of autophagy on urine-concentrating capability through modulating the renal AQP2 expression and renin-angiotensin system in mice ……164
YP-2 miR-22-3p in the rostral ventrolateral medulla promotes hypertension through inhibiting β-arrestin1 ……165
YP-3 心脏肌小节 Z 线的体内邻近蛋白组学研究 ……166
YP-4 心肌再生的时空调控 ……166
YP-5 Transcutaneous Auricular Vagus stimulation reduces depressive symptoms by regulating centralα7nAChR/JAK2 signaling ……167
YP-6 利用单碱基编辑技术在体内纠正 *Lmna* c.1621C>T 致病突变 ……168
YP-7 蒽环类药物心肌病运动训练中的 TRPC6 的作用及对线粒体动态的影响 ……169
YP-8 Macrophage FOXK2 promotes cardiac repair in nondiabetic myocardial infarction with stress hyperglycemia ……170
YP-9 Transcriptomics and molecular docking reveal the potential mechanism of lycorine against pancreatic cancer ……171
YP-10 A new miniMOS tool kit capable of visualizing single copy insertions in *C. elegans* ……172
YP-11 Glutaminolysis boosts cardiac performance under high workload via elevating mitochondrial glutathione ……172
YP-12 耳穴电刺激对糖尿病模型大鼠实时血糖的影响 ……173
YP-13 从系统动力学的视角理解运动损伤的风险因素：因果循环图的使用 ……174
YP-14 多巴胺对鸣禽前脑鸣唱相关通路 HVC-RA 和 LMAN-RA 突触传递的差异性调控 ……175
YP-15 雌二醇调控鸣禽 RA 投射神经元兴奋性突触传递及鸣唱行为 ……176
YP-16 Near-infrared photothermal manipulates cellular excitability and animal behavior in Caenorhabditis elegans ……177
YP-17 三氯乙烯对大鼠心肌细胞发育毒性的影响 ……178

YP-18 Microglial TRPM2 deficiency accelerates seizure development via increasing neuronal excitability ……179
YP-19 Identification of CD38^{high} monocyte as a novel signature driving innate immune dysfunction through metabolic reprogramming during sepsis ……179
YP-20 Erythroid-intrinsic activation of TLR8 impairs erythropoiesis in Diamond-Blackfan anemia-like syndrome ……180
YP-21 二妙散调节 PGC-1α 蛋白乙酰化抑制肝脏糖异生的作用研究 ……182
YP-22 交感-肾上腺轴介导电针天枢穴治疗脓毒症模型大鼠的机制研究 ……182
YP-23 电针调控自主神经干预心肌缺血大鼠心功能动态变化 ……183
YP-24 电针调节 DRG 神经元兴奋性改善溃疡性结肠炎小鼠痛觉超敏 ……184
YP-25 vlPAG 中 GABA 能神经元参与电针缓解 IBS 小鼠内脏痛的机制研究 ……185
YP-26 不同呼吸方法下的中国古典舞动作表现及影响因素探析 ……186
YP-27 联合本体感觉的“倒踢紫金冠”核心力量训练方法研究 ……187
YP-28 牵张反射原理在舞者下肢爆发力训练中的应用研究 ……188
YP-29 Cordycepin exerts anti-exercise fatigue effects and improves learning and memory impairment in mice with exercise fatigue ……189
YP-30 90dB 纯音暴露对食蟹猴听觉及心脑功能的影响 ……190
YP-31 肠道菌群对脊髓损伤后焦虑情绪的调控作用及分子机制研究 ……191
YP-32 Frataxin inhibits ferroptosis to improve myocardial ischemia/reperfusion injury ……192
YP-33 Cognitive effect of a single underwater operation is time-dependent and CCR3-mediated neuroinflammation contributes to cognitive decline induced by prolonged underwater operations ……193
YP-34 Andrographolide exhibits antinociceptive effects in neuropathic rats via inhibiting class Ⅱ MHC associated response and regulating synaptic plasticity ……194
YP-35 人体共生普氏粪杆菌通过调节肠道微生物-丁酸-肾脏 GPR43 轴改善肾脏炎症和损伤 ……195
YP-36 经皮颅-耳穴位电刺激抗抑郁的脑电微状态特征研究 ……196
YP-37 ALDH2 protects blood-brain barrier against cerebral ischemia/ reperfusion injury via alleviating ROS-related NLRP3 inflammasome axis by AKT/ mTOR pathway ……197
YP-38 Voluntary exercise ameliorates post-stroke cognitive impairment by modulating the microbiota-gut-brain axis to protect the brain-gut barriers ……198
YP-39 The mechanism investigation of lipocalin-2 in different pathways of ferroptosis in septic myocardial injury ……200
YP-40 Mechanism investigation of Beclin 1 in mitochondrial ferroptosis in doxorubicin induced mice myocardial injury ……202

YP-41 肠道微生物通过调节能量代谢水平参与老化心脏功能的恢复 ……204
YP-42 Molecular mechanism of natural grass feed improving muscle quality of grass carp through IFN-γ2 regulation ……205

P1 神经生理 ……206

P1-1 dCA1 星形胶质细胞 β2-AR 下调致乳酸分泌减少引起疼痛和记忆障碍 ……206
P1-2 GLP-1 modulates the spontaneous firing activity of globus pallidus neurons ……207
P1-3 Effect of cannabidiol on learning and memory function and neural network oscillation in rats with sporadic Alzheimer's disease ……208
P1-4 Psychological stress-induced masseter pain sensitization in rats may involve the central amygdala-caudal subnuclear mechanism of the trigeminal spinal tract nucleus ……210
P1-5 Effects of dexmedetomidine combined with etomidate on BLA-LC activities of D-galactose-induced aging rats ……211
P1-6 Effects of Emodin on cognitive function and brain energy metabolism in MCAO model rats ……212
P1-7 LncRNA MSTRG.81401 对 2 型糖尿病神经病理痛合并抑郁大鼠海马细胞焦亡的影响 ……213
P1-8 The deficiency of FRMD5 results in neurodevelopment dysfunction and autistic-like behavior in mice ……214
P1-9 Effect of photoperiodic intervention on behavior in Parkinson's disease model rats and its mechanism ……216
P1-10 Effects of chronic psychological stress on rat salivary secretion may involve central amygdala-inferior salivatory nucleus pathway mechanisms ……218
P1-11 突触局部的 mRNA 乙酰化修饰调节神经可塑性 ……219
P1-12 Synapse elimination by phagocytic astrocytes in a Parkinson’s disease mouse model ……219
P1-13 Nano-selenium alleviates LPS-induced microglia activation and dopaminergic neuronal damage ……220
P1-14 Oxytocinergic modulation in mouse medial prefrontal cortex ……221
P1-15 阿司匹林保护大脑缺血再灌注损伤的神经机制 ……222
P1-16 GHSR1a deletion-mediated autophagic dysregulation promotes neurodegeneration in Parkinson’s disease ……224
P1-17 Berberine hydrochloride ameliorates pruritus by inhibiting $MrgprB_2$ receptor on mast cell ……225

P1-18 Astrocyte-derived apolipoprotein D is essential for neuronal survival in Parkinson's disease ……226
P1-19 海马脑区 AdipoR1 神经元活性对 METH 成瘾行为的影响及机制 ……227
P1-20 The role of CRF receptor1 in the hippocampal DG on spatial learning and memory in the chronic stress model of rats ……227
P1-21 NR2A 特异性拮抗剂 NVP-AAM077 对大鼠海马空间学习和记忆能力的影响 ……229
P1-22 慢性压力导致小鼠抑郁和痛敏后大脑皮层神经细胞形态和信号特征的研究 ……229
P1-23 人源 α-突触核蛋白通过铁死亡造成运动功能障碍 ……230
P1-24 Chemokine receptor CXCR2 in primary sensory neurons of trigeminal ganglion mediates orofacial itch ……231
P1-25 Effects of exercise intervention on anxiety/depression-like behaviors in obesity model rats ……231
P1-26 Preliminary observation of effects of riluzole combined with composite pseudostellaria granule on denervated skeletal muscle atrophy ……233
P1-27 Effects of mirtazapine combined with saikosaponin D on depression-like behaviors in CUMS rats ……234
P1-28 枸杞糖肽缓解由氧化应激和铁凋亡导致的焦虑疾病 ……235
P1-29 HDAC6 调控 HSP90-HSF1 影响 APP/PS1 转基因小鼠海马组织病理学及认知行为学功能的变化 ……235
P1-30 KDM4A in the dorsal root ganglia contributes to the development and maintenance of neuropathic pain via regulation of CCL2 in rats ……236
P1-31 Electro-acupuncture modulating corticostriatal dysfunction induces time-dependent motor improvement in Parkinsonian rats ……237
P1-32 Pathological α-synuclein abolishes the maintenance of mitochondrial homeostasis by exosomal hemoglobin under chronic hypoxia ……238
P1-33 二肽基肽酶 4 影响阿尔茨海默症学习记忆功能障碍作用及机制 ……239
P1-34 ABI3BP 在阿尔茨海默症发生发展中的作用及机制研究 ……240
P1-35 Electro-acupuncture alleviates corticostriatal circuit dysfunction in Parkinsonian rats ……241
P1-36 磁共振弥散张量成像在注意缺陷多动障碍临床应用研究 ……241
P1-37 NMDAR 阻断诱导 dCA1 区神经元兴奋性异常于空间行为障碍的相关性 ……242
P1-38 TadA orthologs enable both cytosine and adenine editing of base editors ……243
P1-39 TadA reprogramming to generate potent miniature base editors with high precision ……244
P1-40 外侧臂旁核-下丘脑室旁核兴奋性谷氨酸能神经通路在晕动症发生中的作用 ……245

P1-41 Downregulation of PPP1r17 in the hippocampus drives alcohol-associated behavior in mice ……246
P1-42 Role of extracellular vesicles of Lactobacillus plantarum on alcohol consumption in Sprague-Dawly Rats ……247
P1-43 Effects of calcitonin gene-related peptide on synaptic transmissions in spinal cord motoneurons *in vitro* ……248
P1-44 Activation of TRPV4 induces neuroinflammation through inhibiting the nicotinic acetylcholine receptor α7 subunit ……248
P1-45 A central mechanism for generation and maintenance of vigilance state in zebrafish and mice ……250
P1-46 CB1R antagonist NESS 0327 improved the motor dysfunction of MPTP-induced PD mice ……250
P1-47 Molecular mechanisms of aldosterone-targeting neurons in the nucleus tractus solitarius in mice activated by a low sodium diet and their whole-brain projection ……251
P1-48 Dopaminergic neurodegeneration in the substantia nigra is associated with olfactory dysfunction in mice models of Parkinson's disease ……252
P1-49 远隔缺血适应脑保护的内皮祖细胞动员机制 ……253
P1-50 Inhibition of SOCS3 signaling in the NTS alleviates hypoventilation in diet-induced obese male mice ……254
P1-51 Effects of adenosine on synaptic transmissions in rat spinal cord motoneurons *in vitro* ……255
P1-52 Effects of 2-AG on peripheral afferent synaptic transmission to spinal cord motoneurons ……256
P1-53 基于 mTOR 通路探讨半夏白术天麻汤对缺血性脑卒中的保护作用 ……256
P1-54 Effects of ICAM5 on alcohol dependence behavior in mice through remodeling of synaptic structure ……257
P1-55 Cell-specific NFIA upregulation promotes epileptogenesis by TRPV4-mediated astrocyte reactivity ……258
P1-56 乙酰水杨酸乙酯保护小鼠大脑缺血再灌注损伤的有效性和安全性研究 ……259
P1-57 组胺 H4 受体对阿尔茨海默病大鼠内嗅皮层-海马的调节作用及其脑内机制 ……261
P1-58 Anshen Dingzhi Prescription prevents PTSD-elicited neuroinflammation via inactivating FKBP5-IKKα-NF-κB-NLRP3 signaling ……262
P1-59 G-1 rescues hippocampal synaptic deficits elicited by PTSD through activating GPR30/BDNF/TrkB signaling ……263

P1-60 Regulation of mitochondrial signals in PTSD-like behaviors and ameliorative effects of Anshen Dingzhi prescription ……264
P1-61 参芪益智方通过调节脑周细胞的收缩性来预防 $A\beta_{42}$ 诱导的小鼠记忆损伤 ……265
P1-62 Expression of TRPC6 in mouse retina and its role in STZ-induced early diabetic retinopathy in mice ……265
P1-63 Combined alcohol and cannabinoid exposure leads to synergistic toxicity by affecting cerebellar Purkinje cells ……266
P1-64 Correlation between acupoint sensitization and activation of pruriceptor ……267
P1-65 Astrocytic Nav1.6 knockdown inhibits APP/Aβ abnormal accumulation via autophagy-lysosomal pathway in APP/PS1 mice and reverses its cognitive deficits ……268
P1-66 Molecular and cellular mechanisms of the first social relationship: A conserved role of 5-HT from mice to monkeys, upstream of oxytocin ……269
P1-67 Calpain 介导 DCC 参与抑郁发生的机制研究 ……270
P1-68 Hap1 调控 GR/CREB/BDNF 信号通路在 APP/PS1 小鼠学习记忆中的作用 ……270

P2 内分泌代谢 ……271

P2-1 Ischemic cardiomyocytes-derived small extracellular vesicles promote cardiac fibrosis ……271
P2-2 Vaccarin suppresses diabetic nephropathy through inhibiting the EGFR signaling pathway ……272
P2-3 Inhibition of SAT1-mediated ferroptosis arrests loss of retinal ganglion cells in diabetic retinopathy ……273
P2-4 FXR controls insulin content by regulating Foxa2-mediated insulin transcription ……274
P2-5 GPCR 辅助蛋白 MRAP2 介导的 GLP1R 受体信号通路在代谢疾病中的功能探究 ……275
P2-6 基于 Micro-CT 和血清非靶向代谢组学方法探究孤立性生长激素缺乏的侏儒大鼠骨微结构受损的机制 ……275
P2-7 Nerve activity regulates the crosstalk between pancreatic islet β cells and residential macrophages ……276
P2-8 db/db 小鼠肝脏脂滴和线粒体相互作用机制研究 ……278
P2-9 The effects and mechanism of dapagliflozin in regulating fibrogenic factor 21 on white adipose tissue browning ……278
P2-10 维生素 D 缺乏对肥胖小鼠脂代谢的影响 ……280
P2-11 草鱼 glp-1r 克隆、序列分析及其基因表达的调节 ……280
P2-12 LIPC-514C/T 多态性与运动干预 PDM 人群健康体适能疗效的关联研究 ……281

P2-13 Roux-en-Y Gastric bypass surgery improves metabolism by up-regulating Nesfatin-1 and activating AMPK/PGC-1α/UCP1 pathway to induce white fat browning ……282
P2-14 RYGB surgery suppresses ferroptosis via the PI3K / AKT / mTOR signaling pathway to improve nonalcoholic fatty liver disease ……283
P2-15 RYGB surgery improves obese type 2 diabetes by inhibiting jejunal GLUT 2 levels with Nesfatin-1 ……285
P2-16 Effect and mechanism of vertical sleeve gastrectomy in improving skeletal muscle insulin resistance in mice with polycystic ovary syndrome by regulating IGF-1 ……287
P2-17 神经肽 CRF 参与高原低氧下炎症反应 ……288
P2-18 视前正中核在精氨酸加压素诱导升温中的作用及机制研究 ……289
P2-19 Paeoniflorin relieves arterial stiffness induced by a high-fat/high-sugar diet by disrupting the YAP-PPM1B interaction ……290
P2-20 Increased COX6A2 promotes pancreatic β-cell apoptosis via modulation of Cyclophilin F ……291
P2-21 Nesfatin-1 改善 DSS 诱导的小鼠溃疡性结肠炎 ……291
P2-22 对羟基苯甲酸依赖肠道微生物改善粘膜屏障缓解结肠炎 ……292
P2-23 肝脏 LGR4 加重胆汁淤积引起的肝损伤 ……292
P2-24 *Discovering protective effects of adaptive IDH2 upregulation in diabetic retinopathy* ……293
P2-25 Distal segments of cilia in chemosensory neurons regulate pathogen avoidance and innate immunity in *Caenorhabditis elegans* ……294

P3 应用生理 ……295

P3-1 Preliminary study on kidney hypoxia adaptation mechanism of Pikas（Ochotona curzoniae） based on UHPLC-QE-MS ……295
P3-2 Characteristics of renal mitochondrial hypoxia adaptation in plateau pika at different altitudes ……296
P3-3 Study on metabolic mechanism of Brown adipose tissue（BAT）in pika adapting to extreme plateau environment ……297
P3-4 绞股蓝皂苷的抗缺氧活性及其物质基础研究 ……298
P3-5 深地高温环境下机体急性热应激的多组学研究 ……299
P3-6 外源性 EPO 改善慢性间歇性低氧诱导神经元损伤的作用研究 ……300
P3-7 p53 乳酸化修饰在低氧诱导神经炎症中的机制研究 ……300
P3-8 Study on physiological predictive factors of acute mountain sickness ……301

P3-9 Elevated serum and urinary secreted protein acidic and rich in cysteine (SPARC) levels are novel biomarkers of kidney fibrosis severity ……302
P3-10 Rho 激酶介导的肾内动脉重建增加模拟航天失重肾损伤易感性 ……303
P3-11 脂质组学和质谱成像技术揭示低压低氧对小鼠脑脂质组成的多样性和动态变化的影响 ……304
P3-12 低氧加重结扎诱发牙周炎小鼠的脑内炎症 ……304
P3-13 GP-14 通过 NF-κB 信号通路减轻脂多糖诱导小鼠抑郁样行为 ……305
P3-14 缺氧对能量和营养素代谢以及身体成分的影响 ……306
P3-15 EFTUD2 regulates the apoptosis of NSCs and cerebral cortex development through RNA alternative splicing of Caspase3 ……306
P3-16 间断短时供氧防止低压低氧肺动脉高压的应用基础与保障设备研究 ……307
P3-17 低氧预适应对急性缺氧小鼠行为学特征的影响 ……308
P3-18 OPG/RANKL/RANK 系统介导模拟失重所致动脉钙化的作用和机制 ……309
P3-19 胃食管反流病中食管黏膜上皮屏障功能炎症损伤机制探讨 ……309

P4 中医生理 ……310

P4-1 整合网络药理学和代谢组学揭示白藜芦醇对斑蝥素诱导小鼠肾损伤的保护作用机制研究 ……310
P4-2 Involvement of astroglial glutamate-glutamine in the analgesic process of electroacupuncture for chronic neuropathic pain ……311
P4-3 A network pharmacology-based investigation reveals an inhibitory role of Shenqi Fuzheng injection in glioma via the SRC/PI3K/AKT signaling pathway ……312
P4-4 Study on the effect and mechanism of compound kushen injection in regulating of Lung squamous cell carcinoma ……313
P4-5 网络药理学方法联合体外实验初探金水六君煎辅助放化疗治疗恶性黑色素瘤的分子机制 ……314
P4-6 新型小檗碱晶体药 BJ 改善化疗所致周围神经病变及代谢综合征 ……315
P4-7 疏肝调神夹脊针治疗阈下抑郁：随机对照研究 ……315
P4-8 Astrocyte may participate in the protection of moxibustion against blood–brain barrier damage in rats with multiple cerebral infarctions ……316
P4-9 Exploring the mechanism of *Gastrodia elata* Blume and its active compounds protects ischemic neuronal injury：network pharmacology and experimental validation ……317
P4-10 四君子汤对久坐少动模型大鼠股四头肌 PAX7 和 MyoD 的影响 ……318

P5-比较生理 ……319

P5-1 Transcriptional regulation of retrotransposons by hypoxia ……319

P5-2 Multigenerational exposure of cadmium trans-generationally impairs locomotive and chemotactic behaviors in *Caenorhabditis elegans* ……320

P5-3 内皮素-1 诱导成年雄性斑胸草雀 HVC 缺血损伤致发声障碍模型的建立 ……321

P5-4 Effects of long-term Chlormequat chloride exposure to *C. elegans* ……321

P5-5 高原鼢鼠 Epas1 基因变异及肺纤维化保护机制 ……322

P5-6 低氧下骨髓巨噬细胞分泌的 Metrn 调控造血干细胞动员和分化 ……323

P5-7 White and brown adipose tissues: the fuel for hibernation ……324

P5-8 HCAR2 介导低氧促神经干细胞增殖的作用与途径 ……325

P6-运动生理 ……325

P6-1 12 周重组胶原蛋白补充联合有氧运动对去卵巢大鼠肌骨共减的影响 ……325

P6-2 Arterial smooth muscle cell AKAP150 mediates exercise-induced repression of $Ca_V1.2$ channel function in hypertensive cerebral arteries ……326

P6-3 有氧运动对抑郁症人群睡眠质量干预效果的系统评价和 Meta 分析 ……327

P6-4 孕期运动改善高血压子代血管功能的 *Fgf21* 组蛋白去乙酰化机制 ……328

P6-5 有氧运动改善高脂饮食诱导肥胖小鼠代谢异常的作用机制研究 ……329

P6-6 心率监测在体能训练课运动负荷评价中的实践研究 ……330

P6-7 UVB 照射改善小鼠自主活动量的神经电生理学研究 ……330

P6-8 心率监测在高中女子排球实战训练中的应用及评价 ……331

P6-9 有氧运动对尼古丁成瘾戒断小鼠外侧缰核神经元群体编码特征的影响 ……332

P6-10 运动想象联合干预对脑卒中患者上肢功能和日常生活能力（ADL）的影响：Meta 分析 ……333

P6-11 脂联素对肝脏 PLIN2 降解的调控途径及其与运动减肥促肝脂分解的关系研究 …334

P6-12 一流课程建设背景下运动生理学课程建设现状与方向探讨 ……335

P6-13 有氧和抗阻运动经 IL-18/IL-18R 信号通路对 SAMP8 小鼠皮肤老化的影响 ……335

P6-14 大负荷运动后骨骼肌炎症损伤的关键基因分析及信号通路鉴定 ……336

P6-15 Categorical dose-response and interactions in metabolic syndrome risk: Sedentary behavior, cardiorespiratory fitness, and physical activity ……337

P6-16 运动介导 HIF-1 改善心梗心脏中的作用及其机制探讨 ……338

P6-17 EMR 环境下运动调节电磁-生物信号转导机制及神经保护作用研究进展 ……339

P6-18 Th1/Th2 平衡在运动性免疫抑制大鼠中的作用研究 ……340

P6-19 8 周不同顺序同期训练对普通大学生有氧耐力和力量素质的影响 ……341

P6-20 纹状体不同类型神经元调节小鼠主动运动的电生理学研究 ……342
P6-21 Effects of deep cervical flexor training combined with kinesio taping on chronic non-specific neck pain ……342
P6-22 有氧运动通过 ALCAT1 抑制氧化应激诱导的细胞凋亡发挥心梗大鼠心脏保护作用 ……344
P6-23 运动调控 PI3K/Akt 信号通路改善糖尿病糖脂代谢及炎症的研究进展 ……345
P6-24 力竭运动对超直接通路各核团 NR2B、GABA-Aα1 蛋白表达的影响 ……345
P6-25 有氧运动激活 FGF21/PI3K/AKT/VEGF 信号通路促心梗心脏血管生成 ……346
P6-26 不同运动对肥胖小鼠肝脏自噬相关蛋白表达的影响 ……347
P6-27 有氧运动通过 Irisin 抑制内质网应激和细胞凋亡改善心梗诱导骨骼肌减少 ……347
P6-28 运动性骨骼肌损伤中时钟基因 BMAL1 与 BDNF 的作用 ……348
P6-29 Physical exercise modulates the microglial complement pathway in mice to relieve cortical circuitry deficits induced by mutant human TDP-43 ……349
P6-30 组学技术在运动科学领域研究现状及趋势的知识图谱可视化分析 ……352
P6-31 Wnt 信号通路及 SFRP1 在大负荷运动后骨骼肌修复过程中的作用 ……352
P6-32 NAMPT 在运动性骨骼肌损伤炎症反应中的调控机制研究 ……353
P6-33 运动对肌骨共减综合征的影响研究进展 ……354
P6-34 肾源性 ELA 在有氧运动改善心梗心肌纤维化中的作用及机制研究 ……355
P6-35 抗阻运动上调 Irisin 促进 2 型心肾综合征小鼠肾脏血管生成 ……356
P6-36 乳酸杆菌在规律运动改善与年龄相关肌少症中的作用 ……356
P6-37 推拿经 JAK—STAT 信号通路改善一次性大负荷运动大鼠 EIMD 的效应机制 ….357
P6-38 HIIT 与 MICT 在改善久坐大学生心肺适能中的内部负荷特征及生理机制研究 …358
P6-39 多组学联合分析推拿在改善运动性骨骼肌损伤导致延迟性肌肉酸痛中的作用机制 ……359
P6-40 体力活动强度划分方法的研究进展 ……359
P6-41 不同运动方式调控神经肌肉接头对衰老大鼠骨骼肌蛋白代谢影响的研究 ……360
P6-42 运动上调 FGF21 抑制心肌缺血再灌注小鼠下丘脑室旁核氧化应激和铁死亡 ……361
P6-43 HIIT 对 T1DM 小鼠自身反应性 $CD8^{+}$T 细胞代谢重编程及功能的影响 ……362
P6-44 有氧运动/饮食控制通过 Irisin 受体通路促进肥胖小鼠骨形成 ……363
P6-45 HIIT 对衰老大鼠肝脏代谢的影响及可能机制 ……364
P6-46 肥胖儿童青少年静息代谢率与体成分指标的关系研究 ……365
P6-47 有氧运动诱导 miR-21 调控 PTEN/PI3K/AKT 通路对小鼠缺血再灌注损伤后心肌梗死面积及心肌组织炎症反应的影响 ……366
P6-48 跑台运动改善 MPTP/p 诱导慢性帕金森病小鼠抑郁样行为的机制研究 ……367
P6-49 运动通过 GDF-5 促进血管新生增强肾功能 ……368

P6-50 有氧运动通过 Notch 信号通路调节巨噬细胞极化改善心肌缺血再灌注损伤炎症反应 ……369
P6-51 基于代谢组学分析推拿促进运动性骨骼肌损伤修复的作用途径 ……370
P6-52 少林养生功法通过 Notch 信号通路调节巨噬细胞极化降低心肌缺血再灌注损伤炎症反应 ……370
P6-53 基于 Firstbeat 系统的自由式滑雪空中技巧运动员训练负荷及疲劳恢复研究 ……371
P6-54 The role of OTUD5 in skeletal musclein autophagy after eccentric exercise ……372
P6-55 下肢血流限制力量训练对青年女性代谢和免疫应激水平的影响 ……373
P6-56 膜联蛋白 A6 在一次离心运动小鼠骨骼肌质膜损伤修复中的作用 ……374
P6-57 长期低温下高强度训练对小鼠无氧运动能力的影响 ……375
P6-58 功能动作系统在舞蹈损伤预防与康复中的应用研究现状 ……376
P6-59 水疗对脑瘫患儿运动功能康复疗效及作用机制的研究进展 ……376
P6-60 基于胰高血糖素样肽 1 探讨低氧与运动对心梗后心脏的保护作用 ……377
P6-61 昼夜节律对慢性疾病的研究进展 ……378
P6-62 急性 HIIT 与 MICT 干预对久坐成人血管内皮功能的影响及机制 ……379
P6-63 三种不同方式的急性运动对男大学生认知功能的影响 ……381
P6-64 有氧运动刺激心肌 GDF-5 分泌并促进心梗小鼠血管新生及其机制研究 ……381
P6-65 A bioinformatics approach based on the GEO database to analyze the effects of different training modalities on gene expression in human skeletal muscle ……382
P6-66 The effects of aerobic exercise on the ANXA1/FPR2 pathway and inflammatory response in elderly mice skeletal muscle ……384
P6-67 探究短期 PM2.5 污染暴露下小鼠运动对其认知、情绪及代谢的影响 ……385
P6-68 维生素 D 缺乏对小鼠能量代谢的影响 ……386
P6-69 高强度间歇训练和中等强度持续训练对增龄大鼠脂肪组织不同训练适应性的 miRNAs 分析 ……387
P6-70 Effects of life-long exercise on aging-related inflammatory cytokines, apoptosis, oxidative stress, ferroptosis markers, and NRF2/KAEP 1/Klotho pathway in rat kidneys ……388
P6-71 基于代谢组学研究肠道菌群调控长期大负荷运动小鼠 MSC 稳态的效应机制 ……389
P6-72 推拿经 NAMPT/NAD^+调控 EIMD 大鼠骨骼肌能量代谢的作用研究 ……389
P6-73 运动干预对阿尔兹海默症患者的记忆和脑功能的影响 ……390
P6-74 冲刺间歇训练对阿尔兹海默症患者的认知功能及运动能力的影响 ……391
P6-75 miR-338-5p/JAK2/STAT3 通路轴在运动改善肥胖小鼠认知功能中的作用机制研究 ……392
P6-76 不同运动方式预防 AS 的效果对比与研究 ……393
P6-77 满足身体活动指南和老年人认知功能：基于加速度计的客观测量 ……394

P6-78 低温抗阻运动对 T2DM 大鼠糖脂代谢影响研究 ……394
P6-79 老龄化背景下运动影响晚发型抑郁相关研究的进展 ……395
P6-80 运动预适应在心肌缺血再灌注模型小鼠心脏中的作用及其对 NLRP3 炎症小体的影响 ……396
P6-81 不同的运动强度及方式对肠道菌群的影响综述 ……397
P6- 82 “体医融合”背景下《运动生理学》“SPOC”教学模式研究 ……398
P6-83 Exercise prevents telomere-related diseases ……398
P6-84 虫草素通过 VGSC 改善脂多糖诱导的 C2C12 肌管萎缩 ……400
P6-85 Effects of bacoside A on phenytoin-induced cerebellar disfunction model rats ……402
P6-86 红景天对低氧运动小鼠骨骼肌保护作用机制研究 ……402
P6-87 一次运动对青少年外周血单核细胞基因表达的生物信息学分析 ……403
P6-88 肩胛稳定性训练联合肌肉能量技术对大学生头前伸姿势的干预效果研究 ……404
P6-89 运动通过 FGF21 通路调控肝脏脂代谢改善胰岛素抵抗的机制研究 ……405
P6-90 Treadmill exercise pretreatment ameliorated vascular dementia-induced structural synaptic plasticity impairments in rat prefrontal cortex and improved recognition memory …406
P6-91 心动周期和心电周期之议析——一个生理学名词的建议 ……407
P6-92 骨骼肌疲劳对肌肉收缩产生的被动力量及核心蛋白作用的影响 ……408
P6-93 Supramammillary nucleus-hippocampal neural circuit modulates motor skill learning ·409
P6-94 Tafazzin 介导的心磷脂合成在 HIIT 抑制衰老骨骼肌铁死亡的作用机制研究 ……410
P6-95 个体、家庭和物理环境因素对学龄儿童基本动作技能的影响 ……411

P7 呼吸生理 ……412

P7-1 镁和钙离子之间的相互作用：解码其对肺动脉平滑肌细胞钙化的影响 ……412
P7-2 高镁对慢性低氧肺动脉高压大鼠冠状动脉重构和 TRPCs 介导 ET-1 高反应性的影响 ……413
P7-3 OGG1 通过 miR-145/KLF4 通路影响肺纤维化的机制研究 ……414
P7-4 Preliminary observation of eugenol effects on urethane-induced lung cancer model mice ……415
P7-5 BAX 激动剂 BTSA1 抗肺纤维化的保护作用及机制研究 ……416
P7-6 Tregs 通过 NLRC3 抑制左心疾病相关性肺动脉高压的内皮间质转化 ……417
P7-7 组蛋白甲基转移酶 SETDB1 通过 NUAK1 调控肺动脉平滑肌细胞糖代谢重编程 ··417
P7-8 吡格列酮对 PM2.5 暴露致慢性咳嗽豚鼠的神经源性慢性气道炎症的影响及其机制 ……418
P7-9 细菌溶解产物 OM-85 对早期肺腺癌免疫微环境的调控机制研究 ……419
P7-10 探究 P2Y12 受体在 PM2.5 暴露致慢性咳嗽豚鼠小胶质细胞极化的作用 ……420

P7-11 Circ-calm4 通过调控 COMP 介导肺动脉平滑肌铁死亡 ……421
P7-12 1,25$(OH)_2D_3$ inhibits Lewis lung cancer cells migration via NHE1-sensitive metabolic reprograming ……422
P7-13 TGM2 通过影响内皮功能参与主动脉夹层发生发展的机制研究 ……423
P7-14 HMGA1 调控成纤维细胞炎症促进主动脉夹层的发生 ……424
P7-15 FOSL1 介导血管外膜病变促进主动脉夹层发生的机制研究 ……424
P7-16 HMGA1 调控 Wnt/β-Catenin 信号在肺动脉高压大鼠内皮间质转化中的作用 ……425
P7-17 慢性高原缺氧及高原返回后对小鼠肺功能的影响 ……426

P8 循环生理 ……427

P8-1 Asynchronous changes of hydrogen sulfide and its generating enzymes in most tissues with the aging process ……427
P8-2 Senescence of vascular smooth muscle cells contributed pathogenesis of aortic medial calcification and regulated by α_1-adrenergic receptors in rats ……428
P8-3 Acetate attenuates microglia-mediated neuroinflammation in spontaneously hypertensive rats ……429
P8-4 The role of m^6A demethylase FTO regulation of BMP4 expression in myocardial hypertrophy ……430
P8-5 Rev-erbα regulate diurnal pumping rhythm through repressing Sln transcription and protects cardiomyocytes from pressure overload injury ……432
P8-6 预热适应对高温所致血管内皮细胞损伤的保护作用及其机制 ……434
P8-7 The regulatory mechanism of transcription factor TBX20 in human congenital heart disease ……435
P8-8 Bruton tyrosine kinase inhibitor ibrutinib induces hypertension by upregulating transcription of $Ca_V1.2$ calcium channel ……436
P8-9 HIF-1α 通过调节能量代谢适应途径降低小鼠移植心脏冷保存过程中的冷缺血损伤 ……437
P8-10 交感中枢 RVLM 内 DPP3 促进血管紧张素-(5-7)生成参与高血压交感亢进的机制研究 ……438
P8-11 The hippocampus works as a potential crosslink between hypertension and Alzheimer's disease ……439
P8-12 Ibrutinib induces cardiac arrhythmia by targeting $Ca_V1.2$ calcium channel ……440
P8-13 GADD45G 在心肌肥厚中的表达调控及其介导表观遗传重编程的分子机制研究 ……441

P8-14 Deletion of $CX3CR1^+$ macrophage inhibits the thoracic aortic aneurysm procession in Marfan syndrome ……442
P8-15 Metabolic changes of glycerophospholipids during the reparative phase after myocardial infarction injury ……443
P8-16 Heterogeneity of common carotid artery and abdominal aorta: an angle of sphingolipid metabolism ……444
P8-17 骨髓间充质干细胞来源的微颗粒通过抑制铁死亡减轻阿霉素诱导心肌细胞损伤的作用研究 ……445
P8-18 Cocktail containing Pitavastatin and Resveratrol Alleviate hyperhomocytinemia-induced atherosclerosis through inhibiting ferroptosis and metabolitics change ……446
P8-19 低氧诱导因子 HIF2α 对新生内膜增生的作用和机制研究 ……447
P8-20 PFKFB3-driven vascular smooth muscle cell glycolysis promotes vascular calcification via the altered FoxO3 and lactate production ……448
P8-21 Exogenous H_2S initiating Nrf2/GPx4/GSH pathway through promoting Syvn1-Keap1 interaction in diabetic hearts ……449
P8-22 巨噬细胞中 NLRC5 缺失加重心肌重构和心力衰竭及其机制研究 ……450
P8-23 病理性心肌肥厚治疗新策略：调控线粒体功能的 lncRNAs 网络构建 ……451
P8-24 Smooth muscle-conditional knock-in A‐kinase anchoring protein 150 (AKAP150) exacerbates insulin resistance-related cardiovascular dysfunction ……452
P8-25 Myeloid leukemia factor 1 is an epigenetic orchestrator facilitating chromatin opening in cardiac aging ……453
P8-26 TKT 通过损害线粒体生物能学参与主动脉夹层的发生发展 ……454
P8-27 BACH1 缺失通过调节染色质开放性维持血管平滑肌细胞收缩表型抑制新生内膜增生 ……455
P8-28 Identifying Nox3 and differences between Paraventricular nucleus of hypothalamus (PVN) and rostral ventrolateral medulla (RVLM) and physiological role ……456
P8-29 ATP promotes resident vascular wall $CD34^+$ cells migration mainly through P2Y2-STIM1-ERK/p38 pathway ……457
P8-30 Cardiomyocyte peroxisome proliferator-activated receptor α alleviates heart failure with preserved ejection fraction by inhibiting ferroptosis ……458
P8-31 Activation of endothelial Transient Receptor Potential Vanilloid 4 exacerbates myocardial ischemia-reperfusion injury via vascular integrity impairment ……459
P8-32 恩帕格列净挽救主动脉缩窄诱导的小鼠心律失常和钙稳态 ……460

P8-33 S-propargyl-cysteine promotes the stability of atherosclerotic plaque via maintaining vascular muscle contractile phenotype ……461
P8-34 RNA 可变剪接调控与慢性心衰 ……462
P8-35 富勒醇对心肌细胞增殖的调节作用及机制探讨 ……463
P8-36 Lack of PGC-1α in the hypothalamus paraventricular nucleus leads to mitochondrial malfunction and hypertension ……464
P8-37 Whole brain mapping for afferent and efferent connections of PNMT-expressing neurons in the nucleus tractus solitarii ……465
P8-38 Diagnostic and prognostic value of Lp-PLA2, H-FABP and ST2 in patients with septic cardiomyopathy: A retrospective case-control study ……466
P8-39 α-ketoglutarate promotes cardiomyocyte proliferation and heart regeneration after myocardial infarction ……467
P8-40 Reversing metabolic reprogramming by CPT1 inhibition, via DUSP1 ADP-ribosylation-mediated p38 MAPK phosphorylation, promotes cardiomyocyte proliferation and heart regeneration ……468
P8-41 SMOC1 通过影响血管平滑肌钙化介导主动脉夹层发生进展 ……469
P8-42 TSPAN8 介导血管平滑肌细胞表型转换参与主动脉夹层的发生发展 ……470
P8-43 巨噬细胞通过 C5a/C5AR1 信号轴参与主动脉夹层发生进展 ……471
P8-44 经典蒙药“四味土木香散”通过影响 miR-34a-5p/Notch1 信号通路改善压力超负荷性心肌肥厚 ……472

P9 肾脏生理 ……474

P9-1 Tiliroside protects against lipopolysaccharide-induced acute kidney injury via intrarenal renin-angiotensin system in mice ……474
P9-2 Phosphoglycerate kinase 1 (PGK1) contributes to the development of diabetic nephropathy in enzyme-dependent and -independent manners ……475
P9-3 基于肾病综合征探讨 AQPs 在肝心脾肺肾上腺的变化 ……476
P9-4 中性粒细胞胞外诱捕网在转基因高血压小鼠肾损伤中作用 ……477
P9-5 刺激钙离子敏感受体对 C57BL/6 小鼠肾脏 DCT 钾离子通道 Kir4.1/Kir5.1 调控机制的研究 ……478
P9-6 The role and mechanism of XBP1S in hyperuricemic nephropathy ……479
P9-7 Latanoprost stimulates the basolateral Kir4.1/5.1 channel in the distal convoluted tubule 480
P9-8 维持性血液透析患者低相位角与全因死亡风险增加有关——项前瞻性队列研究 ··480
P9-9 基于临床数据库建立急性肾损伤风险预测模型 ……482

P9-10 A small natural molecule targets cdc42-mediated gsk-3β/β-catenin signaling to combat kidney fibrosis ……483
P9-11 Biochanin A suppressed Klf6-Smad3 signaling to attenuate renal fibrosis ……484
P9-12 Integrin αVβ6 induces macrophage infiltration and activation to promote renal inflammation and fibrosis through activating tubular production of IL-34 ……484
P9-13 Inhibition of ACSS2-mediated H3K9 crotonylation alleviates kidney fibrosis via IL-1β-dependent macrophage activation and tubular cell senescence ……486
P9-14 慢性肾病患者的生物补充剂:随机对照试验的荟萃分析 ……487
P9-15 Btg2 promotes focal segmental glomerulosclerosis via smad3-dependent podocyte-mesenchymal transition ……487
P9-16 LncRNA-gm33782 activates MLL3/MLL4 complex regulated H3K4 methylation to exacerbate renal injury in AKI mice ……488
P9-17 前列环素及其受体在肾脏纤维化中的作用及机制 ……489
P9-18 血管紧张素 II 激活高钾饮食小鼠肾远曲小管末段 ROMK 通道 ……490
P9-19 RfxCas13d-mediated inhibition of Circ1647 alleviates renal fibrosis via PI3K/Akt signaling pathway ……492
P9-20 柴胡皂苷 D 通过抑制 TGF-β/Smad3/HK2 信号通路活化介导的糖酵解反应改善 CKD 肾脏纤维化的作用机制研究 ……493
P9-21 空间联合单细胞转录组测序揭示肾小球细胞分子特征及其机制研究 ……494
P9-22 基于转录组测序分析黄芪三七合剂改善肾脏纤维化的关键 LncRNA ……495
P9-23 TGR5 activation ameliorated hypertension through inhibiting ENaC expression in the kidney of DOCA-salt treated mice ……496

P10 应激生理 ……497

P10-1 The role and mechanism of cardiovascular bioactive peptide intermedin in diabetic vascular calcification ……497
P10-2 Intermedin inhibits DNA damage-mediated vascular aging by activating NAMPT/PARP1 ……499
P10-3 应激反应介导模拟失重大鼠血管内皮改变 ……500
P10-4 NLRP3 inflammasome-dependent pryptosis mediates CUMS-induced reproductive impairment in depressive male mice ……501
P10-5 有氧运动调节伏隔核 D1R-MSN 谷氨酸能突触传递减少尼古丁复吸的机制研究 ·502
P10-6 热射病诱导大鼠血管平滑肌细胞表型转化及血管损伤的初步研究 ……502
P10-7 枸杞多糖对热射病大鼠结肠结构与紧密链接相关蛋白的影响 ……503

P10-8 Preliminary observation of effects of flavanols on learning and memory functions in anxiety disorder model rats ……504
P10-9 幼年高血压应激大鼠模型中肠道胶原纤维的变化特征 ……505
P10-10 SRT1720 ameliorates LPS-induced depressive-like behaviors and activates PINK1/Parkin mediated mitophagy in mice ……506
P10-11 低氧应激神经内分泌反应对高原肺水肿发病的作用研究 ……507
P10-12 NE-arranged fluctuation of BMP7 in hippocampus involves the dynamic effects of stress on rodent cognitions. ……508
P10-13 GLUT1-mediated microglia M1-polarization contributes to development of stress-related learning and memory dysfunction in mice ……509
P10-14 同型半胱氨酸通过上调 Rap1a 表达促进小鼠小胶质细胞 M1 型极化 ……510
P10-15 DDX3X 调控内质网应激功能转换在肝衰竭发病中的分子机制研究 ……511
P10-16 聚乙烯微塑料通过引发鲤鱼鳃的氧化应激和激活 NLRP3 炎性小体来诱导细胞凋亡和炎症反应 ……512
P10-17 Microglial NLRP3 inflammasome activation mediates diabetes-induced depression-like behavior via triggering neuroinflammation ……513
P10-18 Role of the netrin-1/ DCC-Unc5 signaling pathway in inflammation-related depression ……514
P10-19 应激性认知功能障碍中 MALAT1 通过与 VCP 相互作用促进星形胶质细胞 A1 型活化 ……515
P10-20 应激诱导空间记忆损伤中海马乳酸变化及其作用机制研究 ……516
P10-21 缺硒通过氧化应激导致小鼠胃黏膜发生铁死亡和炎症损伤 ……516
P10-22 Hematopoietic stem cells reside in adult mouse steady state meninges ……517

P11 血液生理 ……517

P11-1 Diverse effects of cryopreservation-induced mitochondrial dysregulation on cord blood cells ……517
P11-2 The hematopoietic ecosystem in acute myeloid leukemia ……519
P11-3 Blood transcriptomic disturbance and its clinical and immunology association in Alzheimer's disease ……520
P11-4 Single-cell transcriptomic atlas identified novel immunotherapeutic target for multiple myeloma ……521
P11-5 Landscape of bone marrow T cells in acquired aplastic anaemia reveals an activated state and a potential clonal expansion ……523
P11-6 TMEM56 通过调节自噬过程调控红细胞的生成 ……524

P11-7 单细胞测序技术解析白血病微环境中单核细胞的异质性 ……525
P11-8 白血病相关调节性树突状细胞的基因表达特征 ……526
P11-9 白血病微环境通过调节 IRF7 相关信号通路激活 pDC ……527
P11-10 Fbxw11 延缓 AML 疾病进展的分子机制研究 ……528
P11-11 巨噬细胞训练免疫在白血病中的作用 ……528
P11-12 The alternative splicing of LCK in Treg induction in immune thrombocytopenia ……529
P11-13 *SPI1-KLF1/LYL1* axis regulates lineage commitment during human endothelial-to-hematopoietic transition ……531
P11-14 骨髓巨噬细胞调控造血机理探索 ……532
P11-15 Effects of the Aurora an inhibitor MZ-3B on the biological behaviors of AML cell lines via the JAK2-STAT3 pathway ……533
P11-16 Assessment of intestinal status in MPL^{W515L} mutant myeloproliferative neoplasms mice model ……533
P11-17 ROBO4 抑制照射损伤内皮间质转化促进造血重建 ……534
P11-18 AML-derived small extracellular vesicles promote leukemogenesis by transferring miR-221-3p ……535
P11-19 RNA 结合蛋白 PTBP1 对造血干细胞归巢和迁移以及红系发育的作用研究 ……537
P11-20 不同遗传特征的神经母细胞瘤因免疫状态的改变导致复发或进展 ……538
P11-21 lncRNA NEAT1 对红系发育的作用研究 ……538
P11-22 高原红细胞增多症小鼠红细胞特征解析及干预措施 ……539
P11-23 O-GlcNAc 糖基化修饰转录因子 TWIST1 影响 MDS 克隆细胞耐药的分子机制 ··540
P11-24 Gasdermin E dictates inflammatory responses by controlling the mode of neutrophil death ……541
P11-25 METTL3 和 METTL14 在幼年型粒单核细胞白血病中的作用及机制研究 ……541
P11-26 单细胞层面解析 allo-UCBT 和 allo-PBSCT 的造血重建规律差异 ……542
P11-27 Molecular characteristics of MPN malignant hematopoietic stem cells across distinct driver mutations ……543
P11-28 From integrin structures to explore: What does the future of structural biology look like? ……544
P11-29 IDF-11774 对弥漫大 B 细胞淋巴瘤的作用机制研究 ……545
P11-30 CARMA1 介导 Notch1 激活 NF-κB 信号影响 T-ALL 细胞增殖 ……546
P11-31 ACAT1 通过调控多发性骨髓瘤细胞代谢重编程促进疾病进展 ……546
P11-32 AURKA 与 AURKB 异常活化调节 CALR 基因突变的 MARIMO 细胞的生长及代谢机制研究 ……547
P11-33 IGF1-R 抑制剂 AEW541 对伊马替尼杀伤 SUP-B15 细胞的增效作用 ……548

P11-34 Novel c-Myc G4 stabilizer EP12 promotes myeloma cytotoxicity by disturbing NF-κB signaling ……549
P11-35 Impaired platelet function and thrombus formation in PDE5A-deficient mice ……550
P11-36 Thrombin receptor activating peptide-6 regulates T-cell mediated allogeneic reaction 550

P12 消化与营养 ……551

P12-1 黄连素改善 6-羟基多巴大鼠抑郁样行为和便秘症状 ……551
P12-2 Based on the 5-HT2B receptor and PLCβ- IP_3R pathway to explore the intervening mechanisms of amitriptyline on gastrointestinal dysfunction in FD Rats ……552
P12-3 Neuroprotective effect of a compound comprising Taurine and L-serine on cerebral ischemia: An integrated basic and clinical investigation ……554
P12-4 葡聚糖硫酸钠诱导的结肠炎中热受体（TRPV1）和冷受体（TRPM8）的功能表达及相关性研究 ……555
P12-5 急性肝损伤中巨噬细胞 β-catenin 信号通过外泌体/α-SNAP 通路调控肝脏 Treg 细胞的分子机制 ……557
P12-6 黄连厚朴治疗慢性胃炎湿热证的疗效和分子机制 ……558
P12-7 Investigation of the L-Glu-NMDA receptor-H_2S-NMDA receptor pathway regulating gastric function in rats nucleus ambiguus ……558
P12-8 PMCA4 抑制 NO 信号通路调节乳鼠结肠 ICC 的起搏电位 ……559
P12-9 Maternal intermittent fasting deteriorates offspring metabolism via suppression of hepatic mTORC1 signaling ……560
P12-10 黄连素改善 6-OHDA 帕金森病大鼠胃底纤维化和氮能神经元受损 ……561
P12-11 慢性应激通过蓝斑-中缝神经环路抑制肝再生的机制研究 ……562
P12-12 QX-314 通过 TRPV1/VGSC 通道抑制食管高敏感的机制研究 ……563
P12-13 胆汁酸受体 TGR5 对 DSS 诱导的小鼠结肠炎 NF-κB 通路的调节作用 ……564
P12-14 枳壳水煎剂对小鼠胃肠功能的影响 ……564

P13 疼痛转化 ……565

P13-1 Development of multifunctional and orally active cyclic peptide agonists of opioid/neuropeptide FF receptors that produce potent, long-lasting peripherally restricted antinociception with diminished side effects ……565
P13-2 Spinal interleukin-16 contributes to persistent inflammatory pain hypersensitivity ……566
P13-3 Effect of aromatherapy on pain sensitization in pain empathy model rats ……567
P13-4 The central mechanism of trigeminal neuralgia mediated by HMGB1/TLR4 signaling pathway in rats ……568

P13-5 Thrombospondin 2 in peripheral sensory neurons regulates SNL-induced neuropathic pain ……569
P13-6 DNMT3a-triggered upregulation of $GABA_A$ receptor in mPFC contributes to paclitaxel-induced neuropathic pain and anxiety-like behavior ……570
P13-7 YL-0919 对小脑浦肯野细胞自发性活动和运动行为的影响机制 ……572
P13-8 卫星胶质细胞在 A 纤维脱髓鞘诱导的神经病理痛中的作用机制研究 ……573
P13-9 Roles of transient receptor potential channels TRPV1 and TRPM8 in paclitaxel-induced neuropathy pain ……573
P13-10 Sleep deprivation causes hyperalgesia via suppressing the activity of medial habenula cholinergic neurons ……574
P13-11 A study on the role of dopamine D2 receptors in the anterior cingulate cortex in participating in the regulation of pain aversion in rats ……575
P13-12 Mechanism of pregabalin regulates complex spike activity of Purkinje Cells in mice ……576
P13-13 Mechanism of noradrenaline enhances CF-PC LTD in mouse cerebellar cortex ……577
P13-14 Mechanism of noradrenaline suppresses the facial stimulation-evoked MLI-PC synaptic transmission in mouse cerebellar cortex *in vivo* ……578
P13-15 Mechanism of ganoderma lucidum polysaccharide improves learning and memory impairment in chronic stress rats ……579
P13-16 Mechanism of ANP regulates CRF-mRNA expressing neuronal activity in mouse hypothalamic PVN *in vitro* ……580
P13-17 混合型阿片类受体激动拮抗药：酒石酸布托啡诺的药理作用以及临床应用进展 ……581
P13-18 老年慢性疼痛患者抑郁症研究进展 ……581
P13-19 经颅磁在缓解神经性疼痛康复中的应用现状 ……582
P13-20 肱骨外上髁炎疼痛治疗的研究进展 ……583
P13-21 The Lysine-specific demethylase 1 in medial prefrontal cortex facilitates chronic stress–induced pain and emotional dysfunction in female mice ……583
P13-22 Upregulation of KDM6B aggravates inflammatory pain through H3K27me3 demethylation-dependent production of TNF-α in the dorsal root ganglia and spinal dorsal horn in rats ……585
P13-23 Spinal cord injury enhances complex spike activity of cerebellar purkinje cells in mice *in vivo* ……585
P13-24 Effects of different decibel noise exposure on pain sensitization in chronic migraine model rats ……586

P13-25 Activation of 5-HT_{1A} receptors alleviates the neuropathic pain-induced depression through GABAergic neurons in the ventrolateral orbital cortex ……587
P13-26 Hemoglobin α derived peptides VD-hemopressin (α) and RVD-hemopressin (α) are involved in electroacupuncture inhibition of chronic pain ……589
P13-27 The RNA demethylase ALKBH5 in the spinal cord promotes neuropathic pain via NMDA receptor GluN2B ……590

P14 生殖生理 ……591

P14-1 生物钟在 PCOS 排卵障碍中的作用及机制研究 ……591
P14-2 Sertoli cell-only phenotype and scRNA-seq reveal hnRNPU as a regulator required for spermatogonial stem cell pool establishment in mice ……591
P14-3 节律紊乱通过降低 SERPINE1 基因甲基化促进 PCOS 高雄激素血症 ……592
P14-4 Effects of genistein combined with mifepristone on uterine leiomyoma model rats ……593
P14-5 TNFα-GSDME mediated pyroptosis in placental trophoblast contributes to systemic inflammation in EOPE patients ……594
P14-6 A gonadal gap junction/notch signaling axis suppresses gut defense through an intestinal lysosome pathway ……595
P14-7 HnRNPK regulates the spermatogonia differentiation and meiosis initiation by interact with DAZL and MILI in male mice ……596
P14-8 RAD21L1 调控过表达 *DAZ* 家族基因重编程人支持细胞为精原干细胞的分子机制研究 ……597
P14-9 Single-cell transcriptome characteristics of testicular terminal epithelium lineages during aging in the *Drosophila* ……598
P14-10 CBS-线粒体转位介导 Miro2 硫巯基化修饰调控滋养细胞侵袭及其机制研究 ……600
P14-11 The Rose26 locus is inactive in the spermatogenesis of C57BL/6 mice ……601
P14-12 胚胎 SGLT1 在早期胚胎发育和着床中的作用 ……602
P14-13 Redox homeostasis in the uterine epithelium is critical to embryo implantation ……602

P15 体适能研究 ……603

P15-1 基于 CiteSpace 的运动干预抑郁症研究热点及趋势的可视化分析 ……603
P15-2 老年人体力活动水平对肺功能的影响：肌肉适能的中介效应 ……604

P16 基质生物 ……605

P16-1 Cyclic substrates softening strengthens cell mechanoresponse by accumulating force signaling molecules ……605

P17 整合生理 ……606

P17-1 High-altitude hypoxia exposure inhibits erythrophagocytosis by inducing macrophage ferroptosis in the spleen ……606

P17-2 肝 X 受体对肾缺血再灌注损伤的保护作用及机制探讨 ……607

P17-3 db/db 小鼠肝脏脂质沉积与脂滴代谢机制研究 ……608

P17-4 棕榈酸处理不同时长对肝细胞线粒体功能及 LONP1 表达的影响 ……609

P17-5 大电导钙激活钾通道（BK）在嗜血细胞现象中的新作用 ……609

P17-6 The ubiquitin ligase UBR-1 regulates the synaptic strength between the GABAergic and glutamatergic signaling ……610

P17-7 非酒精性脂肪性肝炎中 CHCHD2 表达的增加促进肝纤维化的发生 ……611

P17-8 不同体力活动水平的超重肥胖老年人群血清脂联素水平与静息能量代谢、糖脂代谢的相关关系研究 ……612

P17-9 Heart-enriched long noncoding RNA NPPA-AS1 regulates pathological cardiac hypertrophy by initiating the EP300-GATA4 axis ……613

P17-10 Mechanosensitive channels mediate transcranial ultrasound-induced neuronal electrophysiological activity ……614

P17-11 有氧运动改善卵巢切除联合慢性束缚应激大鼠焦虑抑郁样行为的雌激素受体机制研究 ……615

P17-12 心脏老化与纤维化的机制及其代谢干预策略 ……616

P18 中医药与脑稳态调控 ……616

P18-1 生脉地黄汤调控突触微环境改善 CIH 诱导认知障碍的作用机制 ……616

P18-2 以溶酶体为靶点探索槲皮素改善脑缺血损伤的机理研究 ……617

P18-3 Naotaifang Formula ameliorates cerebral ischemia-reperfusion injury by attenuating ferroptosis and m6A demethylases via FTO/ALKBH5/GPX4 signaling pathway ……618

P18-4 蒙药珍宝丸治疗对大鼠脑缺血再灌注后血脑屏障的影响 ……619

P18-5 青蒿琥酯通过抑制 cGAS-STING 通路改善缺血性脑损伤的机理研究 ……620

P18-6 Microglial sphingolipid metabolism regulate inflammatory response to alleviate ischemia reperfusion-induced cerebral injury ……620

P18-7 Annexin A2 deficiency alleviates neuronal damage by suppressing microglia-mediated inflammation upon cerebral ischemic reperfusion injury ……621

P18-8 Curcumin targets identify in epileptic mice brain ……622

P18-9 Neural vesicle GABA suppresses lysosomal lipase LIPL-1 to promote anoxia tolerance via PMK-1/p38 pathways ……623

P19 人体微生态 ……624

P19-1 在菌种水平探究肠道菌群在阿尔茨海默症发生发展中的作用 ……624

P19-2 肠道微生物及其代谢途径对心血管疾病的潜在影响 ……625

P20 自主神经 ……626

P20-1 Sex-dimorphic kidney-brain connectivity map of mice ……626

P20-2 Elaborate spontaneous activity atlas-driven behavior patterns in both sexes ……627

P20-3 电刺激迷走神经诱导的 SDF-1α 参与梗死心脏的血管生成及修复 ……628

P20-4 RGC32 在心肌梗死后心脏重构与血管新生匹配中的作用及机制 ……629

P20-5 NE 介导 Noggin 调节间充质干细胞成骨分化的作用机制 ……629

P21 干细胞生理 ……630

P21-1 LncRNA-CIR6 诱导间充质干细胞转化为心肌细胞并抵制心肌梗死的作用 ……630

P21-2 KPC1 基因敲除小鼠体重、肌纤维类型及其糖代谢变化特征 ……631

P21-3 A novel function of p21 in maintaining the self-renew of normal hematopoietic stem cell through c-Kit ……632

P21-4 Tibetan umbilical cord mesenchymal stem cell exosomes improve hypoxic pulmonary hypertension by inhibiting pulmonary vascular remodeling ……633

P21-5 Wnt2/β-catenin 通路在 C57BL/6 小鼠肝再生修复中的变化研究 ……634

P21-6 单细胞水平揭示淋系偏向 HSC 亚群的分子及功能特征 ……634

P21-7 干细胞在神经肌肉疾病修复中的作用与机制 ……635

P21-8 Exosomes derived from hypoxia-pretreated human umbilical cord mesenchymal stem cells inhibit endothelial-to-mesenchymal transition of human pulmonary arteriole endothelial cells ……636

P22 血栓与止血 ……637

P22-1 Potential mechanism of platelet-derived miR-126-3p/PI3K/Akt axis in modulating the platelet responsiveness ……637

P22-2 单血小板力学图谱的观测 ……638

P22-3 Repurposing of Rilpivirine for preventing platelet β3 integrin-dependent thrombosis by targeting c-Src active autophosphorylation ……638

P22-4 胞外巯基异构酶 ERp72 调控整合素 Mac-1 活性影响中性粒细胞募集 ……639

P23 衰老与健康 ……640

P23-1 巨噬细胞胰岛素敏感性下降促进内皮细胞衰老及其机制 ……640
P23-2 6PPD-quinone induced cellular senescence in differentiated H9c2 cardiomyocytes via blockage of autophagic flux ……641
P23-3 推拿促进肌肉干细胞自我更新改善肌少症的作用研究 ……642
P23-4 推拿改善 SAMP8 小鼠骨骼肌衰老的炎性机制研究 ……643
P23-5 The neuroinflammation mediates extracellular matrix remodeling to regulate the pathogenesis of Alzheimer's disease ……644
P24 细胞和分子生理 ……645
P24-1 The ATF4-RPS19BP1 axis modulates ribosome biogenesis to promote erythropoiesis ·645
P24-2 7,8-二羟基黄酮对 H_2O_2 诱导的 H9c2 心肌细胞损伤的保护机制 ……646
P24-3 Inhaled nanotherapeutic agent for ischemic cerebrovascular disease by inducing ROS and abnormal mitochondrial autophagy ……646
P24-4 GJB2/HNRNPA2B1 axis promoted the metastasis of pancreatic cancer under hypoxia via suppressing the exitrons-splicing of CTNNB1 ……647
P24-5 A novel cuproptosis-related LncRNA signature predicts prognosis in patients with esophageal carcinoma ……649
P24-6 血管平滑肌细胞外泌体对模拟失重所致心肌重塑的生物学作用及机制研究 ……650
P24-7 内质网应激促进模拟失重相关的内皮细胞炎症和凋亡 ……651
P24-8 The unfolded protein response (UPR) regulates phenotype switching and proliferation of vascular smooth muscle cells of cerebral artery under simulated microgravity ……651
P24-9 Propionic acid maintains neuronal mitochondrial division and autophagy homeostasis during Alzheimer's Disease pathologic process via GPR41 and GPR43 ……652
P24-10 Polystyrene microplastics induced inflammation with activating the TLR2 signal by excessive accumulation of ROS in hepatopancreas of carp (Cyprinus carpio) ……653
P24-11 聚苯乙烯微塑料通过破坏鲤鱼肠道菌群诱导内质网应激、细胞凋亡和炎症 ……654
P24-12 程序性细胞死亡分子 5 在自噬中的作用研究进展 ……655
P25 脑节律 ……656
P25-1 突触结合蛋白 7 通过弓状核 kiss1 神经元调控小鼠休息-运动节律的机制研究 ····656
P26 虚拟仿真与人工智能 ……656
P26-1 人工智能与虚拟仿真技术在 PBL 教学中的应用探索 ……656
P26-2 新冠疫情下基于“人工智能和虚拟仿真”的生物安全实验室“PAIOT”监管模式构建及实施 ……657

P26-3 人工智能在教育信息化中的应用与挑战 ……658

P27 生理学教学专题研讨会 ……659

P27-1 Physiology education in China: The current situation and changes over the past 3 decades ……659

P27-2 课内课外结合，全面开展生理学课程思政 ……660

P27-3 以岗位胜任力为导向的临床专业《生理学》教学模式的构建 ……661

P27-4 案例教学改革在体育院校运动人体科学专业课程中的实践 ……662

P27-5 人体生理科学实验教学改革的初步探索 ……662

P27-6 Improving undergraduate medical students' science communication: from the perspective of new media ……663

P27-7 机能学实验报告书写分析及举措 ……664

P27-8 The quality of group interactions in medical problem–based learning in China: The roles of intercultural sensitivity and group ethnic composition ……665

大会报告（Plenary Lecture, PL)

大会报告 PL 1：血液与慢病

陈国强 院士
上海交通大学医学院附属仁济医院

祖国医学认为，“血浊致百病，血净病自消”。大样本研究显示，血液生态健康是人体健康的根本，而血液生态失衡如未知潜能的克隆造血(CHIP)是多种重大慢病发生发展的重要根源。新时代技术变革正在孕育，血液生态研究初露锋芒，利用血液生态重新认知重大慢病的发生发展，将为重大慢病研究思路新突破与治疗模式新变革奠定重要的科学理论基础，开发围绕血液生态的新一代重大慢病防治策略也已日益成为国际竞相追逐的下一个基础研究高地。

大会报告 PL 2：Glucose sensing and physiological functions

林圣彩 院士
厦门大学

We previously delineated a signaling pathway that senses glucose levels and signal to control the activities of AMPK and mTORC1. In low glucose, the v-ATPase/proton pump-associated aldolase senses low levels of fructose-1,6-bisphosphate and inhibits the proton pump. This allows AXIN/LKB1 to translocate to the surface of the lysosome, where LKB1 phosphorylates and activates AMPK, leading to concomitant inhibition of mTORC1. In contrast, high glucose can maintain mTORC1 association on the surface of the lysosome. We have also used aldolase as a target for drug screening, and identified a drug termed as Aldometanib that exhibits the ability to block aldolase binding to FBP, thereby eliciting a pseudo-starvation signal to exert roles including hypoglycemic effect, extension of lifespan and healthspan, inhibition of cancer growth.

Metformin is an anti-diabetic drug. It was known that metformin requires AMPK to lower blood glucose levels. However, the molecular target of metformin remained elusive for many decades. We have identified PEN2 as the metformin target, and demonstrated that metformin takes a ride with the glucose sensing-AMPK route.

Tracking the path to longevity through calorie restriction, we have explored the metabolic pattern shift, from glucose to glutamine after AMPK activation. We found that AMPK phosphorylates a protein called PDZD8, which in turn interacts and promotes the activity of

glutaminase. Along with the increased utilization of glutamine, ROS is transiently increased during the lifespan of nematodes. Intriguingly, this ROS burst is required for the extension of lifespan. We have also identified a signaling pathway that senses low glucose metabolite 3-phosphoglycerate (3-PGA). In low 3-PGA, PHGDH (phosphoglycerate dehydrogenase), a catalytic enzyme for biosynthesis of serine from 3-PGA, acts as a scaffold to activate p53 to induce apoptosis.

This seminar will present and discuss our overall finding that glucose is a messenger regulating a myriad of physiological functions.

S1：“新时代”和“新医科”背景下的《生理学》教学问题

S1-1 “新时代”整合课程体系《生理学》的教学创新与实践

王韵
北京大学

北京大学医学部基础医学专业和临床医学专业“新时代”器官系统整合课程改革，是一次具有里程碑意义的医学教育改革。不同专业依据培养目标进行不同形式的整合，既包含基础医学专业的基础医学课程的整合，也包含了临床医学专业基础医学与临床课程融合,两种整合模式彻底打破了以学科为主的传统的教学模式。北京大学王韵教授将为我们介绍，她主持开展的整合课程体系下《生理学》如何打破学科壁垒有机融入整合课程体系的教学创新与实践。

S1-2 教育部《生理学》课程思政示范课建设与实践

罗自强
中南大学

中南大学罗自强教授为负责人的《生理学》课程，2021 年 5 月入选首批教育部课程思政示范课，罗自强教授及团队成员也入选教育部课程思政示范课教学名师和教学团队。彰显源自湘雅的教书育人的传承、深刻理解课程思政的内涵、探索生理学课程思政的融入路径、创新的课程思政建设模式及多元化的课程思政成果，罗自强教授将向大家介绍如何做到教好书 ，更育好人！

S1-3 激越四段式教学+IPE 在跨地域跨校际教学中的应用

王庭槐
中山大学

中山大学中山医学院王庭槐教授是国家“万人计划”教学名师，教育部高等学校医药学科（专业）教学指导委员会委员，教育部本科教学工作水平评估专家，教育部临床医学专业认证工作委员会委员。担任人民卫生出版社 “十四五”规划教材《生理学》（8 年制临床医学/第 4 版，2023）主编，在王庭槐教授组织撰写的教材即将出版之际，他将为大家解读新版教材中的传承与创新。

S1-4 智能+背景下虚拟教研室建设与实践

武宇明
河北医科大学

河北医科大学武宇明教授牵头的“生理课程虚拟教研室”，2022 年 6 月获批“教育部第二批虚拟教研室建设试点”。该虚拟教研室涵盖全国中、东、南和西部 7 个省（市、自治区），联合 15 所高校生理学专家共同组建，引导团队教师回归教学、热爱教学、研究教学，成为“名师引领+同伴互助+辐射带动”的教师合作共同体，为提升国内生理学课程教育教学质量发挥积极作用。武宇明教授将向大家介绍申报经验与课程建设。

S1-5 运用数字技术赋能《生理学》课程

林默君
福建医科大学

福建医科大学林默君教授为课程负责人的《心血管生理学》2018 年获首届中国学位与研究生教育学会医药科研究生精品课程，2022 年获福建省研究生教育教学精品课程，2023 年 3 月在医药学研究生在线教育平台上线。课程以模块化的研究性心血管实验为基础，充分运用数字技术，整合多学科的心血管内容，开展以问题中心的线上线下融合式教学，培养医学研究生创新能力，具有高阶性和挑战性。林默君教授将以该课程为例与大家分享研究生课程建设的经验。

S2：神经细胞再生与修复

S2-1 Feeling force with PIEZOs

肖百龙
清华大学

PIEZO1 and PIEZO2 have been identified by Patapoutian and colleagues as bona fide mechanoreceptors, which mediate the sense of gentle touch, proprioception, blood pressure, tactile pain and regulate cardiovascular function and bone formation and remodeling. For the landmark discovery of PIEZO2 as touch receptor in mammals, Dr. Ardem Patapoutan has shared the 2021 Nobel Prize in Physiology or Medicine with Dr. David Julius, who discovered the first temperature receptor TRPV1. In this talk, I will introduce the history of the PIEZO discovery and our current understanding of PIEZOs with a particular focus on their unique structural designs and physical principles that might enable them to serve as versatile and professional mechanosensors.

S2-2 死亡与新生：关于小胶质细胞的哲学

彭勃
复旦大学

Dysfunctions of gene-deficient microglia contribute to the development and progression of multiple CNS diseases. Microglia replacement by nonself cells has been proposed to treat microglia-associated disorders. However, some attempts have failed due to low replacement efficiency, such as with the traditional bone marrow transplantation approach. Based on our understanding in microglial regeneration, we develop three efficient strategies for microglia replacement: microglia replacement by bone marrow transplantation (mrBMT), microglia replacement by peripheral blood (mrPB), and microglia replacement by microglia transplantation (mrMT). mrBMT and mrPB allow microglia-like cells to efficiently replace resident microglia in the whole CNS. On the other hand, mrMT achieves microglia replacement in brain regions of interest. In summary, we developed effective tactics for microglia replacement with diverse application scenarios, which potentially opens up a window on treating microglia-associated CNS disorders.

S2-3 Positive emotions, regeneration strengthens

韩齐
上海交通大学

Spinal cord injury (SCI) often leads to physical limitations, chronic pain, significant life changes, and social isolation, increasing the risk of chronic psychological stress such as anxiety and depression. Despite the recognition of the negative effects of chronic stress on SCI recovery, the mechanisms linking stress and regeneration are not fully understood. In this study, we examined the impact of chronic stress on primary sensory axon regeneration in a mouse model of preconditioning lesions. Our findings showed that chronic stress caused mitochondrial damage and energy crisis within primary sensory neurons, hindering the regrowth of their central axons. The stress hormone corticosterone was identified as a critical factor in this process, impacting satellite glial cells instead of neurons by suppressing Kir4.1 expression and leading to increased neuronal hyperactivity and elevated ROS levels. These high levels of ROS altered the shape of the mitochondrial cristae and disrupted ATP production, which is essential for powering axonal regeneration. Our results highlight the importance of addressing psychological stress in SCI patients to promote sensory-motor rehabilitation.

S2-4 Functional regeneration of spiral ganglion neurons and their synapses

万国强
南京大学

Spiral ganglion neurons (SGNs) in the mammalian cochlea are the primary afferent neurons that relay acoustic signals from the sensory hair cells to the central auditory system via the specialized ribbon synapses. Damages to the SGNs and their ribbon synapses are the primary causes of sensorineural hearing loss caused by noise and aging. In this study, we revealed important contributions of synaptic degeneration to noise-induced hearing loss, and identified key neurotrophic factors to promote regeneration of the SGN synapses and hearing recovery. In addition, we identified remarkable intrinsic regenerative potential of cochlear glial cells after damage in vivo, and that these glial cells can be cultured as neurospheres and differentiated into SGN-like cells. We further identified combinations of small molecules and transcription factors that mediate reprogramming of both fibroblasts and glial cells towards functional SGNs. Overall, our study revealed key molecules and pathways for functional regeneration of SGNs and their

synapses, which may pave new ways for treatment of sensorineural hearing loss.

S2-5 Genetic and functional hearing and balance restoration in mice by *in vivo* template independent gene editing and repairing (TIGER) technique

熊巍
北京脑科学与类脑研究中心

Although frameshift mutations lead to 22% of inherited Mendelian disorders in humans, there is no efficient in vivo gene therapy strategy available to date, particularly in nondividing cells. Here, we leveraged a newly-discovered mechanism that nonhomologous end-joining (NHEJ) mediates nonrandom repaire outcomes from double-stranded breaks (DSBs), and developed a highly efficient template independent gene editing and repairing (TIGER) technique. Using TIGER technique, we showed that TIGER profiles compensate the frameshift mutation in the *Pcdh15* gene and restore the lost mechanotransduction function in postmitotic hair cells of $Pcdh15^{av\text{-}3J}$ mice, an animal model of human nonsyndromic deafness DFNB23. In cultured cochlear explants, the TIGER strategy restores reading frame in approximately 50% of indel products and recovers mechanotransduction in more than 70% of targeted hair cells. In vivo TIGER treatment shows that half of the animals gain improvements in auditory responses, and balance function is restored in the majority of injected mutant mice. These results demonstrate that TIGER is a simple and efficient strategy for in vivo therapeutics.

S3：呼吸生理基础与转化研究专题研讨会

S3-1 以临床问题为导向的肺纤维化基础研究

唐潇潇
广州医科大学

我们坚持以临床问题为导向的肺纤维化基础研究。例如：我们揭示了糖皮质激素治疗特发性肺纤维化效果不佳的关键原因。特发性肺纤维化（IPF）是一种病因不明、进展迅速、死亡率高的间质性肺疾病，患者的中位生存期只有 2-3 年，且缺乏有效的治疗药物。糖皮质激素被用于 IPF 的治疗，但临床疗效欠佳。有研究者推测 IPF 患者对糖皮质激素的敏感性下降，但一直未有定论。

我们的研究发现，IPF 患者肺组织中糖皮质激素敏感性相关因子（如 GRα、HDAC2、HSD11b1）的表达与健康对照肺组织相比并无统计学差异。在糖皮质激素地塞米松（DEX）的刺激下，IPF 来源的肺成纤维细胞中，细胞核内糖皮质激素受体增多，激素诱导性基因表达上调，且上调程度不亚于正常对照组，表明 IPF 患者的激素敏感性和反应性正常。在博莱霉素诱导的肺纤维化小鼠肺部，DEX 虽可有效降低炎症因子的表达，但却无法扭转肺纤维化的发展，这与糖皮质激素治疗 IPF 的临床效果相符。

体外实验显示，DEX 促进了 IPF 来源的肺成纤维细胞中纤连蛋白（Fibronectin) 和 α-平滑肌肌动蛋白（α-SMA）的表达。进一步探究其中的分子机制，我们发现 DEX 对不同的促纤维化因子具有不同的调控作用，即 DEX 虽可降低转化生长因子-β1（TGF-β1）和血小板源性生长因子-b（PDGF-b）的表达，但同时也上调了结缔组织生长因子（CTGF）的表达。进一步通过使用中和抗体、siRNA 和抑制剂等在 IPF 患者来源的肺成纤维细胞中进行功能性实验，我们证实了 CTGF 为介导 DEX 上调 Fibronectin 和 α-SMA 表达的关键分子。

本研究首次证明了 IPF 患者的激素敏感性和反应性正常，明确了领域内这一长期有争议的问题，并揭示了糖皮质激素治疗 IPF 效果不佳的关键原因，阐明了糖皮质激素通过上调 CTGF 介导促纤维化效应，为 IPF 的治疗提供新思路和重要的科学依据。

S3-2 嗜酸性粒细胞病理生理功能新认识

陈志华
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已知嗜酸性粒细胞（eosinophil, EOS）与过敏、哮喘、寄生虫感染以及肿瘤密切相关，然而关于 EOS 在这些疾病中作用的分子机制并不完全明确。此外，EOS 作为机体重要的免疫细胞之一，其在肺部区域免疫以及除哮喘之外的其它呼吸系统疾病生理病理中的作用所知甚少。新近研究表明，EOS 不只是作为哮喘过敏性炎症的效应细胞，它能通过分泌 CCL6 等因子反作用于骨髓干细胞动员，继而从源头调控哮喘炎症的发生发展；通过诱导 EOS 的不同死亡方式如凋亡、坏死、铁死亡，或者通过 CAR-T 靶向杀死 EOS，均可有效缓解过敏性气道炎症。然而 EOS 在其它呼吸系统疾病中的作用和机制却不完全相同。EOS 可以通过分泌 IL-13 和溶酶体 CTSL 促进慢阻肺和肺气肿的发生发展；EOS 可促进肿瘤细胞肺部转移；然而，静息状态的 EOS 是肺部免疫防御的屏障，可抑制病原体诱导的急性肺损伤，在肺动脉高压中也能起到保护作用。因此，EOS 不只是传统意义上的炎症效应细胞，它参与了多种呼吸疾病的发生发展，其具体功能和分子机制各不相同。对于 EOS 在生理病理中新功能的全面认识有待更进一步的研究。

S3-3 固有免疫在肺动脉高压发病机制的研究进展

李圣青
复旦华山医院呼吸科

S3-4 突触-线粒体与中枢呼吸可塑性调控

刘莹莹
中国人民解放军空军军医大学

前包钦格复合体 (pre-Bötzinger complex，pre-BötC) 位于延髓腹外侧，被认为是呼吸节律产生中枢。生长抑素（SST）和神经激肽 1 受体（NK1R）已广泛用于 pre-BötC 神经元的形态学标志物。pre-BötC 同时参与呼吸可塑性调控，温和的急性间断性缺氧（AIH）可产生有益于机体的呼吸长时程易化（LTF），而严重的慢性间断性缺氧（CIH）被用于睡眠呼吸暂停（OSA）疾病的实验动物研究。

我们应用 SST 和 NK1R 免疫电镜双标记技术，结合线粒体细胞色素氧化酶（CO）组化技术，进行了 pre-BötC 神经元超微形态学三标记。我们研究发现：① dAIH、CIH 诱导了 pre-BötC NK1R 神经元兴奋性-抑制性突触组成的改变：兴奋性突触可能更多的参与 dAIH→LTF 过程，而在 CIH→OSA 中，抑制性突触发挥重要作用；② dAIH 干预增加了突触后致密体的长度、面积及穿孔突触数量，而 CIH 干预明显减少了突触后致密体的长度、面积及穿孔突触数量；③ 明确了 pre-BötC 神经元线粒体融合-分裂的超微形态学特征，融合线粒体多呈高 CO 活性，而分裂线粒体 CO 活性较低。线粒体与突触功能紧密偶联，可见高 CO 活性线粒体近突触分布，并伸入到树突棘内，近距离为突触提供能量；④ 发现了 pre-BötC 神经元的桥粒样接触（desmosome-like contacts，DLC）结构，多分布于突触附近，与突触比较，线粒体更近距离分布于 DLC 周围，认为 DLC 可能协同突触功能，共同参与 pre-BötC 呼吸可塑性调控。

S3-5 呼吸系统感染、炎症与免疫缺陷

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S3-6 MRGPRX2——过敏性哮喘潜在药物靶标

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过敏性哮喘是机体对抗原性或非抗原性刺激引起的一种气管、支气管反应性过度增高的疾病。作为一种复杂的疑难疾病，目前的临床诊治种面临诸多问题。首先其确切的发病机制和靶点至今仍未完全阐明；其次临床常用的抗过敏性哮喘药物基本均为缓解症状制剂，并无可真正治疗哮喘药物；同时哮喘的发病率逐年上升，有发病迅速和致死率高的特点。因此，过敏性哮喘已成为严重威胁人类健康的疾病之一，寻找新的抗过敏哮喘靶点药物迫在眉睫。

肥大细胞是参与过敏性哮喘发生发展的重要炎症细胞。其膜上受体被激活导致细胞活化并释放过敏的介质，可导致血管扩张、平滑肌收缩和黏膜分泌，也可以引起过敏性炎症后期的炎细胞浸润。2015 年，《Nature》有论文证实肥大细胞直接活化与 MAS-Related G Protein-Coupled Receptor X2 (MRGPRX2)密切相关。MRGPRX2 一种 G 蛋白偶联受体，在人树突细胞、嗜碱性粒细胞及肥大细胞上广泛表达，其内源性配体为 P 物质，小鼠同源蛋白为 MRGPRB2，可介导变异性皮炎的发生，并在在病人皮肤和血中表达增高。MRGPRX2 和 P 物质在哮喘患者的肺部和血浆中升高，加重肥胖小鼠的哮喘症状。因此，MRGPRX2 可能参与过敏性哮喘发生，成为治疗过敏性哮喘的潜在靶标。

课题组开展了临床试验，探究 MRGPRX2 和 P 物质在健康人群和哮喘病人间、在高 IgE 组病人和低 IgE 组病人间的区别及其与哮喘严重程度的相关性。研究结果表明，哮喘患者外周血 MRGPRX2 基因拷贝数和蛋白表达增加。但 MRGPRX2 表达量和哮喘严重程度无关，其表达水平与 IgE 具有交互作用，可能对 IgE 水平较低的哮喘发病具有指示作用；哮喘患者血清 P 物质含量显著升高，是影响哮喘发病危险的显著因素。无论 IgE 水平如何，P 物质含量与哮喘风险独立相关。

课题组随后利用野生型小鼠和 MRGPRB2-/-小鼠构建了 OVA 诱导的过敏性哮喘模型，结果表明 OVA 不能引起敲除小鼠明显的气道高反应性，证明 MRGPRB2 直接参与 OVA 诱导的小鼠气道高反应。野生型小鼠肺部和血清中 P 物质含量显著高于对照组和敲除鼠组，因此课题组利用 P 物质构建了新型过敏性哮喘模型，进一步利用 P 物质研究了 MRGPRX2 在过敏性哮喘中的作用。研究结果表明，P 物质雾化吸入可以引起野生型小鼠的气道高反应性、肺部炎症和病理改变并导致肺部肥大细胞脱颗粒。然而 P 物质不能引起 MRGPRB2-/-小鼠肺部炎症，其诱发气道高反应依赖于 MRGPRB2。此外，P 物质受体 NK-1R 拮抗剂并未导致肺部炎症和气道高反应的显著降低。因此，P 物质通过肥大细胞诱导小鼠气道高反应和肺部炎症，不是通过 NK-1R 受体。

上述临床研究表明，与正常人相比，MRGPRX2 表达量和 P 物质含量在哮喘患者中显著升高；与高 IgE 哮喘患者相比，在低 IgE 组患者中显著升高，两种指标对 IgE 水平较低的哮

喘具有指示作用，可能作为哮喘的新型诊断指标。动物研究利用 MRGPRB2-/-小鼠，成功构建了 P 物质诱导的小鼠哮喘模型；P 物质在 OVA 诱导的哮喘小鼠血清和肺部含量显著升高，且通过 MRGPRB2 诱导小鼠肺部炎症、粘液分泌、胶原沉积和肥大细胞脱颗粒。

综上所述，肥大细胞上 MRGPRX2 是抗类过敏反应的全新药物靶标。

S3-7 环氧二十碳三烯酸调节肺上皮稳态在肺纤维化中的作用研究

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近年来肺泡上皮细胞（AECs）衰老被认为是肺纤维化（PF）的关键病理改变之一，而 AECs 衰老和抗衰老的机制尚未完全阐明。新近研究发现花生四烯酸（ARA）经细胞色素 P450（CYP）途径的代谢产物环氧二十碳三烯酸（EETs）在细胞衰老中可能具有重要的负性调节作用，但体内 EETs 易被可溶性环氧化物水解酶（sEH）降解。亚细胞器的功能紊乱在细胞衰老中的作用越来越明确，研究表明持续的内质网应激（ERS）在细胞衰老的进程中发挥重要作用。本研究旨在探讨 EETs 能否通过减缓 ERS 从而发挥抗 AECs 衰老和减轻 PF 的作用。整体水平，本研究观察到 sEH 抑制剂 TPPU 或 PTUPB 均可减轻博来霉素诱导的小鼠 PF，并显著降低 PF 小鼠肺内衰老相关标志分子的表达水平。细胞水平，BLM 诱导的 AECs 中衰老相关蛋白 p16、p53、p21 及 γH2AX 表达显著升高，β-gal 阳性细胞数显著增多，同时衰老 AECs 中 sEH 蛋白表达显著升高，且与衰老相关蛋白表达呈正相关。多途径增加胞内 EETs 含量可降低 AECs 中衰老相关蛋白表达，减少 β-gal 阳性细胞数。衰老 AECs 中 ERS 相关蛋白 XBP1s 及 ATF6 表达升高，同时 ATF6 核转位明显增多；EETs 可显著降低衰老 AECs 中 ERS 相关蛋白表达；同时 EETs 可抑制衣霉素诱导的 AECs 中 ERS 及细胞衰老相关蛋白表达。机制上，本研究观察到 EETs 可通过上调 AECs 中 E3 泛素连接酶 TRIM25 表达，泛素化降解 Keap1 蛋白，促进 Nrf2 核转位，减轻 ERS。最终，本研究表明 AECs 衰老时，EETs 含量下降，ERS 持续存在；EETs 可通过减缓 ERS 抑制 AECs 衰老，减轻 PF。

S4：脑病的脑-外周稳态失衡及中医药干预机制与前景

S4-1 从系统角度探索阿尔茨海默病

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中国人民解放军陆军特色医学中心

S4-2 非人灵长类抑郁猴肠-脑机制探索

郑鹏
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S4-3 越鞠丸抗抑郁研究：抑郁症的新致病菌株及其代谢-炎症机制

陈刚
暨南大学

S4-4The crosstalk between nervous and immune system

曹罡
华中农业大学 / 深圳理工大学

S4-5 逍遥散通过肠脑互作途径缓解抑郁症药效机制研究

黄俊卿
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S5：运动生理学专题

S5-1 运动与代谢健康-多组学队列与干预研究

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目的：我国体力活动不足的流行现状严峻，有 62.8%的居民未达到经常参加体育锻炼的标准。体力活动不足作为全球第四大死亡危险因素，体力活动不足会导致 7.2%的全因死亡，同时也增加了包括心血管疾病、代谢性疾病等在内的多种慢性疾病的发生风险。运动具有“多效药物（polypill）”的作用，可产生多种健康效应。与传统的关注运动对某一组织或器官的局部效应不同，在运动整合生物学的背景下，本研究以“效应-多组学-分子-功能”为范式，探索改善代谢性疾病的新的运动干预方式，为进一步揭示运动对代谢性疾病机体的整体作用和分子机制提供理论依据。

方法：人群研究 1：37 名超重和肥胖青少年受试者（13-16 岁）随机分为常氧训练组和低氧训练组，受试者运动干预为有氧训练（强度: 7.5mets），运动强度 60%-80 %最大心率，运动频率 6 天/周，2 次/天，2 小时/次；低氧干预方案：初次入住低氧实验室先预适应 1 天，从入住第 2 天开始受试者于每晚 21:00 进入低氧实验室，每天干预 10 个小时，每周七天，低氧浓度约为 14.7%（对应模拟海拔 2700 米高度）。低氧训练干预共持续 4 周。人群研究 2：34 名超重和肥胖青少年（13-16 岁）根据受试者血镁浓度的中位值分为低镁组和高镁组，低镁组和高镁组再分别随机分为常氧训练和低氧训练组，低氧训练干预方式同人群研究 1。动物研究：8 周龄 C57BL/6J 雄性小鼠给予高脂饮食干预 12 周构建肥胖模型。12 周干预结束后，随机将肥胖小鼠分为 4 组，肥胖对照组（DIO， n=10），镁补充组（Mg，n=10），和低氧训练组（HT，n=10），低氧训练联合镁补充组（HT+Mg，n=10）。肥胖小鼠对照组不进行任何干预，Mg 组按照 100mg/kg/d 的剂量在饮水中加入镁；HT 组每天进行中等强度跑台训练 1h，每周 6 天，低氧干预 8 小时（低氧浓度 14.7%）；HT+Mg 进行低氧训练和镁补充联合干预。所有小鼠均进行为期 4 周的干预，干预结束后取材，进行后续代谢相关指标检测。队列研究：建立上海体育学院运动人群队列，纳入 220 名男性受试者（17-20 岁）的临床试验、粪便微生物组、体脂率和体适能数据进行后续肠道菌群微生物的测序分析。代谢表型和分子生物学实验数据采用平均值±标准差表示，数据处理采用 Graphpad Prism 9 统计软件完成，两组间对比采用独立样本 t 检验，组间比较采用单因素方差分析。

结果：（1）与常氧训练组相比，低氧训练组受试者干预后体重降低更多，BMI 改善更为显著；（2）与低镁常氧训练组、低镁低氧训练组、高镁常氧训练组相比，高镁低氧训练组受试者干预前后体重降低最多。（3）与 HT 组小鼠相比，HT+Mg 组小鼠在体重、体脂、胰岛素敏感性和肝重、肝脏脂质累积等肝脏代谢表型均未有显著变化。但与 DIO 组小鼠相比，单纯镁补充就可以显著降低肝重，改善肝脏脂质累积，转录组测序分析结果显示，SMSR 在镁补充后显著升高，且在小鼠肝实质细胞系（AML12）中敲低 SMSR 可加重肝细胞的脂质累积。（4）建立上海体育学院运动人群队列（n=1738 人，17~20 岁），收集了包括体适能、身体形态、身体成分、骨密度以及常见临床指标的表型数据，建立了包括血液和粪便在内的生物样本库，初步绘制了“表型组学-生理生化-多组学”三位一体的运动健康特征图谱。（5）通过 6 种不同的体适能测试包括坐位体前屈（cm）、握力（kg）、仰卧起坐（/min）、立定跳远（cm），最大摄氧量（VO_2max；ml/kg/min）和俯卧撑（/min）评估受试者运动表现，将纳入的受试者分为低、中或高体适能组，与 1000 人糖尿病前期或糖尿病病人肠道菌群的变化进行联合分析，结果表明，在运动员队列中被证明与体适能的高低密切相关的肠道菌，其相对丰度变化与糖尿病的发生发展存在高度相关，且大部分肠道菌的相对丰度变化在两个队列中完全相反。

结论：（1）低氧训练减控体重，改善 BMI，效果优于常氧训练；（2）机体血清镁浓度高低影响低氧训练对减控体重效果；（3）低氧运动联合镁补充的干预效果并未优于单纯低氧运动干预效果；单纯镁补充可减少肝脏脂质堆积，鉴别到其可能的有效作用靶点 SMSR；

（4）运动通过将肠道菌群调节到类似于“更健康”状态的水平来潜在地预防糖尿病。

关键词：肥胖；低氧训练；镁补充；队列；肠道菌群

S5-2 The role of PGC-1α in the antidepressant effects of exercise preconditioning in SATD mice

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The recent studies on depression indicated that skeletal muscle peroxisome proliferator-activated receptor γ activating factor 1α (PGC-1α) improves tryptophan metabolism, reduces the central nervous inflammation, thereby improving depressive behaviors. miR-696 is an motion-sensitive miRNA involved in PGC-1α translation regulation and skeletal muscle metabolism in mice. PGC-1α can promote neuronal survival in hippocampus and also exert antiinflammatory effects in skeletal muscle. This study aims to explore the effects of simplified acute tryptophan depletion (SATD) and exercise preconditioning on depressive behaviors in mice, and further reveal the role of miRNA-696 /PGC-1α pathway. Male C57BL/6 mice were fasted 15 hours and then fed with neutral amino acid mixture without tryptophan twice (90min apart) to establish SATD model. We found that exercise preconditioning alleviated SATD-induced depressive behaviors and enhanced PGC-1α expression levels in hippocampus and skeletal muscle. The exercise effects may be related to the upregulation of synaptic plasticity related proteins such as GFAP, SYN and GAP-43 in hippocampus. Exercise preconditioning inhibited NF-κB inflammatory signaling, whereas miR-696 interference in skeletal muscle didnot affect central inflammatory response through PGC-1α/ NF-κB signaling pathway. It is thus necessary to study PGC-1α action in the "muscle-brain Crosstalk", which may contribute to find some peripheral cytokines as depression biomarkers used for biopsy, suggesting new targets for novel antidepressants research and personalized exercise intervention of depression.

Keywords: PGC-1α; exercise preconditioning; simplified acute tryptophan depletion (SATD); synaptic plasticity; inflammatory response

S5-3 青少年持续训练和冲刺间歇训练的生理学适应特征

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《中国居民营养与慢性病状况报告（2020 年）》显示，我国 6-17 岁儿童青少年超重肥胖率接近 20%。截至 2016 年，我国 6-17 青少年人群中体力活动不足者占比 84.3%，超重或肥胖儿童在未来更容易发展为糖尿病、高血压和心血管等疾病。青少年积极参与体育运动，不仅提高体质健康水平，还能循序渐进形成良好的运动习惯，也是主动健康坚持预防为主，立足全人群和全生命周期的着力点。因此有效、适宜的运动干预方法选取是引导青少年积极参与体育运动的重点。青少年目前常用的训练方法是中等强度连续训练（MICT），但 MICT 运动时间较长、形式单调乏味，不易坚持。因此增加多样性、趣味性的运动方法，使体育锻炼可持续化成为可能。冲刺间歇训练（SIT）具有低运动量、短耗时、高可变性等优点，在促进健康方面起到良好作用，可能成为 MICT 的一种潜在的补充/替代手段。但前期研究少有关于 SIT 在青少年群体的推广应用报道。本课题组依据青少年生长发育特点，选取青少年有氧能力可训性敏感期 12-14 岁男生，从整体生理机能、生理学表观指标及代谢物小分子变化特征等方面，系统探讨了 MICT 和 SIT 两种训练方法在提高该年龄段男生有氧能力效果及生理学的适应特征。研究发现两种训练方法在提高该年龄段男生有氧运动表现方面训练效果相似，但生理学适应有差别。MICT 提高有氧耐力与能量代谢适应高度相关，SIT 主要与心脏收缩功能适应性增强高度相关；两种训练方法均引起受试者体内炎性因子发生适应性变化，其中 IL-6 明显增加，IL-10/TNF-α 比值明显增加，其余促炎及抗炎因子均明显下降；SIT 训练引起的炎性因子变化与脂质分子 LPC, HexCer 和 FFA 明显相关，MICT 训练组多种 PC 均表现出与炎症因子的相关性；两种训练方法受试者血浆蛋白分子均呈现 7 种模式变化轨迹，但 MICT 主要通过 HSPB1 和 FABP1 影响体内氧化/抗氧化平衡；SIT 主要通过 SOD2 和 NQO2 发挥作用；MICT 通过 CRP 和 IGKV2-28 影响免疫功能；SIT 则引起多种与炎症和免疫功能相关蛋白表达水平的变化；MICT 主要靶向氧化与抗氧化平衡、免疫功能调节、能量代谢通路蛋白的变化。本研究为运动训练提升青少年有氧耐力素质，进而全面改善青少年健康状况提供了理论依据；也为青少年时期确定运动强化干预、解决主要健康问题提供了可行的方法。

关键词：青少年；中等强度持续训练；冲刺间歇训练；生理学适应

S5-4 有氧运动调控脑内 DA 改善遗传性 PD 行为障碍的研究

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目的：帕金森病(Parkinson's disease，PD)是一种慢性神经退行性疾病，发病原因主要是中脑黑质多巴胺能神经元的死亡。PARK7 基因突变引起的 DJ-1 蛋白缺乏作为引起早发型遗传 PD 的原因之一，常表现为进行性运动障碍和多巴胺能神经传递异常。运动作为一种物理干预手段，通过调节神经营养因子，减少炎症发生，抑制氧化应激，改善线粒体功能，对帕金森疾病具有神经保护作用。然而，运动如何调控由 DJ-1 基因突变引起的运动障碍和多巴胺能神经传递仍不清楚。

方法：选用 3-5 月龄 DJ-1 转基因小鼠，小鼠随机分为对照组（WT、DJ-1 KO）和运动组（WT-EX、DJ-1 KO-EX），采用 4 周匀速跑台运动（18 m/min，40 min/天，连续 5 天/周）。运动干预后，通过旷场实验和 24h 自主活动观察小鼠运动能力、探索能力及自主活动功能；利用快速扫描循环伏安法检测各组小鼠纹状体 DA 神经元轴突末梢瞬时释放的能力；采用 Western Blot 和免疫组化回答运动调控 DJ-1 KO 小鼠突触传递过程的分子机制。

结果：（1）通过旷场和 24h 自主活动监测发现 DJ-1 KO 后，活动总距离、运动速度、探索能力及自主活动能力显著降低，通过运动干预可以改善 PD 小鼠的运动功能；（2）利用快速扫描循环伏安法，在纹状体给予 70mM 高钾刺激，发现 DJ-1 KO 后，突触前膜多巴胺释放显著降低，运动干预可以恢复 PD 小鼠的多巴胺能神经元递质释放的水平；（3）α-synuclein 作为突触前膜蛋白，其表达异常会影响递质释放，发现 DJ-1 KO 后 α-synuclein 蛋白总量异常增多，通过运动干预减少了 α-synuclein 蛋白表达；（4）前期研究发现，DJ-1 KO 后多巴胺神经传递过程中，D2DR 减少引发情绪障碍，通过运动干预后可以提高 DJ-1 KO 小鼠纹状体 D2DR 表达。

结论： 4 周运动干预恢复 DJ-1 缺陷小鼠的多巴胺释放，从而改善运动障碍。进一步研究表明，α-synuclein 表达的降低和 D2DR 表达的增加是多巴胺能神经传递改善的主要原因。这一发现不仅提供了运动恢复多巴胺释放与 PARK7 基因突变引起的帕金森病病理之间的直接联系，也有助于进一步了解运动神经保护能力的分子基础。（NSFC：31971095）

关键词：帕金森; 运动; DJ-1; 多巴胺释放; α-syn

S5-5 Smyd1 介导抗阻训练改善衰老心脏功能的机制研究

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年龄是心血管疾病的独立危险因素，氧化应激是心脏衰老的核心环节。近年来研究发现，氧化应激是导致内质网应激（ERS）、细胞凋亡和铁死亡等细胞损伤的直接因素。运动可有效改善衰老心脏中氧化应激水平，抑制心血管疾病风险，但其可能机制及作用靶点尚未完全阐明。组蛋白赖氨酸甲基转移酶 1（Smyd1）在心脏和骨骼肌的生长发育和功能维持中发挥重要作用。但其在运动改善衰老心脏功能中的作用和可能机制尚不清楚。本研究通过检测不同年龄小鼠和斑马鱼心脏 Smyd1 蛋白表达并给与衰老早期小鼠抗阻训练干预，构建 Smyd1 基因敲除斑马鱼模型，建立衰老细胞模型并给与 Smyd1-shRNA 和过表达病毒载体干预，检测衰老早期进行抗阻训练对心脏氧化应激、ERS、细胞凋亡和铁死亡相关基因表达的影响，探讨 Smyd1 在其中的可能作用及分子机制。动物实验发现，心脏 Smyd1、ROS 水平、ERS 和铁死亡相关蛋白表达随年龄而变化，衰老后心脏 Smyd1 表达降低，ROS、ERS 和铁死亡水平升高；衰老早期进行抗阻训练可有效上调心肌 Smyd1 表达，改善线粒体功能，抑制氧化应激、ERS、细胞凋亡和铁死亡现象。细胞实验发现，Smyd1 过表达可有效改善 D-gal 诱导的 H9C2 细胞 ERS 和铁死亡水平，敲除 Nrf2 抑制了 Smyd1 的部分改善效应。该研究证实衰老早期进行抗阻训练可有效改善心脏 ROS、ERS、细胞凋亡和铁死亡水平，上调 Smyd1 表达可能是其重要机制。

关键词：Smyd1；抗阻训练；衰老；心脏功能

S6：应激生理学专题讨论会

S6-1 从应激致抑郁的炎症机制到精神医学的挑战

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精神医学的重要挑战是症状学诊断和对症治疗，除了“非经典”的神经认知障碍外，寻找特异性生物学指标未果。抑郁症是一类重要的精神心理疾患，因高患病率、高致残性和高复发率等特征成为困扰全球的严重健康问题。基于高达三分之一的抑郁症患者对现有抗抑郁药无效，寻求抑郁症炎症机制及诊疗新的策略，并以此为切入点，探索精神医学从抽象的精神病学调整为精神病的神经生物学基础之路。

S6-2 A liver-brain axis responds to environmental stress and induces anxiety-like behaviors

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Chronic environmental stress induces anxiety disorders via both neural pathways and circulating factors. Although amounts of studies are elucidating the neural circuits in stress-coping behaviors, the origin and regulatory mechanism of peripheral cytokines in central mental regulation under stress condition is far from complete. Here we identified a serum cytokine lipocalin 2 (LCN2) to be upregulated in patients with anxiety disorders. Using a rodent model of chronic restraint stress (CRS), circulating LCN2 was found to be related with stress-induced anxiety disorders, mainly via its modulation on neural activity of medial prefrontal cortex (mPFC). Molecular and anatomical dissections revealed the activation of a vagal efferent pathway originated from dorsal motor vagal nucleus (DMX) under CRS, leading to elevated hepatic biosynthesis of LCN2. These results collectively establish a brain-liver loop in which environmental stress increased hepatic LCN2 via a neural pathway, leading to disrupted cortical functions. Our study shed new insights for understanding the liver-brain axis in mental disorders, providing novel targets for the diagnosis and intervention of anxiety disorders.

S6-3 氨基酸代谢与运动应激

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S6-4 细胞对环境毒物亚硝胺的应激反应研究

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环境毒物暴露所引起的应激反应与疾病的发生发展密切相关。亚硝胺作为一类具有高致畸，致癌，致突变特性的环境化学物，是世界公认的三大强致癌物质之一，对人类生命健康所构成的威胁不可忽视。研究表明，饮用水氯化消毒后产生的亚硝胺类副产物的问题日益凸显，人群经饮水长期持续暴露于亚硝胺类消毒副产物可引增加食管癌的发病风险。已知，应激可以通过调节癌症的大多数特征来促进癌症的进展。但亚硝胺暴露引起的食管上皮细胞应激反应机制并不明晰。基于研究报道亚硝胺对转录的有害影响大于 DNA 突变，课题组立足

于转录调控层面，高通量筛选出关键应激分子组蛋白 H4（Histone H4）。在亚硝胺诱导下，H4C3 编码的 Histone H4 表达异常升高，具有明显的浓度和时程依赖性；敲低 H4C3 后，Histone H4 总蛋白水平显著下降，抑制食管上皮细胞的增殖能力，细胞周期阻滞在 G2/M 期，纺锤体移向两极距离变短；干扰 Histone H4 表达后，着丝点相关基因 BUB1、CDK1、TTK、CCNB1 的表达水平显著下降；转染 H4K16 乙酰化突变质粒 H4K16R 后，细胞周期阻滞在 G2/M 期，着丝点相关基因表达水平降低。上述结果表明，在亚硝胺诱导下，Histone H4 可经 H4K16 位点的乙酰化修饰介导着丝点相关基因的表达从而促进有丝分裂进程。

S7：极端环境与脑认知

S7-1 潜水作业对人体认知功能影响及其机制研究

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S7-2 空间脑科学研究进展与规划

陈晓萍
中国航天员科研训练中心

S7-3 低氧适应改善极端环境脑缺血损伤的作用机制研究

任长虹
首都医科大学宣武医院

S7-4 脑血管病内源性保护机制的研究进展

吴迪
北京市老年病医疗研究中心

S7-5 低温应激致脑认知损伤的防护研究

卢环宇
中国人民解放军空军军医大学

S7-6 西藏高原环境对脑认知的影响

韩军伟
西北工业大学

《生理学报》编委会会议

“泰盟杯全国高等学校人体生理学教师教学大赛”作品展示和交流会

《生理学报》专题论坛：受体信号与生理调控及疾病发生

胰岛细胞环路中的 GPCR

于晓
山东大学

核受体与血压的节律调控

杨光锐
上海健康医学院

脑-肠多巴胺与帕金森病胃轻瘫机制探讨

郑丽飞
首都医科大学

核受体与肾脏功能调控

张晓燕
华东师范大学

S8：心血管研究新进展专题研讨会

S8-1 天然免疫与血管损伤

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S8-2 下丘脑室旁核参与高血压中枢机制的研究进展

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下丘脑室旁核(PVN)是调节神经内分泌功能和心血管交感神经活动的重要部位，在调节机体血压和心血管活动等方面起着关键性的作用。长期高盐饮食能够引起脑脊液(CSF)和血液 Na^+水平升高以及内源性哇巴因(OLC)的改变。经双侧室旁核慢性给予高盐诱导的高血压大鼠 NKA α2 腺相关病毒载体 shRNA (NKA α2 shRNA)，明确了高盐诱导的高血压能够通过 NKA α2 增强室旁核 TLR4/MyD88/NF-κB 依赖的炎性反应以及 PKCγ/p-Rac1/NAD(P)H 依赖的氧化应激，进而引起外周交感神经活动增强以及血压升高。小胶质细胞在心血管疾病中被激活并释放炎性细胞因子。血管紧张素 II (AngII)诱导的高血压大鼠室旁核给予小胶质细胞活化抑制剂米诺环素(MIN)或 NF-κB 抑制剂吡咯烷二硫氨基甲酸酯(PDTC)可降低室旁核小胶质细胞活性，炎性细胞因子(PICs)减少，改善神经递质(NT)失平衡，并使血压降低。PICs 不仅与中枢肾素-血管紧张素系统(RAS)有相互调节作用，而且其本身也可促进 NAD(P)H 氧化酶的活性，NAD(P)H 氧化酶是血管系统的超氧化物的主要来源之一，而中枢过度产生的活性氧簇能够诱发交感兴奋作用。高血压大鼠室旁核给予氧自由基清除剂 tempol 可引起大鼠 RAS 组分表达减少；给予血管紧张素 II 的 1 型受体(AT1R)阻断剂或 TNF-α 抑制剂后可降低室旁核 NF-κB p65 活性；给予 NF-κB 抑制剂后可通过降低 NAD(P)H 氧化酶依赖的活性氧簇(ROS)而引起外周交感神经活动减弱。

环境、饮食和其它诱发心血管疾病的诱因或信号传递给自主神经活动调控脑区(如 PVN)，经信号整合，引起肠道交感神经活动增强，增强的交感神经活动导致肠道通透性增加、炎性反应增强、菌群紊乱，释放的产物和代谢物入血，这些代谢物会对脑内神经元活动有一定的影响。运动可改善高血压状态下心血管功能异常，降低高血压病人的交感神经活动和血压，且运动与机体肠道菌群特点的关系较为密切。运动训练导致自发性高血压大鼠(SHR)收缩压持续下降，这与肠道微生物改变以及有益细菌属的多样性和丰富度增加有关。此外，运动后高血压大鼠下丘脑室旁核的激活小胶质细胞数量减少，神经炎症、肠道病理、炎症和通透性改善；移植运动大鼠的粪菌可引起 SHR 大鼠肠-脑轴改善和血压降低；高血压时肠道微生物紊乱、肠-脑轴受损，运动可改善高血压所致的这种变化，从而产生降压作用。

根据上述结果可以看出，室旁核 PICs、ROS、RAS、NT 及 NF-κB 彼此之间可能存在着密切的联系并相互影响，最终导致外周交感神经活动增强而引起血压升高。

S8-3 孤束核 PNMT 神经元在血压调控中的作用及其环路基础

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高血压是最常见的慢性非传染性疾病，是导致中风、心脏病和肾功能衰竭的独立危险因素。神经调控对于维持血压的稳定非常重要，因此解析血压调控的神经环路，对于揭示高血压发生发展机制具有重要意义。孤束核（NTS）是调控血压的关键脑区，NTS 神经元包括谷氨酸能、GABA 能和儿茶酚胺能亚群。尽管谷氨酸能和 GABA 能神经元已被证明可以调节心血管活动，但表达苯乙醇胺 N-甲基转移酶（PNMT）的儿茶酚胺能神经元在血压调控中的作用仍有待进一步阐明。以往研究表明，延髓头端腹外侧区的肾上腺素能神经元（C1）表达 PNMT，是调节血压的重要神经元，本研究旨在观察表达 PNMT 的 NTS 神经元（NTS^{PNMT}）在心血管调控中的作用及其环路机制。

实验主要选用 PNMT-Cre 小鼠。应用单细胞 PCR 技术，血压监测，神经示踪，免疫荧光技术以及光遗传学等方法阐述其作用和机制。结果显示：①应用 PNMT-Cre 小鼠证实 PNMT 神经元主要分布在 NTS 的头端区和中间区，而尾端分布较少。②NTS^{PNMT} 神经元的纤维投射到延髓腹侧（CVLM、RVLM、Amb、preBötC）、脑桥（NA5、MVePC、MVeMC、LDT、PCRtA、IRt、LC、LPBN、VLPAG）、丘脑（PV）及下丘脑（DMH、LH、Arc、PVN、VMPO、MnPO）等区域。③原位激活小鼠 NTS^{PNMT} 神经元引起动脉血压出现升高或降低的双向变化。特异性激活 NTS^{PNMT} 神经元投射到 PVN、LPBN 和 CVLM 的轴突末梢，起降低动脉血压和心率的作用。而激活 NTS^{PNMT} 神经元投射向 RVLM 的轴突末梢，升高动脉血压，降低心率。④损毁 NTS^{PNMT} 神经元和 RVLM-projecting NTS^{PNMT} 神经元钝化压力感受器反射。⑤而激活 NTS^{TH} 神经元不影响动脉血压及心率。⑥NTS^{PNMT} 神经元从中脑、髓质和脑桥的细胞核接收到密集的单突触输入（Pr、DPGi、PCRt、Gi、PnC、PnO、Mo5、DMTg、SubC 和 VeCb 等），提示 NTS^{PNMT} 神经元可能参与情绪与能量稳态有关的血压调节。

综上 NTS^{PNMT} 神经元差异性调控血压是依赖不同神经环路实现的。通过支配 PVN、LPBN 和 CVLM 发挥降压作用，通过支配 RVLM 发挥升压作用。而且，此类神经元是动脉压力感受器反射所必需的。因此，NTS^{PNMT} 参与血压调节的一类重要的神经元。

S8-4 固有免疫细胞在腹主动脉瘤发病机制中的作用

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腹主动脉瘤（abdominal aortic aneurysm，AAA）是在多因素作用下，腹主动脉壁退化变

薄进而膨胀，并且最终超过正常血管直径 50%的一类严重的血管疾病，是一种可危及生命的血管疾病。AAA 的主要并发症是主动脉破裂，最常见的是导致致命的腹膜后出血或腹部出血。腹主动脉破裂的风险与最大腹主动脉直径密切相关，直径分别为 40-54 mm、55-60 mm、60-70 mm 和≥70 mm 的患者每年发生破裂的风险分别约为 1%、3%、4%和 6%，每年全球死于 AAA 破裂的人数估计达 15 万-20 万。我国 AAA 患者已超百万，且其发病率和检出率呈快速增长态势。但目前临床的治疗方案仅限于开放手术和介入治疗，且只局限于针对直径大于 5.5cm 的 AAA。而对于直径小于 5.5cm 的 AAA，早期施行手术并不能使患者获益。因此阐明 AAA 发生和转归的内在机制，并寻找有效的预警诊断标记物和干预靶点是该病防治的关键和基础，也是心血管疾病领域亟待解决的前沿科学问题。

AAA 形成机制复杂，包括与主动脉平滑肌细胞（Smooth muscle cells，SMC）凋亡相关的主动脉壁细胞外基质（Extracellular matrix，ECM）降解和动脉壁各层广泛的炎性细胞浸润等有关。近年的研究已表明 AAA 是一种以慢性炎症为特征的疾病，血管壁的透壁性炎症贯穿整个 AAA 发病过程，炎性反应在 AAA 发展的各个阶段都起着重要作用，并严重影响动脉壁重塑。因而深入研究 AAA 形成过程中炎症反应的类型和变化，有助于进一步阐释 AAA 发生发展的内在机制。

固有免疫细胞是机体固有免疫（非特异性免疫）的一个重要组成部分，是生物体在长期种系进化过程中形成的一系列免疫效应细胞。在个体出生时就已具备，可对侵入的病原体迅速应答，产生非特异抗感染免疫作用。已有研究表明，固有免疫细胞如巨噬细胞、中性粒细胞、树突状细胞(dendritic cell，DC) 、自然杀伤(natural killer，NK) 细胞及自然杀伤 T(natural killer T，NKT) 细胞等可参与 AAA 的发生发展。我们团队长期从事炎症微环境的免疫调控与血管重构的关系研究，获得系列原创性成果并逐渐形成自己的特色，重点关注固有免疫细胞在血管疾病中的作用研究，并独辟蹊径，拓展了肥大细胞、嗜酸性粒细胞（EOS）等在除超敏反应之外在 AAA 形成和进展过程中的作用及机制，且发现不同类型的固有免疫细胞在 AAA 发病中扮演的角色各不相同，不仅丰富了人们对疾病状态下炎性调节复杂性的认知，更为精准、系统的揭示 AAA 血管壁炎症调控平衡和调控网络提供了更加全面的切入点。

S8-5 孕期氨基酸失调致子代先天性心脏病的分子机制

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孕妇代谢失调与子代先天性心脏病（先心）紧密相关，过往研究多聚焦维生素与糖脂，对氨基酸罕有关注。我们前期的系列遗传学研究发现，很多与先心风险相关的致病型遗传变异均会导致细胞同型半胱氨酸（Hcy）升高，这一发现引起我们思考：作为一种不参与蛋白合成的含硫氨基酸，Hcy 为何会增大先心的发生风险？伴随代谢物信号理论的出现，我们对

Hcy 的非代谢功能展开了深入研究，发现 Hcy 可被细胞内甲硫氨酰 tRNA 合酶（MARS）感知并转化为细胞信号，Hcy 在低浓度时主要参与细胞代谢，然而在其浓度升高时能在 MARS 催化下修饰一系列蛋白，通过抑制细胞 DNA 损伤修复、胰岛素信号和 Wnt 信号来增大先心风险。除了 Hcy 的升高，MARS 的激活也会敏化其对 Hcy 的感知能力并产生 Hcy 信号。在此基础上，我们进一步探索除了 Hcy，孕期常见氨基酸的失调是否与子代先心风险相关。基于先心病临床队列，我们发现孕早期亮氨酸水平与子代先心风险显著相关。进而应用孕鼠模型检测发现，孕期亮氨酸水平的升高可致子代先心发生率增高，提示孕早期高水平的亮氨酸是先心的诱发因素。利用生化及分子生物学手段，我们发现亮氨酸在亮氨酰 tRNA 合成酶催化下通过亮氨酰化共价修饰心脏发育关键转录因子 TBX5，阻滞其核转运和转录活性的发挥，进而增大先心的发生风险。这一系列发现进一步丰富了代谢物的信号传导理论，并为先心等出生缺陷研究开辟了氨基酸信号研究新领域。

S8-6 ncRNA Gpr137b-ps 调节巨噬细胞的自噬促进晚期动脉粥样硬化

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由于晚期动脉粥样硬化的发病机制复杂且具有多因素性，目前的治疗方法仍具有残余风险。西方饮食导致血液中的氨基酸水平升高，引起巨噬细胞 mTORC1 -自噬信号通路异常，动脉粥样硬化斑块加速进展。自噬-溶酶体功能障碍进一步导致斑块坏死核心增大和脂质堆积。因此，有必要研究改善晚期动脉粥样硬化患者巨噬细胞中氨基酸-mTORC1-自噬信号功能障碍的新机制及关键分子。

LncRNA Gpr137b-ps 在晚期动脉粥样硬化斑块中表达显著上调。ApoE-/-小鼠尾静脉注射含有 sh-Gpr137b-ps 的腺相关病毒，使 Gpr137b-ps 表达减低，并通过西方饮食构建晚期动脉粥样硬化斑块，研究 Gpr137b-ps 对动脉粥样硬化进展的影响。进一步分析 Gpr137b-ps 对斑块内及体外巨噬细胞的自噬调控作用。通过对细胞进行饥饿和氨基酸刺激，研究 Gpr137b-ps 对氨基酸-mTORC1-自噬信号通路的影响。

我们的研究结果表明，Gpr137b-ps 缺乏导致巨噬细胞自噬增强，降低动脉粥样硬化病变负担，使坏死核心和脂质含量减低。沉默 Gpr137b-ps 减少巨噬细胞自噬，并阻止氨基酸诱导的 mTORC1 信号激活。质谱分析显示 HSC70 是 Gpr137b-ps 的下游结合蛋白，HSC70 挽救了 Gpr137b-ps 诱导的自噬功能异常。此外，Gpr137b-ps 干扰 HSC70 与 G3BP (G3BP1/2) 的结合。体外合成 G3BP 的 NTF2 结构域与 HSC70 蛋白互相结合，使用计算机模拟预测 HSC70 的 W90-F92 区域与 G3BP 的 NTF2 结构域结合。

以上结果揭示 Gpr137b-ps 在巨噬细胞自噬的调节中具有重要作用，可调节晚期动脉粥样硬化进展。Gpr137b-ps 通过破坏下游蛋白 HSC70 和 G3BPs 的结合进一步调控氨基酸

-mTORC1-自噬，为晚期动脉粥样硬化的治疗提供新的靶点和潜在治疗方向。

S9：神经干细胞与抑郁障碍

S9-1 神经干细胞调控机制研究

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The mammalian brain contains millions of neurons and glial cells. Normal cerebral brain development plays an important role in controlling behavior, learning and cognition. During neurogenesis, neural progenitor cells (NPCs) proliferate and differentiate into neurons of cortical layers, which are precisely controlled by various intracellular and extracellular signaling pathways. NPCs of the brain are mainly PAX6-positive apical progenitor cells and TBR2-positive basal progenitor cells. Although more and more molecules are reported involved in the proliferation of progenitor cells, how neurogenesis is regulated by epigenetic factors during the embryonic development of the cerebral cortex remains largely to be investigated. Here, we found a series of epigenetic molecules and modifications are essential for the proliferation and self-renewal of neural stem cells.

S9-2 心理韧性的生物学机制

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In facing different types of stressors, we need a system that is capable of reacting to difficult and possibly dangerous situations. Acute stress, such as the fight-or-flight response, enable us to avoid threats, while chronic stress can cause adverse effects such as depression. In reality, nearly everyone will experience a traumatic event over a lifetime, but most do not develop depression, suggesting that many people have a character of resilience. Resilience in chronic stress is defined as the ability to rebound from adversity in a healthy manner. Here, we identified a microcircuit and molecular adaptations within it that play a role in natural resilience. Chronic stress usually consists of three aspects: exposure to ‘repeated’ distressing events, personal perception of stress, and subsequent responses to these stresses. The chronic social defeat stress (CSDS) paradigm

feasibly mimics these aspects: a 10-min physical phase, in which an intruder is attacked by an aggressor CD1 mouse (stressor), mimics ‘distressing events’. During the separated phase, the intruder could perceive and respond to the stress during approaches by a CD1 mouse. In this study, we found that ‘attacks’ induced a short-term hyperpolarization of MGPV neurons (located in the MG) of resilient mice during the early stages of the CSDS paradigm, and this adaptation process induces trafficking of GluA2 type AMPA receptors to the postsynaptic membrane of thalamic inputs onto MGPV neurons (located in the A1), possibly through homeostatic scaling. In the subsequent stress responses, brain-derived neurotrophic factor (BDNF) ‘donor’ neurons were activated and released BDNF, which acts on presynaptic TrkB receptors resulting in activating MGPV neurons, promoting synaptogenesis onto MGPV neurons. This process strengths synaptic transmission between MGPV and MGPV neurons, leading to activation of MGPV neurons in response to stress. However, susceptible mice lack such a trait.

S9-3 Plasma proteomic profiling of major depressive disorder versus schizophrenia and healthy control and its association with clinical outcomes

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Objective The present study aimed to identify biological processes and plasma biomarkers associated with the risk and treatment efficacy of major depressive disorder (MDD). Methods Using Olink proteomics based on proximity extension assays, baseline plasma concentrations of 1452 unique proteins were measured in 319 participants, including 149 patients with MDD, 70 age- and gender-matched healthy controls (HC), and 100 patients with schizophrenia (SCZ). The MDD group was further divided into treatment responders (TR) and non-responders (NTR) based on changes in the Hamilton Depression Rating Scale (HAMD) score after 4 weeks of antidepressant treatment. Differential protein expression analysis was performed following pathway enrichment analysis to identify the key proteins that were significantly altered in the MDD group and the TR group and to explore their potential biological functions and interactions. The FDR correction was applied for multiple tests, and proteins with $P_{fdr} < 0.05$ and an absolute fold change > 1 were considered as differentially expressed proteins (DEPs). The partial correlation analysis was conducted to explore the relationship between DEPs and treatment efficacy in patients with MDD. We developed a random forest model with Boruta-selected DEPs to classify MDD from SCZ and HC. The protein profiled samples were split into a training dataset (240 individuals) and a test dataset (79 individuals) with a ratio of 7.5:2.5. Prediction models were

trained through 10-times 10-fold cross validation in the training stage to avoid underfitting and overfitting issues and were evaluated by area under the curve (AUC) for classification in the test dataset. Results Differential protein expression analysis showed that a total of 131 DEPs were identified in the MDD group compared to the HC group, with 13 being up-regulated (LTA4H, PKLR, OSM, CA1, and AHSP, etc.) and 118 being down-regulated (SUSD1, CD69, CNST, PLXNA4, and MPIG6B, etc.). Meanwhile, 23 up-regulated (LTA4H, PPY, LXN, IL4, and OSM, etc.) and 106 down-regulated (BANK1, MPIG6B, CALCOCO1, PPP1R9B, and CD69, etc.) DEPs were identified in the MDD group versus the SCZ group. Cytokine-mediated signaling pathway, ion channel binding pathway, T cell costimulation pathway, and syntaxin binding pathway were among the top enriched pathways of the DEPs. Furthermore, the TR group had a significantly lower expression of 10 proteins compared to the NTR group. Eight DEPs were shared in the three comparisons: DOK2, MAP3K5, CALCOCO1, MGMT, EIF4G1, PDLIM7, STAT5B, and SRC, which were enriched in the RET signaling pathway (P_{fdr}= 0.0012). Partial correlation analysis indicated that these overlapping proteins were negatively correlated with the change rate of the HAMD score (*P*-values from 1.08×10^{-9} to 1.87×10^{-5}). The AUC of the receiver operating characteristic curve in the classification model employing these overlapping proteins to distinguish patients with MDD from SCZ and HC was 0.9045 (95% CI: 0.8478–0.9473). The protein level of CALCOCO1 was the most important predictor for the classifier. Conclusion Our study identified several differential proteins and pathways associated with MDD that may serve as potential biomarkers or therapeutic targets. Our results suggest that MDD is characterized by a dysregulation of the inflammatory response, neuronal activity, T cell function, and synaptic transmission. Our results further imply that TR and NTR subgroups may have distinct molecular profiles, with NTR exhibiting greater protein expression in the RET signaling pathway. Our results are consistent with some previous studies but also reveal some novel findings that warrant further investigation to validate.

S9-4 双相障碍的发病机制研究

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双相障碍是一种遗传力较高的重性精神疾病，严重影响患者的认知、情感、行为等，并伴随高自杀和其它慢性病症状。但双相障碍的病因不明、发病机制不清且缺乏有效分子病理特征。我们结合遗传学、多组学、脑影像学、分子生物学等方法，遵循风险变异→基因表达→病理生理改变这一逐层深入的思路，探讨了我国人群双相障碍的遗传基础与机制：①牵头

开展了我国首个多中心的大规模双相障碍遗传学研究，推动了对该疾病遗传基础的理解。②率先应用多组学大数据的整合分析方法发掘双相障碍风险基因，并刻画其在生理层面的影响。③以双相障碍风险基因的功能研究入手揭示该疾病的病因，提出关键脑区中树突棘异常的双相障碍病理机制假说。

S9-5 人脑类器官与重性抑郁症研究

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重性抑郁症是一种高度异质性且全球流行的情感障碍疾病，给家庭和社会带来沉重的负担。重性抑郁症是造成自杀行为最常见因素，但目前我们对伴有自杀行为重性抑郁症的病理基础仍缺乏足够认识，其主要原因在于缺乏可靠的人源性研究模型。本研究中我们将伴有自杀行为抑郁症（sMDD）病人的体细胞重编程成诱导多功能干细胞，并在体外分化成人脑类器官，以此为基础探究重性抑郁症的致病机制：1. 体外构建 sMDD 病人来源的神经元和多脑区类器官模型；2. 通过单细胞转录组学分析探究 sMDD 组在细胞组分和功能通路上的异常，筛选可能导致疾病症状的关键分子；3. 体外模型验证转录组分析的结果，并通过基因编辑和小分子抑制等手段对关键分子进行干预，挽救 sMDD 病人来源的神经元和类器官中的疾病表型。我们的工作为研究 sMDD 的疾病机制开辟了新途径，同时也为确定 sMDD 的治疗目标和筛选治疗药物提供了理论依据。

S10：中医院校生理专业委员会专题研讨会

S10-1 唤醒沉睡的中医古方-百合地黄汤治疗抑郁症的物质基础及分子机制

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百合地黄汤为心肺阴虚内热之百合病的经典名方，而《金匮要略》中百合病的情志失调导致的行为表现与现代抑郁症的临床症状基本相似。其中，百合地黄汤对阴虚内热型抑郁有明显的治疗效果，可有效改善大便干、盗汗、悲伤易哭、失眠等症状。 然而，国内外尚缺乏百合地黄汤干预阴虚内热型抑郁中枢神经生物学基础的深入研究。 项目以百合病作为切入点，提出“多情交织暗耗阴液致心肺阴虚而渐生内热”科学问题， 阐明百合病虚热与郁闷不舒躯体化症状可归因于阴虚内热情志失调；通过审证求因、 审证求机、以证验方、以方

佐证，构建百合病情志失调表征的阴虚内热型抑郁（慢性应激联合甲状腺激素）动物证候模型及评价体系；考证百合地黄汤本草关键信息，完成仲景原方基准样品制备。采用指纹/特征图谱结合多成份指标表征基准样品的化学物质组成，确定薯蓣皂苷、阿魏酸、毛蕊花糖苷及梓醇作为物质基准的关键质量属性； 对药材、饮片、制剂开展相关性研究，确定制备工艺关键参数，明确阿魏酸、毛蕊花糖苷作为全过程质量控制体系的标记物；采用多项指标联合分析、综合评价百合地黄汤（仲景原方）缓解虚热与抑郁样行为与上调单胺类神经递质，降低外周与中枢炎症水平，拮抗 HPA 轴兴奋，纠正兴奋/抑制性神经递质失衡，减轻应激诱导的皮层神经细胞损伤相关；基于动物与细胞抑郁模型交叉佐证实验揭示百合地黄汤多种组分可改变一系列微小 RNAs 介导 GABA/谷氨酸能突触、突触可塑性及轴突引导、昼夜节律、神经免疫与炎症等信号通路，实现机体多系统生理功能的协调与统一。项目的研究成果丰富百合地黄汤多途径治疗阴虚内热型抑郁的中枢神经细胞与分子机制，为从表观遗传修饰角度解析该方中医治则治法的生物学基础及中药新药研发提供充分科学依据，实现百合地黄汤的中医药源头创新。

S10-2 补阳还五汤及其有效组分抗脑缺血炎性神经损伤的机制研究

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补阳还五汤是治疗气虚血瘀型中风的经典名方，具有补气、活血、通络之功效，善治中风的正气亏虚，血瘀脉络之症。大量文献证实补阳还五汤可通过多靶点、多环节、多途径调控脑缺血的炎性反应，从而发挥脑保护作用。我们团队在邓常清教授带领下，围绕焦亡这一与炎症密切相关的神经细胞死亡及其机制，揭示了补阳还五汤及其苷类组分抗脑缺血炎性损伤的作用及其机制。这一研究成果深化了补阳还五汤脑保护作用的药效物质和作用机制认识，对于指导其临床应用，研制成分相对清楚、作用机制明确的中药制剂具有重要意义。

S10-3 中医药改善 AD 样小鼠突触功能异常：聚集小胶质细胞和神经炎症

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大量的研究支持阿尔茨海默病在病程早期脑内即出现明显的小胶质细胞激活，并诱发神经炎症反应，成为破坏突触功能的主要因素，最终导致患者出现记忆障碍和精神异常等临床症状。因此，在 AD 早期抑制小胶质细胞激活和突触功能下降有可能成为阻止 AD 病程发展的治疗时机。中医药在未病先防的作用中具有显著优势，且多种中药具有清热、解毒、安神

等作用功效。本课题组近年来利用行为学、电生理、分子生物学和化学遗传学等技术，发现桂枝、甘草等中药及其有效成分对 AD 小鼠海马的小胶质细胞激活和突触功能下降具有显著的调节作用，从而改善 AD 小鼠记忆障碍，并探讨其深入的药理机制。

S10-4 非靶代谢组学筛选特应性皮炎分子标记及其致痒机制研究

于光
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特应性皮炎是最常见的皮肤病之一，患者伴发皮肤屏障结构损伤与强烈瘙痒感觉，形成“屏障结构破坏-瘙痒-抓挠”恶性循环，但是其皮肤代谢产物变化与痒觉之间的关系还有待深入解析。利用非靶代谢组学技术，我们从特应性皮炎模型小鼠皮肤中鉴定出 300 种差异代谢化合物，基于 VIP 值从中筛选出 157 种化合物开展进一步分析，这些差异化合物集中于脂质代谢，尤其是甘油磷脂和鞘磷脂代谢途径，通过二级质谱比对和定量分析发现花生四烯酸代谢产物 20-HETE 的含量显著升高。特异性皮炎模型小鼠皮下注射 20-HETE 显著增加小鼠痒觉行为，而抑制 20-HETE 合成则显著减少 AD 模型诱导的小鼠痒觉行为。细胞实验发现 20-HETE 主要诱导 $TRPV1^+$神经元内钙浓度的升高；特应性皮炎小鼠皮下注射辣椒素（TRPV1 特异激动剂）诱导痒觉行为显著增加的结果证明 TRPV1 在特应性皮炎中扮演了“痛-痒觉”信号传递功能转换的角色。进一步的研究发现特应性皮炎中，TRPV1 介导的痒觉信号传递依赖于 $MrgprA3^+$神经元的兴奋而不是 Mrgprs 的表达。总之，我们从特应性皮炎皮肤中分离并证明了化合物 20-HETE 通过激动 TRPV1 诱导痒觉增加，并且这种增强的痒觉行为依赖于 $MrgprA3^+$神经元的兴奋。

S10-5 “肚腹三里留”的神经生物学基础

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中医针灸选穴歌诀中的“肚腹三里留”高度概括了足三里作为胃的下合穴是临床胃肠疾病首选穴的特征，也是针灸学研究的热点。以往我们观察到，针刺下肢足三里主要通过非节段性体表-迷走反射调节胃运动，这与神经解剖提示脊髓水平坐骨神经支配的下肢不存在体表-交感-内脏节段性联系相一致，但又与足三里治疗胃肠疾病的优效性相悖，而成为目前穴位-靶器官效应机制研究的难点。我们感兴趣的是，与具备体表-交感节段性联系的胃同节段穴位中脘和非节段性联系的上肢穴位内关比较，足三里调控胃功能的特点是什么，脑胃肠中枢参与调控机制如何？这些问题的回答不仅为临床“肚腹三里留”的效应机制提供系统和科

学解释，更是对以往主要从脊髓节段性联系解释针刺效应进行的拓展与深入，属于引领性和开创性的工作。我们采用病毒标记和神经束路示踪、光遗传、化学遗传、多导微阵列电极及全细胞脑片膜片钳等神经科学前沿技术，从脊髓和脊髓上水平阐明“肚腹三里留”的作用途径及机制。脊髓水平的研究聚焦在足三里穴调控胃功能与自主神经、不同传入纤维类型的关系，及对上行传导通路的依赖等方面。脊髓上水平的研究将集中于与胃-足三里投射相关的核团与脑干胃肠中枢的联系，局部神经元网络功能活动变化及突触兴奋性和可塑性改变等，在介导针刺调节胃功能中的作用。这些问题的厘清，对神经解剖上具有不同体表-内脏联系特点的穴位-靶器官效应规律和机制进行深入研究，理解以“肚腹三里留”为代表的特定穴选择有重要的科学意义。

S11：体适能与健康促进

S11-1 不同运动方式对肥胖女大学生血管内皮功能的影响研究

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研究目的: 本研究通过观察有氧、抗阻以及联合训练对肥胖女大学生身体成分、炎症因子、血管内皮相关因子和血管内皮功能的变化。分析三种运动方式对肥胖女大学生血管功能及相关因素的影响；探讨联合运动对肥胖女大学生血管内皮功能的改善效果。

研究方法：本研究招募并筛选出 47 名肥胖（体脂率＞30%）女大学生。随机分为 3 组，分别为有氧训练组、抗阻训练组和联合训练组。每周训练 3 次，持续 8 周。有氧训练组：采用功率车进行训练，进行 50 分钟的中等强度（前 4 周 60%储备心率，后 4 周 70%储备心率）的正式训练，。抗阻训练组： 依次进行史密斯深蹲、卧推、硬拉；每项练习包含 2 组热身组与 4 组正式组，每组完成 10 次，组内休息 1 分钟，组间休息 1 分钟，变换动作间歇 2 分钟；热身强度 50%最大重复次数，正式训练强度 75%最大重复次数。联合训练组：热身和放松同有氧训练；正式训练先进行 25 分钟抗阻训练，训练强度同抗阻训练，组数减半；其后进行 25 分钟有氧训练，强度同有氧训练。三组运动干预的热身和放松相同，为 5 分钟功率车的低强度（40%-50%储备心率）热身和 5 分钟的放松拉伸。在运动前、运动 4 周和运动 8 周后的安静状态下分别测量受试者身体成分、炎症因子、血管内皮相关因子和血流介导的血管舒张功能。各指标采用重复测量方差分析，组间基础值存在差异的采用独立样本 t 检验进行分析。

研究结果：（1）8 周运动干预后， 有氧组、抗阻组以及联合组体脂率后测显著低于前测（$p<0.05$）。抗阻组和联合组体脂率中测显著低于前测（$p<0.05$）。有氧组和抗阻组体

脂率后测显著低于中测（p＜0.05）；抗阻组和联合组受试者肌肉含量后测显著高于前测和中测（p＜0.01）。联合组肌肉含量中测显著高于前测（p＜0.01）；抗阻组和联合组握力后测显著高于前测（p＜0.01）。联合组受试者静息心率后测显著低于前测（p＜0.05）。（2）8 周运动干预后，有氧组、抗阻组、联合组 C 反应蛋白后测显著低于前测（p＜0.05）；联合组 C 反应蛋白中测显著低于前测（p＜0.05）；有氧组和联合组白介素-8 中测、后测相对于前测出现显著性下降（p＜0.01），有氧组白介素-8 后测相对于中测出现显著性下降（p＜0.05），有氧组与抗阻组白介素-8 组间有显著性差异（p＜0.01）；有氧组白介素-10 中测、后测显著高于前测（p＜0.01），后测显著高于中测（p＜0.05），联合组白介素-10 中、后侧显著高于前测（p＜0.05）。（3）8 周运动干预后，有氧组、抗阻组以及联合组一氧化氮中测、后测显著高于前测（p＜0.05），有氧组和联合组一氧化氮后测显著高于中测（p＜0.01），有氧组、联合组与抗阻组一氧化氮后测组间存在显著性差异（p＜0.01）。（4） 8 周运动干预后，有氧组、联合组血流介导的舒张功能中测和后测显著高于前测（p＜0.01），联合组血流介导的舒张功能后测显著高于前测（p＜0.01）。有氧组、联合组与抗阻组血流介导的舒张功能干预后组间存在显著性差异（p＜0.01）。（5）8 周运动干预后，血流介导的血管舒张功能变化率与一氧化氮变化率呈低度正相关（r=0.420, P＜0.01）；血流介导的血管舒张功能与白介素-8 呈低度负相关（r=-0.356, P＜0.05）；体脂率与 C 反应蛋白呈低度正相关（r=0.372，p＜0.05）。

结论：（1）三种运动均能降低肥胖女大学生体脂率，联合运动的增肌效果与抗阻运动相似，优于有氧运动。（2）中等强度联合运动能够改善肥胖女大学生炎症因子水平，其效果与有氧运动相似，优于抗阻运动；（3）中等强度联合运动能够提高肥胖女大学生一氧化氮表达并改善其血管内皮功能，其效果与有氧运动相似，优于抗阻运动；（4）中等强度联合运动能够提高肥胖女大学生血流介导的血管舒张功能，其效果与有氧相似，优于抗阻。（5）中等强度运动训练改善肥胖女大学生血管内皮功能可能是通过提高血管内皮相关因子一氧化氮的表达，降低炎症因子白介素-8 和 C 反应蛋白的表达来实现的。

S11-2 身体活动能量消耗与代谢综合征及其组分的量效关系研究

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研究目的：通过对成年人群身体活动的横断面调查，以代谢综合征所界定的风险因素为主，了解身体活动能量消耗（PAEE）与代谢综合征各指标的关联性，分析 PAEE 与代谢综合征及其组分患病风险的相关性，利用限制性立方样条阐明量效关系及其曲线形态。

研究方法：参加健康体检的 450 名成年人为研究对象，通过问卷调查、体格检查和生化指标检测收集研究对象基本数据。根据四分位数法将 PAEE 分为四组（Quartile1-Quartile4，

Q1-Q4），分析总人群、男性人群和女性人群中 PAEE 各分组间与代谢综合征各指标的差异，采用 logistic 回归模型计算 PAEE 与谢综合征及其组分患病风险之间的 OR 值和 95%CI，并使用限制性立方样条模型拟合 PAEE 与代谢综合征及其组分患病风险的量效关系。

研究结果：(1)总体情况分析显示：代谢综合征的总患病率为 27.8%，男性代谢综合征患病率（20.7%）显著高于女性代谢综合征患病率（7.1%），代谢综合征及各组分指标均具有显著性差异，男性代谢综合征各组分患病率均超过于女性人群，具有显著差异（P＜0.05）。随着 PAEE 的增加，总人群年龄、FPG 指标、TG 指标、高血糖、代谢综合征和低 HDL-C 患病率逐渐降低（P＜0.05），男性人群中 TG 指标、高血糖、代谢综合征和低 HDL-C 患病率逐渐降低（P＜0.05），女性人群中 FPG 指标、代谢综合征和低 HDL-C 患病率逐渐降低（P＜0.05）。

（2）PAEE 与代谢综合征及其组分患病风险的相关性分析结果显示，调整混杂因素后，总人群中随着 PAEE 水平的升高，代谢综合征、低 HDL-C 和高血糖的患病风险降低（P＜0.05），以最低分位数 Q1 为参照组，代谢综合征（OR=0.21，95% CI：0.10~0.44），低 HDL-C（OR=0.29，95% CI：0.16~0.54）高血糖患病（OR=0.48，95% CI：0.26~0.89），总人群中未发现 PAEE 与中心性肥胖、高血压和高 TG 患病风险的关联；按性别分层分析后，男性人群随着 PAEE 水平的升高，代谢综合征、低 HDL-C 和高血糖的患病风险下降（P＜0.05），以男性的 PAEE 最低分位数 Q1 为参照组，代谢综合征（OR=0.11，95% CI：0.04~0.32）低 HDL-C（OR=0.19，95% CI：0.08~0.49）高血糖（OR=0.42，95% CI：0.18~1.01），男性人群中未发现 PAEE 与中心性肥胖、高血压和高 TG 患病风险的关联；女性人群随着 PAEE 水平的升高，代谢综合征和低 HDL-C 的患病风险降低下降（P＜0.05），以女性人群 PAEE 最低分位数 Q1 为参照组，代谢综合征（OR=0.34，95% CI：0.12~0.95）低 HDL-C 患病（OR=0.29，95% CI：0.11~0.78），女性人群中未发现 PAEE 与高血糖、中心性肥胖、高血压和高 TG 患病风险的关联。（3）综合前两部分分析结果，使用限制性立方样条模型拟合 PAEE 与代谢综合征及其组分患病风险的量效关系显示，总人群 PAEE 与代谢综合征、高血糖和低 HDL-C 的患病风险均呈非线性剂量效应关系，患病风险均随着 PAEE 的增高而下降，身体活动对代谢综合征发生风险的 PAEE 阈值为 19.9kJ/kg/d，身体活动对高血糖发生风险的 PAEE 阈值 18.7kJ/kg/d，身体活动对低 HDL-C 发生风险的 PAEE 阈值 19.9kJ/kg/d；男性人群中 PAEE 与代谢综合征和高血糖呈非线性剂量效应关系，身体活动对代谢综合征发生风险的 PAEE 阈值为 20.1kJ/kg/d ，PAEE 对高血糖发生风险的阈值为 20.6kJ/kg/d，与低 HDL-C 呈线性量效关系无明显阈值效应；女性人群 PAEE 增加与代谢综合征呈非线性剂量效应关系，身体活动对代谢综合征发生风险的阈值为 15.9kJ/kg/d，PAEE 与低 HDL-C 呈线性剂量效应关系，无明显阈值效应。

研究结论：（1）PAEE 与代谢综合征相关风险指标呈负相关，代谢综合征相关指标随 PAEE 的增加而降低，增加 PAEE 对代谢综合征相关风险指标具有改善作用。

（2）PAEE 与代谢综合征患病风险之间存在非线性的剂量反应关系呈近似“L”型曲线，随着 PAEE 增加的患病风险逐渐降低，到达相应阈值后存在平台期，平台期后患病风险不会

随着 PAEE 的增加而发生明显变化。

（3）在男性人群中，PAEE 与高血糖患病风险呈非线性剂量效应关系呈似“U”型曲线，过低和过高的 PAEE 都会使得男性高血糖患病风险升高，在女性人群中 PAEE 与高血糖患病风险无量效关系。

（4）在男性人群和女性人群中，PAEE 与低 HDL-C 患病风险均呈线性剂量效应关系，随着 PAEE 的增加，低 HDL-C 患病风险越低，故增加 PAEE 对低 HDL-C 患病风险具有一定的保护作用。

关键词：身体活动；身体活动能量消耗；代谢综合征；量效关系

S11-3 “体医融合”干预糖尿病促进社区居民健康新模式研究

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目的：探索“体医融合”干预糖尿病促进社区居民健康新模式，并将“体医融合门诊”落地服务社区患者。背景：糖尿病是全球流行性疾病，中国是糖尿病发病率最高的国家之一，2021 年我国糖尿病健康支出达 1653 亿美元，全球排名第 2，久坐等不良生活方式加速了糖尿病的进程，全球约 27%的糖尿病患者体力活动不足。生活方式干预是糖尿病的一线治疗方案，其中运动锻炼最具重要性。关于运动干预糖尿病的研究非常多，《中国 2 型糖尿病防治指南》也提到了糖尿病的运动方案，但是未提及个体化精准化运动诊疗方案、如何开展及如何落地等。方法：我们团队和上海市医疗机构联合建立了“糖尿病体医融合门诊”，医生和社区（运动）健康师共同门诊。运动前开展运动风险和能力评估，运动中制定精准运动处方，运动后完善再评估和依从性方案，将运动处方 AI 化并应用于“社区老者之家”，提高大样本运动干预效率。结论： “体医融合”系统化精细化的糖尿病健康管理体系，提高了社区糖尿病管理效率，促进社区糖尿病患者自主健康管理。

关键词：体医融合；糖尿病；健康管理；新模式

S11-4 长期运动干预对 ADHD 儿童核心症状和执行功能的影响：基于随机对照试验的 meta 分析

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研究目的：探索长期运动干预对改善注意缺陷多动障碍（Attention Deficit Hyperactivity Disorder，ADHD）儿童青少年的核心症状（注意力不集中、多动、冲动）和执行功能（抑

制控制、工作记忆、认知灵活性）的影响。

研究方法：在 PubMed、Embase、Web of Science、Google Scholar、Cochrane Library 和 CNKI 等数据库中，对运动干预 ADHD 的文献进行检索，筛选出符合纳入标准的随机对照实验（Randomized Controlled Trial，RCT），并辅以文献追溯、手工检索等进行文献补充。根据 Cochrane 系统评审手册建议的方法，采用 Review Manager 软件独立评估纳入的 RCT 研究的偏倚风险。采用随机效应模型对纳入研究进行 meta 分析，所有统计分析使用 STATA14.0 软件进行合并效应量分析和亚组分析。

研究结果：在各数据库中共检索出 876 篇文献，通过纳入排除标准进行筛选，最终纳入 18 篇文献。其中 10 篇报道了核心症状，13 篇报道了执行功能。meta 分析结果发现，长期运动可以显著改善 ADHD 儿童青少年核心症状（SMD=-0.32,95%CI:-0.51,-0.13,I^2=0.00%, P=0.001）及执行功能(SMD=-0.69,95%CI:-0.98,-0.40,I^2=57.8%,P<0.001)。亚组分析结果显示：就核心症状而言，长期运动干预对注意力不集中症状有小的积极影响(SMD=-0.32,95%CI-0.63,-0.004)，对多动/冲动症状没有显著影响(SMD=-0.18,95%CI:-0.52,0.17)；此外，闭合式运动对核心症状的改善有中等大小的积极影响(SMD=-0.55,95%CI:-0.85,-0.25)，而开放式运动对核心症状的改善没有显著的影响（SMD=-0.17,95%CI:-0.42,0.08）；运动结合吃药的干预方式对核心症状的改善也存在中等大小的积极影响(SMD=-0.56,95%CI:-0.89,-0.24)，而单纯进行运动干预效果不显著(SMD=-0.20,95%CI:-0.44,0.04)。就执行功能而言，长期运动干预对 ADHD 儿童青少年执行功能的改善效果不受药物使用情况的影响(SMD=-0.76,95%CI:-1.15,-0.38 vs SMD=-0.68,95%CI:-1.13,-0.23)。此外，长期运动干预对抑制控制(SMD = -1.04,95%CI:-1.66,-0.43)改善的效果最大，其次是认知灵活性(SMD=-0.78,95%CI:-1.2,-0.37)和工作记忆(SMD=-0.42,95%CI:-0.75,-0.09)；开放式运动对执行功能的改善有小的积极影响(SMD=-1.09,95%CI:-1.50,-0.67)，而闭合式运动则没有显著影响(SMD=-0.28,95%CI:-0.61,0.05)。

研究结论：长期运动干预对改善 ADHD 儿童青少年核心症状和执行功能具有积极作用。此外，闭合式运动对核心症状的改善效果较好，而开放式运动对执行功能的改善效果较好。

关键词：注意缺陷多动障碍；儿童；青少年；运动

S11-5 基于心肺运动试验的中国部分居民心肺耐力等级标准研究

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目的：通过心肺运动试验来测试峰值摄氧量，建立中国部分城乡居民的正常参考等级标准。方法：在 2017 年 1 月-2018 年 12 月分别在北京城乡和广西贺州城乡四个社区进行招募

符合条件的受试者进行横断面调查和心肺耐力的测试。采用国际通用的 PAR-Q 问卷和自制健康问卷进行运动测试前的健康筛查，并采用功率自行车和便携式气体代谢分析仪进行心肺运动试验，测出每位受试者的峰值摄氧量。共招募了 1642 名受试者，其中 1114 名受试者完成了心肺运动试验且心电图无异常表现。按照百分位法将 2%-98%定为正常参考值的下限和上限。结果：（1）男性和女性，不同年龄平均峰值摄氧量有明显差异；（2）根据不同性别、不同年龄得出每 10 岁为一年龄段峰值摄氧量的百分位正常参考值。结论：首次基于中国社区人群的峰值摄氧量制定出不同年龄、性别的心肺耐力正常分级标准。

关键词： 心肺运动试验；心肺耐力；中国居民；等级标准

S12：RNA 生理与病理

S12-1 Ctnnb1 enhancers mediates neocortical neurogenesis and intestinal homeostasis

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The non-coding regulatory elements, particularly enhancers, are essential components for selective gene expression and suppression during cell identity establishment and maintenance. β-catenin-dependent canonical Wnt signaling plays a plethora of roles in organ development, tissue homeostasis and cancer. Here we identified *neCtnnb1*, an evolutionarily conserved *cis*-regulatory element with typical enhancer features in developing Ncx. *neCtnnb1* locates 55 kilobase upstream of and spatially close to the promoter of *Ctnnb1*, the gene encoding β-catenin. CRISPR/Cas9-mediated activation or interference of the *neCtnnb1* locus enhanced or inhibited *Ctnnb1*'s transcription. Knockout of *neCtnnb1* in mice resulted in compromised expression of *Ctnnb1* and the Wnt reporter in developing Ncx. Importantly, knockout of *neCtnnb1* lead to reduced production and transit-amplification of intermediate progenitors (IPs), which subsequently generated fewer upper-layer Ncx projection neurons (PNs). In contrast, enhancing the canonical Wnt signaling by stabilizing β-catenin in *neCtnnb1*-active cells promoted the production of IPs and upper-layer Ncx PNs. ASH2L was identified as a key *trans*-acting factor that associates with *neCtnnb1* and *Ctnnb1*'s promoter to maintain *Ctnnb1*'s transcription in both mouse and human Ncx progenitors. Parallelly, we identified another evolutionarily conserved upstream enhancer of *Ctnnb1* - *ieCtnnb1* - that controls intestinal homeostasis. *ieCtnnb1* is active in crypts of small and large intestines. Knockout of *ieCtnnb1* slows down turnovers of intestinal epithelia at physiology, regeneration, and cancer conditions in the Wnt/β-catenin dependent

manner. Moreover, single-cell sequence revealed that *ieCtnnb1* knockout biased epithelial composition of small intestinal crypts – more absorptive cells at the expense of secretive cells. The human *ieCTNNB1* contains a SNP that is associated with *CTNNB1* expression levels in human gastrointestinal epithelia. Key trans-factors that bind to *ieCtnnb1* and regulate *Ctnnb1* transcription were identified. These findings advance understanding of transcriptional regulation of *Ctnnb1* and provide insights into how enhancers control cell fate determination during organ development and homeostasis.

S12-2 长链非编码 RNA 的功能与机制研究：打开基因组宝库的一把密匙

汪香婷
中国科学技术大学

报告简介：LncRNA 是高等动物基因组的重要组成部分，在几乎所有的生理和病理过程中均发挥着重要的调控功能。在此次题为“长链非编码 RNA 的功能与机制研究：打开基因组宝库的一把密匙”的报告中，汪香婷研究员将围绕 Wang Lab 近期在 lncRNA 异构体方面研究的进展进行介绍，与听众共同探讨揭示人类基因组宝库—lncRNA 神秘功能的重要意义。

S12-3 新 microRNA novel-m009C 调控冰毒的奖赏效应

官方霖
西安交通大学

S12-4 Characterizing physiological roles of RNA modifications

姬生健
南方科技大学

RNA modifications provide an important post-transcriptional regulation in gene expression. N^6-methyladenosine (m^6A) modification, as the most prevalent internal modification on mRNA, has been implicated in many biological processes through regulating mRNA metabolism. Given that m^6A modification is highly enriched in vivo both in developing and adult animals, this dynamic modification provides a crucial new layer of epitranscriptomic regulation of normal physiological functions. In this talk, I will discuss our recent progresses on studies of m^6A modification in the mammals ranging from development, normal functions, to disorders.

S12-5 ADRAM is an experience-dependent long noncoding RNA that drives fear extinction through a direct interaction with the chaperone protein 14-3-3

李翔
武汉大学中南医院

Here, we used RNA capture-seq to identify a large population of lncRNAs that are expressed in the infralimbic prefrontal cortex of adult male mice in response to fear-related learning. Combining these data with cell-type- specific ATAC-seq on neurons that had been selectively activated by fear extinction learning, we find induc- ible 434 lncRNAs that are derived from enhancer regions in the vicinity of protein-coding genes. In particular, we discover an experience-induced lncRNA we call ADRAM (activity-dependent lncRNA associated with memory) that acts as both a scaffold and a combinatorial guide to recruit the brain-enriched chaperone pro- tein 14-3-3 to the promoter of the memory-associated immediate-early gene Nr4a2 and is required fear extinction memory. This study expands the lexicon of experience-dependent lncRNA activity in the brain and highlights enhancer-derived RNAs (eRNAs) as key players in the epigenomic regulation of gene expres- sion associated with the formation of fear extinction memory.

泰盟 ·人工智能与生理学 Satellite Symposium

SS-1 人工智能与医学虚拟仿真

朱亮
大连医科大学

SS-2 智能医学与神经科学

郑晨光
天津大学

SS-3 人工智能原理及其在生理学实验中的应用

黄武
成都泰盟软件有限公司

大会报告（Plenary Lecture, PL)

大会报告 PL 3：脑科学与脑损伤

王以政 院士
复旦大学附属华山医院
中国人民解放军军事医学研究院

探索脑疾病诊断与治疗是人口健康的需求也是脑计划的重要内容。创伤后应激障碍（PTSD）是影响人们健康的疾病，目前还没有有效的治疗方法。采用创伤后应激障碍小鼠模型，发现深部脑刺激（DBS）BLA 可以改善小鼠恐惧与焦虑的行为表现，探讨了 DBS 改善 PTSD 模型行为的分子和环路机制。此外，在探索缺血性脑损伤的研究中，发现了 Sonic hedgehog（Shh）在缺血性脑损伤模型中，通过影响 glutamate 的转运体的活性，参与了 glutamate 兴奋性神经毒，抑制 Shh 通路可以保护缺血性脑损伤，为早期干预 glutamate 兴奋性神经毒达到保护缺血性脑损伤,提供了新的思路。

大会报告 PL 4：类精子干细胞介导半克隆技术的建立与应用

李劲松 院士
中国科学院分子细胞科学卓越创新中心

通过核移植可以将精子重编程为孤雄单倍体胚胎干细胞系，这些细胞可以替代精子通过卵子注射高效产生半克隆小鼠（又称为类精子干细胞介导半克隆技术）。该技术为构建复杂遗传改造小鼠模型提供新的工具，可以用于：（1）一步获得携带多基因突变的杂合小鼠模型，用于模拟人类多基因介导的复杂疾病；（2）快速获得携带人类疾病相关点突变小鼠用于研究疾病发生的分子机制；（3）一步获得针对不同基因的突变小鼠，实现小鼠个体水平的遗传筛选；（4）一步获得针对编码特定基因的不同碱基突变的小鼠，实现蛋白质关键氨基酸的在体遗传筛选；（5）建立携带蛋白质标签敲入的类精子干细胞库，进而获得携带蛋白质标签的小鼠库（genome tagging project, GTP），目前已获得 2000 余株标签细胞系，380 余个小鼠品系，为全球 90 余个实验室提供了服务；（6）在类精子干细胞中靶向着丝粒切割产生了染色体头

对头的融合，获得了一系列 19 对染色体的小鼠品系，模拟了自然界漫长过程形成的染色体融合事件。类精子干细胞介导半克隆技术为发育、疾病和演化研究提供了新手段。

张锡钧基金第十七届全国青年优秀生理学学术论文交流会议

The 17th Chang His-Chun Youth Outstanding Paper Forum

C1 The peripheral-central crosstalk underlying exercise training and brain health

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Abstract: Physical exercise effectively improves brain functions such as mental or cognitive behaviors. Its detailed peripheral-central mechanism, however, remains to be elucidated. In the recent decade, the applicant has been focusing on the mechanism of exercise in improving brain health, and has obtained novel insights at molecular, synaptic and neural circuitry layers. Major research outputs include:

(1) The identification of key peripheral molecules underlying the improvement of brain functions by endurance exercise. We generated a mouse model by overexpressing mutant human TDP-43 (M337V) in the primary motor cortex, leading to prominent motor learning deficits. In vivo 2-photon imaging shows an active approach of microglia toward parvalbumin interneurons, resulting in disrupted cortical excitatory-inhibitory balance. Proteomics studies suggest that activation of the complement pathway induces microglial activity. To develop an early interventional strategy, treadmill exercise successfully prevents the deterioration of motor dysfunction under enhanced adipocytic release of clusterin to block the complement pathway. These results demonstrate a previously unrecognized pathway by which TDP-43 induces cortical deficits and provide additional insights for the mechanistic explanation of exercise training in disease intervention (***Cell Reports*** 2023).

(2) The elucidation of molecular mechanism in improving synaptic plasticity by exercise-related peripheral derived molecules. We show that chronic treadmill exercise activates the mechanistic target of rapamycin (mTOR) pathway in mouse motor cortex. Both ex vivo and in vivo recordings suggest that mTOR activation leads to potentiated postsynaptic excitation and enhanced neuronal activity of layer 5 pyramidal neurons after exercise, in association with

increased oligodendrogenesis and axonal myelination. Exercise training also increases dendritic spine formation and motor learning. Taken together, exercise activates mTOR pathway, which is necessary for spinogenesis, neuronal activation and axonal myelination leading to improved motor learning. This model provides new insights for neural network adaptations under exercises and supports the intervention of cognitive deficits using exercise training (***Science Advances*** 2019).

(3) The investigation of neural circuit by which exercise-related molecules can improve the brain function. We report that one-week treadmill training restores cocaine-induced synaptic deficits, in the form of improved in vivo spine formation, synaptic transmission and spontaneous activities of cortical pyramidal neurons, as well as motor learning ability. The synaptic and behavioral benefits relied on de novo protein synthesis, which are directed by the activation of mechanistic target of rapamycin (mTOR)- ribosomal protein S6 pathway. These findings establish synaptic functional restoration and mTOR signaling as the critical mechanism supporting physical exercise training in rehabilitating the addicted brain (***Molecular Psychiatry*** 2021).

In sum, our work performed has provided more evidence for the peripheral-central axis of brain function improvement under exercise training and facilitated the translational study of exercise intervention against brain diseases.

Keywords: Exercise training; Synaptic plasticity; Mental disorders; Peripheral factors

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C2 细胞铁死亡的代谢调控机制

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死亡不仅是所有细胞的最终命运，而且它与细胞分裂、增殖一样，在整个机体的正常运转中具有不可替代的作用。铁死亡（ferroptosis）是一种 2012 年才被报道的以铁依赖的脂质过氧化为特征的新型程序性细胞死亡方式，已被揭示是多种重大疾病的关键病理生理机制，迅速成为国际研究前沿与热点。面对这种“年轻”的生命现象，当下的重要挑战是将前沿生命科学理念与技术应用于细胞铁死亡研究，从分子水平多层次地理解其调控机制。

近年来，我们对铁死亡这种代谢性细胞死亡的调控机制及其在心肝等重要脏器疾病中的

转化价值进行了一系列富有成效的探索：（1）应用小鼠阿霉素心肌病和心肌缺血再灌注两种经典的心脏疾病模型，通过基因敲除等一系列技术手段首次揭示了心肌细胞铁死亡的存在与地位，并阐明了 HMOX1 过度激活介导线粒体铁过载/铁死亡的分子机制（*PNAS*，高被引/热点论文）。凝练提出五种有效策略靶向铁死亡防控心肌病：即铁死亡抑制剂、铁螯合剂、线粒体特异性抗氧化剂、HMOX1 抑制剂以及低铁膳食；其中铁死亡抑制剂与 HMOX1 抑制剂对心脏损伤疗效的原创发现分获国家发明专利授权。受邀在 *Nature Reviews Cardiology* 和《科学通报》发表长篇封面综述，系统总结铁死亡在心脏疾病中的最新进展。（2）率先构建了铁蛋白重链（FTH）基因的心肌细胞特异性敲除小鼠，该模型可在高铁饲料诱导下发生显著的心肌细胞铁死亡并呈现典型肥厚型心肌病表现，成为首个可稳定遗传的心脏铁死亡动物模型。在国际上首次成功制备了心肌细胞特异性胱氨酸/谷氨酸转运蛋白 SLC7A11 过表达小鼠，通过增加细胞内的胱氨酸促进谷胱甘肽合成，成功逆转了 FTH 心肌细胞敲除小鼠的铁死亡及其诱发的心衰表型。明确了谷胱甘肽缺乏是诱发 FTH 敲除小鼠发生心脏铁死亡这一分子机制，并率先发现 SLC7A11 是治疗铁死亡相关心脏疾病的关键靶点（*Circulation Research*，高被引论文）。（3）设计了基于 NADPH 分解与合成通路的筛选思路，揭示苹果酸酶 ME1 的下调是缺血再灌注损伤中肝脏 NADPH 耗竭的直接原因，进而导致了半胱氨酸与还原型谷胱甘肽（GSH）合成不足以及铁死亡易感性增加，为丰富完善铁死亡调控体系及相关肝脏疾病的防治提供了重要依据（*Advanced Science*，内封面论文）。

上述成果通过将发轫于体外细胞培养体系的铁死亡现象拓展到体内领域，为认知铁死亡的生理和病理生理学功能打开了一个新的窗口，增加了我们对相关生命现象的理解，从而立足铁死亡及其调控通路制定治疗策略和寻找潜在靶点。

关键词：铁死亡；程序性细胞死亡；心肌病；肝损伤；铁代谢

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C3 精神活性物质调控调控脑功能的神经机制

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大麻和阿片类药物作为两种常见的精神活性物质，其临床药用价值研究一直是基础和临床的重点领域。尽管国内外研究已经发现大麻和阿片类精神活性物质治疗阿尔兹海默症、睡眠障碍、癫痫以及各种急、慢性疼痛等神经系统疾病的效果显著，但精神活性物质调控脑功能的许多科学问题尚不清楚，严重阻碍了精神活性物质的临床药用价值研究。在聚焦精神活性物质调控脑功能的研究中，我们发现低剂量的 THC 和酒精协同导致运动障碍的神经机制，

并提出基于突触外抑制性甘氨酸受体(esGlyR）的干预策略。我们首先通过脑区筛选和神经电信号记录分析等手段发现 THC 和酒精联用显著降低了小脑 4/5Cb 区域浦肯野细胞的神经活动，并证实浦肯野细胞突触前的 CB1 受体和突触外的 esGlyR 是 THC 和酒精协同导致运动毒性的关键靶点。随后，利用化学荧光探针和高效液相质谱技术，我们进一步发现低剂量的酒精还可以改变血脑屏障的通透性，进而提高 THC 进入大脑的速率，最终增强 THC 对其脑内神经靶点的调控作用。最后，我们通过对 THC 进行化学结构修饰得到新型双脱羟基的 THC 化合物 DD-THC。神经药理学和动物行为学结果表明 DD-THC 可以特异性的阻断 THC 对 esGlyR 的调控作用，进而恢复小脑 4/5Cb 区域浦肯野细胞的神经活动，最终实现了对 THC 和酒精协同导致运动障碍的干预。该工作运用多学科交叉手段系统研究了 THC 和酒精协同导致运动障碍的机制，提出开发基于 esGlyR 的新型药物，为大麻和酒精滥用的临床治疗提供了新思路。阿片类药物如吗啡作为临床广泛使用的精神类药物可以引起临床常见的环境偶联的阿片镇痛耐受（AOAT）。我们利用光遗传学、化学遗传学、活体钙成像和活体脑电记录等手段，发现 Glu^{vHPC}→CCK^{dmPFC}→Glu^{BLA} 神经环路是调控环境偶联的阿片镇痛耐受的关键神经环路，并提出基于 BLA 脑区 CCKB 受体的干预策略，为临床治疗阿片类药物的耐受、成瘾和滥用等精神副作用提供了新思路和新靶点。除此之外，$GABA_AR$ 作为神经系统除 esGlyR 外重要的抑制性离子通道受体，同样引起我们的广泛兴趣。运用化学结构生物学和神经药理学等手段，我们及合作团队阐明了 GABARAP 介导 $GABA_AR$ 在细胞膜上动态转运的结构基础，为神经系统疾病的治疗和创新药研发提供了全新的结构信息和分子基础。

关键词：精神活性物质，大麻，阿片类药物，esGlyR，$GABA_AR$，运动障碍，药物耐受

C4 Neurotransmitter sensors elucidate the mechanism of memory coding and coincidence detection in the olfactory learning of *Drosophila*

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To survive and proliferate in this constantly changing world, animals evolve associative learning to optimize their behavior according to previous experience. Associative learning requires 3 key factors: neutral conditioned stimulus (CS), rewarded or punitive unconditioned stimulus (US), and coincident timing. To elucidate the neural basis of associative learning, it is critical to understand how CS and US are encoded in the brain, and how the associative timing is regulated.

In order to answer above questions, this research focused on the Drosophila olfactory learning center Mushroom Body (MB), which has simplified and well-characterized anatomy. Previous behavioral and genetic studies have established that CS (odor) is encoded by cholinergic Kenyon Cells (KCs), while US (electrical shock) is encoded by dopaminergic neurons (DANs). To monitor in vivo dynamics of different neurotransmitters with high spatiotemporal resolution, transgenic flies were created expressing novel G-protein coupled receptor-activation based (GRAB) dopamine (DA) and acetylcholine (ACh) sensors. The sensors' applicability was verified using two-photon in vivo imaging and they have good chemical specificity, sub-second kinetics and single cell spatial resolution. When the fly was stimulated with physiological relevant stimuli, such as odor and electrical shock, sensors reveal stimulus-specific compartmental DA and ACh release patterns, suggesting the functional independence of different MB compartmens.

The coincidence between conditioned stimulus (CS) and unconditioned stimulus (US) is essential for associative learning, however, the mechanism regulating the duration of this temporal window remains unclear. Here, we found that serotonin (5-HT) bi-directionally regulates the coincidence time window of olfactory learning in Drosophila, and affects synaptic plasticity of

Kenyon cells (KCs) in mushroom body (MB). Utilizing GPCR-activation–based (GRAB) neurotransmitter sensors, we found that KCs-released acetylcholine (ACh) activates a serotonergic DPM neuron, which in turn provides feedback inhibition on KCs. Physiological stimuli induce spatially heterogenous 5-HT signals, which proportionally gate the intrinsic coincidence time windows of different MB compartments. Artificially reducing or increasing the DPM neuron-released 5-HT shortens or prolongs the coincidence window, respectively. In a sequential trace conditioning paradigm, this serotonergic neuromodulation helps to bridge the CS-US temporal gap.

Thus, this research reveals how CS and US are represented by DA and ACh in an olfactory learning center, and identified a 5-HT mediated mechanism that can regulate the associative time window for learning, which contribute a simplified model about how the brain times the environmental events and determines their relationship.

Keywords: GRAB sensor; associative learning; coincidence time window; olfaction; serotonin; synaptic plasticity.

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C5 丘脑-初级听觉皮层环路介导慢性压力模型中心理韧性的产生

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心理韧性使个体在逆境中具有恢复能力。在这项研究中，我们探索了在内源性心理韧性中发挥重要作用的神经环路和相应的分子机制。我们发现，初级听觉皮层（Primary auditory cortex,A1）中接受来自同侧内侧膝状体(Medial geniculate body, MG)兴奋性神经元投射的小清蛋白(PV)中间神经元在慢性社交失败模型中的激活对于小鼠的恢复能力至关重要。在社会失败模型应激的早期阶段，应激事件诱发投射到 A1 的 MG 神经元(MG^{A1} 神经元)的短期超极化。此外，MG^{A1} 神经元的这种时间依赖的神经可塑性在随后的应激反应中通过突触前 BDNF-TrkB 信号介导 MG^{PV} 神经元上突触的发生。此外，光遗传学模拟 MG^{A1} 神经元的短期超极化，而不仅仅是激活 MG^{A1} 神经元，在多种动物模型中引发了应对应激的内源性心理韧性机制，并取得了持续的抗抑郁样效果，表征了靶向神经调节治疗抑郁症的一种新策略。

关键词：小清蛋白中间神经元；初级听皮层；内侧膝状体；抑郁症

A thalamic- primary auditory cortex circuit mediates resilience to stress

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Resilience enables mental elasticity in individuals when rebounding from adversity. In this

study, we identified a microcircuit and relevant molecular adaptations that play a role in natural resilience. We found that activation of parvalbumin (PV) interneurons in the primary auditory cortex (A1) by thalamic inputs from the ipsilateral medial geniculate body (MG) is essential for resilience in mice exposed to chronic social defeat stress. Early attacks during chronic social defeat stress induced short-term hyperpolarizations of MG neurons projecting to the A1 (MG^{A1} neurons) in resilient mice. In addition, this temporal neural plasticity of MG^{A1} neurons initiated synaptogenesis onto thalamic PV neurons via presynaptic BDNF–TrkB signaling in subsequent stress responses. Moreover, optogenetic mimicking of the short-term hyperpolarization of MG^{A1} neurons, rather than merely activating MG^{A1} neurons, elicited innate resilience mechanisms in response to stress and achieved sustained antidepressant-like effects in multiple animal models, representing a new strategy for targeted neuromodulation.

Key words: Resilience; Parvalbumin interneurons; Primary auditory cortex; Medial geniculate body; Depression.

C6 PHB2 maintains the contractile phenotype of VSMCs by counteracting PKM2 splicing

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Phenotypic transition of vascular smooth muscle cells (VSMCs) accounts for the pathogenesis of a variety of vascular diseases during the early stage. Recent studies indicate the metabolic reprogramming may be involved in VSMC phenotypic transition. However, the definite

molecules that link energy metabolism to distinct VSMC phenotype remain elusive. We collected cell energy-regulating genes by using Gene Ontology annotation and applied RNA-Seq analysis of transforming growth factor-β or platelet-derived growth factor BB stimulated VSMCs. Six candidate genes were overlapped from energy metabolism-related genes and genes reciprocally upregulated by transforming growth factor-β and downregulated by platelet-derived growth factor BB. Among them, prohibitin 2 has been reported to regulate mitochondrial oxidative phosphorylation. Indeed, prohibitin 2-deficient VSMCs lost the contractile phenotype as evidenced by reduced contractile proteins. Consistently, Phb2SMCKO mice were more susceptible to postinjury VSMC proliferation and neointima formation compared with Phb2flox/flox mice. Further protein interactome analysis, co-immunoprecipitation, and mammalian 2-hybrid assay revealed that prohibitin 2, through its C-terminus, directly interacts with hnRNPA1, a key modulator of pyruvate kinase M1/2 (PKM) mRNA splicing that promotes PKM2 expression and glycolysis. Prohibitin 2 deficiency facilitated PKM1/2 mRNA splicing and reversion from PKM1 to PKM2, and enhanced glycolysis in VSMCs. Blocking prohibitin 2-hnRNPA1 interaction resulted in increased PKM2 expression, enhanced glycolysis, repressed contractile marker genes expression in VSMCs, as well as aggravated postinjury neointima formation in vivo.

Keywords: PKM; glycolysis; hnRNPA1; neointima; prohibitin 2; restenosis; vascular smooth muscle cell.

C7 2 型糖尿病心肌损伤的机制以及分型研究

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糖尿病心肌病（Diabetic cardiomyopathy, DCM）是由糖尿病(Diabetes mellitus, DM)独立引发的原发性心肌损伤，也是导致 DM 患者死亡的最大风险因素。研究促进 DCM 发生发展的分子机制，寻找潜在 DCM 防治靶点，是相关领域研究者的共同目标。通过对 2 型糖尿病（Type 2 Diabetes mellitus, T2DM）小鼠心肌组织的转录组测序分析，我们发现心肌中的视黄醇（Retinol, Rol）代谢相关分子在 T2DM 发展各阶段均存在显著改变。进一步的 LC-MS/MS、WB 和 IHC 实验结果显示，T2DM 小鼠心肌以及 T2DM 患者心肌组织中存在以视黄醇（Retinol, Rol）过载、视黄酸 (Retinoic acid, atRA)缺乏和视黄酸受体（Retinoic acid receptors, RARs）表达降低为特征的视黄醇代谢失衡现象。

为验证视黄醇代谢失衡是否参与 DCM，并评估其在 DCM 发生发展中的作用，我们对

T2DM 小鼠分别长期补充 Rol 和 atRA，发现这两者对 DCM 的进展表现出截然不同的影响，证明心肌 Rol 超载和 atRA 缺乏都会加重 DCM。视黄醇脱氢酶 10（Retinol Dehydrogenase, RDH10）是 Rol 向 atRA 代谢转化的关键酶，对维持视黄醇代谢平衡至关重要。我们通过构建心肌细胞特异性 RDH10 条件敲除小鼠，和采用腺相关病毒在 T2DM 小鼠心肌中过表达 RDH10，明确了 RDH10 在心肌视黄醇代谢中的关键作用，证实 RDH10 表达改变引起的视黄醇代谢紊乱是 DCM 的始动因素。进一步的机制研究发现，DCM 时，心肌细胞 RDH10 表达下调造成的视黄醇代谢失衡，一方面通过造成 Rol 的堆积加重心肌中的细胞凋亡和心肌纤维化；另一方面通过减少 atRA 的生成导致心肌细胞视黄酸/RARs 信号转导异常，造成心肌脂质堆积和心肌细胞铁死亡。同时，基于以上研究结果，我们提出通过恢复心肌中的 RDH10 表达水平或 atRA 含量，纠正心肌视黄醇代谢失衡，是潜在的 T2DM 心肌损伤防治新策略。

此外，通过系统性的对比分析，我们发现尽管肥胖型和非肥胖型 T2DM 小鼠均表现出 DCM 表型，但在心脏的结构功能、能量代谢模式和氧化应激适应性方面表现出较大差异。具体表现在，相对于非肥胖型 T2DM，肥胖型 T2DM 小鼠显示出更严重的心脏结构重塑和更早发的心脏收缩功能障碍，更严重的心肌脂毒性是造成肥胖型 T2DM 小鼠更易出现心力衰竭的原因。此外，尽管肥胖型和非肥胖型 T2DM 小鼠心肌均表现出大量的活性氧积聚，但在心脏收缩功能障碍发生时，抗氧化应激相关分子 Nrf2 及其下游关键靶基因的表达在肥胖型 T2DM 小鼠心肌中显著上调，而在非肥胖型 T2DM 小鼠心肌中则显著下调，提示抗氧化功能障碍可能在非肥胖型 T2DM 小鼠心肌损伤的病理机制中起到更关键的作用。以上研究的关键性结果我们也在法医提供的 T2DM 患者心肌组织中进行了相应验证。在此基础上，我们提出，可以用 BMI 或腹部脂肪厚度等辅助性指标对 T2DM 心肌损伤进行代谢分型，为临床精准诊治提供依据和参考。

关键词：视黄醇脱氢酶 10；糖尿病心肌损伤；视黄醇代谢；心肌脂毒性

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C8 心肌重构的表观修饰机制

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【研究背景】

随着我国人口老龄化加剧，衰老相关的心血管疾病已是目前严重威胁人类健康的主要因素之一。心肌重构是多种心脏疾病的病理基础，但是心肌重构的分子病理机制尚待阐明。表观修饰对生长发育、稳态维持和疾病发生至关重要。解析心肌重构的表观修饰机制对认识和

治疗病理性心肌重构具有重要意义。细胞代谢及其中间物是调节表观修饰的重要因素。代谢紊乱是心肌重构的关键病理因素，但表观调控机制不明。一方面，代谢紊乱如何通过表观修饰驱动转录组重塑和线粒体氧化应激等病理过程的机制不明确。另一方面，表观修饰如何调控代谢紊乱的机制也需要阐明。我们过去几年围绕这两个方面开展研究，取的下列关键成果。

【结果】

（1）巴豆酰化和乙酰基化修饰调控心肌转录组稳态与心肌重构。我们系统分析了酰基化修饰在心肌细胞转录组稳态和心肌重构中的功能，发现线粒体脂代谢酶 ECHS1 的缺失是驱动组蛋白巴豆酰化修饰、染色质重塑和心肌重构的关键机制，提出了组蛋白巴豆酰化修饰介导线粒体代谢紊乱驱动心肌细胞转录组重塑和心肌重构的理论（Circulation 2021）。此外，我们发现心肌核心转录因子 Nkx2.5 的乙酰化修饰调控其转录活性和心肌细胞转录组并参与心肌发育和重构，揭示了临床上 Nkx2.5 乙酰化位点突变导致先心病的关键分子机制。据此，我们提出靶向酰基化修饰促进心肌细胞转录组稳态来治疗心脏疾病（eBioMedicine 2023）。

（2）乙酰化修饰调节线粒体氧化应激和心肌重构。我们聚焦线粒体的抗氧化系统和促氧化系统研究线粒体氧化应激的表观修饰机制。我们首先基于抗氧化酶 MnSOD 研究了心肌重构中代谢紊乱调控线粒体氧化应激的表观修饰机制，阐明了线粒体表观修饰酶 SIRT3 和 SIRT4 是线粒体代谢紊乱导致线粒体氧化应激和心肌重构的关键表观调控因子（Eur Heart J 2017）。我们发现线粒体中的促氧化系统受去乙酰化酶 SIRT2 调控。SIRT2 通过乙酰化-磷酸化机制控制 $p66^{Shc}$ 进出线粒体来调节线粒体 H_2O_2 的产生和心血管重构（Eur Heart J 2023）。此外，我们发现线粒体氧化应激调节心血管重构依赖于免疫微环境重塑（J Exp Med 2022），并提出线粒体氧化应激是心肌重构的关键机制（Trends Endocrinol Metab 2023）。

（3）乙酰化修饰调节心肌细胞代谢和心肌重构。我们早期研究了心肌细胞代谢稳态如何受到表观修饰调控，发现去乙酰化酶 Sirtuin 家族成员 SIRT2 通过介导代谢感受器 AMPK 对 Acetyl-CoA 和 NAD^+的响应来改善细胞代谢（如 NAD^+增加或 Crotonyl-CoA 降低）并延缓心肌衰老与重构（Circulation 2017，STTT 2023），揭示了 AMPK-miR-146a-Nampt 信号轴障碍是心脏重构和衰老中 NAD^+-Sirtuin 介导的表观修饰和代谢稳态失衡的关键机制（STTT 2022），发现了线粒体中去乙酰化酶 SIRT3 的关键下游分子 VDAC 是控制脂质代谢参与心肌重构的关键分子（Redox Biol 2023）。

【总结】

上述科学发现阐释了巴豆酰化和乙酰化修饰如何调控“转录组重塑”、“线粒体氧化应激”和“代谢紊乱”等关键分子病理事件来参与心肌重构，扩展了心肌重构的表观修饰机制理论。揭示了临床上 ECHS1、SIRT2/3/4 等关键表观修饰因子突变增加心脏疾病风险的分子基础，为心肌重构的防治提供了新靶点。

关键词：心血管疾病；表观修饰；重构

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Epigenetic modifications in myocardial remodeling

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Background

With the increasing aging of the population in China, age-related cardiovascular diseases have become one of the major factors threatening human health. Myocardial remodeling is the pathological basis of many heart diseases, but the molecular mechanism of remodeling remains to be elucidated. Epigenetic modification is essential for growth and development, homeostasis maintenance, and disease occurrence. The analysis of the epigenetic modification mechanism of myocardial remodeling is of great significance for the understanding and treatment of myocardial remodeling. Cell metabolism and the metabolites are important factors regulating epigenetic modification. Metabolic dysregulation is the key factor underlying myocardial remodeling, but the epigenetic mechanisms are unknown. On one hand, the mechanism of how metabolic dysregulation drives pathological processes such as transcriptome remodeling and mitochondrial oxidative stress through epigenetic modification is unclear. On the other hand, the mechanism of how epigenetic modifications regulate metabolic dysregulation also needs to be elucidated. Our research over the past few years has focused on these two areas and has yielded the following key results.

Results

(1) Crotonylation and acetylation regulate transcriptome homeostasis and myocardial remodeling. We systematically analyzed the function of acylation in transcriptome homeostasis and myocardial remodeling of cardiomyocytes. The dysregulation of mitochondrial lipid metabolic enzyme ECHS1 was a key mechanism driving histone crotonylation modification, chromatin remodeling, and myocardial remodeling. Thus, we proposed the theory that transcriptome remodeling and myocardial remodeling driven by mitochondrial metabolic disorders were mediated by histone crotonylation modification (Circulation 2021). In addition, we found that the acetylation modification of the myocardial core transcription factor Nkx2.5 regulated its transcriptional activity and the transcriptome of cardiomyocytes, and participated in myocardial

development and remodeling, revealing the key molecular mechanism of Nkx2.5 acetylation site mutation leading to congenital heart disease. Accordingly, we proposed targeting acylation to promote cardiomyocyte transcriptome homeostasis for the treatment of heart disease (eBioMedicine 2023).

(2) Acetylation regulates mitochondrial oxidative stress and myocardial remodeling. We focused on the antioxidant and pro-oxidative systems of mitochondria to investigate the epigenetic modification mechanism of mitochondrial oxidative stress. We first studied the epigenetic modification mechanism of mitochondrial oxidative stress regulated by metabolic dysfunction during myocardial remodeling by focusing on the antioxidant enzyme MnSOD. We found that mitochondrial epigenetic SIRT3 and SIRT4 were key epigenetic regulators of mitochondrial oxidative stress and myocardial remodeling caused by mitochondrial metabolic disorders (Eur Heart J 2017). We also found that the pro-oxidation system in mitochondria was regulated by the deacetylase SIRT2. SIRT2 regulated mitochondrial H_2O_2 production and cardiovascular remodeling by controlling the translocation of $p66^{Shc}$ into the mitochondria through an acetylation-phosphorylation mechanism (Eur Heart J 2023). In addition, we found that the regulation of cardiovascular remodeling by mitochondrial oxidative stress was dependent on the immune microenvironment (J Exp Med 2022) and proposed that mitochondrial oxidative stress was a key mechanism of myocardial remodeling (Trends Endocrinol Metab 2023).

(3) Acetylation regulates cardiomyocyte metabolism and myocardial remodeling. We studied early on how cardiomyocyte metabolic homeostasis was regulated by epigenetic modifications. We found that SIRT2, a member of the Sirtuin family of deacetylases, improved cell metabolism (such as increased NAD+ or decreased Crotonyl-CoA) and delayed myocardial aging and remodeling by mediating the response of metabolic receptors AMPK to Acetyl-CoA and NAD^+ (Circulation 2017, STTT 2023), and revealed that AMPK-miR-146a-Nampt signal axis dysfunction was a key mechanism of NAD^+-Sirtuin-mediated epigenetic modification and metabolic homeostasis imbalance during cardiac remodeling and aging (STTT 2022). We also found that VDAC, a key downstream molecule of the deacetylase SIRT3 in mitochondria, was a key molecule that controlled lipid metabolism and participated in myocardial remodeling (Redox Biol 2023).

Conclusions

These scientific findings explained how crotonylation and acetylation modifications regulate key molecular pathologic events such as "transcriptome remodeling", "mitochondrial oxidative stress" and "metabolic dysregulation" to participate in myocardial remodeling and expanded the theory of epigenetic modification mechanisms of myocardial remodeling. These studies also revealed the molecular basis of the increase in risk of heart disease caused by mutations of ECHS1,

SIRT2/3/4, and other key epigenetic modifiers, and provided new targets for the prevention and treatment of myocardial remodeling.

Keywords

Cardiovascular disease; Epigenetic modification; Remodeling

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C9 运动锻炼促进心脏健康的 RNA 表观遗传分子机制研究

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缺乏身体活动是包括心血管疾病在内的多种慢性疾病发生的主要原因之一。心血管疾病是全球人类死亡的主要原因，严重危害人类健康。运动锻炼有益心血管健康，能显著降低心血管危险事件的发生和改善心血管疾病患者的预后。尽管运动锻炼对心脏健康的保护效应已经被广泛接受，但是其调控的分子机制仍有许多未知，进一步深入研究有望发掘出新的心力衰竭乃至心脏疾病防治策略。生活方式和环境因素等已被证明通过表观遗传修饰影响人类健康，运动锻炼是在促进人类健康和预防疾病中发挥积极作用的关键因素之一。从 RNA 表观遗传的角度探索运动锻炼在保护心血管健康与防治心血管疾病中的机制将为阐明运动锻炼保护心血管健康的分子机制提供新思路。

在围绕运动锻炼促进心脏健康的 RNA 表观遗传分子机制研究中，我们前期研究鉴定出了响应运动锻炼促进心脏健康的关键长链非编码 RNA CPhar、RNA 腺苷脱氨酶 ADAR2，并揭示出其对心脏疾病防治效应的分子机制。接着，解析了运动锻炼心脏中 mRNA m^6A 修饰图谱变化，发现运动锻炼降低小鼠心脏中 mRNA m^6A 甲基化水平；运动锻炼后心脏 RNA m^6A 甲基转移酶 METTL14 在 RNA m^6A 甲基化水平和蛋白质水平均显著性下调；沉默 METTL14 会抑制 *Phlpp2* mRNA m^6A 修饰并激活 Akt-S473，进而调节心肌细胞的生长和凋亡。在体内，野生型 METTL14 过表达可以增加心脏 mRNA m^6A 的甲基化水平并阻断运动诱导生理性心肌肥厚的发生，然而 MTase 失活突变体 METTL14 则不具有该功能；心脏特异性抑制 METTL14 可以减轻急性心肌缺血再灌注损伤以及心肌缺血再灌注重构所致的心功能障碍。

进一步，我们发现受 METTL14 调控的环状 RNA circ-ZNF609 可以和 RNA m^6A 形成反馈调节环路，从而实现对于心脏损伤的保护效应，明确了抑制 circ-ZNF609 保护心脏缺血再灌注损伤和阿霉素所致心肌毒性的关键分子机制。机制研究表明，RNA m^6A 修饰参与介导 circ-ZNF609 对 YAP 的调控作用，抑制 circ-ZNF609 降低 m^6A 读码蛋白 YTHDF3 的表达，进而调节被 m^6A 修饰的 *Yap* mRNA 与 YTHDF1 和 YTHDF2 结合比例，实现对下游分子 YAP 的调控并促进其入核。我们的系列工作研究了运动锻炼促进心脏健康的 RNA 表观遗传分子机制，为深入理解运动锻炼保护心血管健康的理论知识和开发运动锻炼替代性药物治疗心脏疾病提供了的研究思路和潜在的防治策略。

关键词：运动锻炼；心脏保护；METTL14；环状 RNA circ-ZNF609

C10 DNA 修复定量报告系统的开发及其在衰老相关研究中的应用

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基因组不稳定是衰老的核心特征，而 DNA 修复是维持基因组稳定性的关键机制。然而，由于缺乏定量研究系统，学界对于衰老发生过程中 DNA 修复的变化及调控机制仍存在许多未知，这也极大限制了通过靶向 DNA 修复干预衰老发生的新方法的研发。因此，近年来我们围绕上述科学问题，在衰老及 DNA 修复的交叉领域开展了一系列研究工作。

同源重组（HR）及非同源末端连接（NHEJ）是两条相互配合又彼此竞争的 DNA 双链断裂修复途径，二者对于基因组稳定性的维持至关重要。然而，如何定量研究两条通路的修复效率及其平衡是 DNA 修复领域的一大难点。我们首先开发了一种细胞水平的 DNA 修复双色荧光报告系统，该系统可同时定量检测 HR 及 NHEJ 两条通路的修复效率。我们目前以实验材料转让的方式将该系统提供给海内外近 30 家单位，促进了 DNA 修复及其交叉学科的研究进展。利用该系统，我们揭示了损伤位点周边较为松散的染色质环境有利于 HR 修复的进行，而 NHEJ 对染色质松散程度要求较低。有趣的是，我们发现著名的长寿基因 SIRT1 可对染色质重塑因子 BRG1 的 1029 及 1033 位赖氨酸进行去乙酰化从而增强其 ATPase 活性，促进核小体结构松散，有利于 HR 相关因子 RPA2 及 RAD51 的招募，最终推动 HR 修复的进行。

基于上述基础，我们还开发了一种以 DNA 修复为读出端的高通量筛选平台，并对 722 种天然小分子化合物进行高通量筛选，获得了一批具有潜在抗衰老效应的新型药物（促进 HR 及 NHEJ）、促进基因打靶的药物（促进 HR、抑制 NHEJ）及一批可能的抗肿瘤药物（抑制 HR 及 NHEJ），为不同领域学者提供了大量候选药物资源。我们还利用靶向长寿基因 SIRT6 的新型激动剂成功改善年老个体来源多能干细胞的基因组稳定性与分化潜能，为衰老相关疾

病的细胞治疗奠定基础。

为进一步理解 DNA 双链断裂修复在不同生理及病理过程中的作用，我们在上述工作的基础上构建了国际首个可在体内多器官同时定量研究两条 DNA 修复通路效率的动物模型。该动物模型可实现脑、心、肾、胰、胃、肠、皮肤中 HR 及 NHEJ 修复的体内可视化与定量分析，为不同领域学者开展 DNA 修复相关研究提供新的选择。利用该系统，我们揭示了组织特异性的 DNA 修复偏好差异，并初步阐述了衰老过程中 DNA 修复的组织特异性变化。有趣的是，神经系统焦虑与衰老关系密切。我们还利用上述动物模型创新性地揭示了焦虑可引发胃与肾中 DNA 修复能力下调，为 DNA 修复的器官间串话提供新的证据。

关键词：衰老，DNA 修复报告系统，动物模型，DNA 双链断裂修复，基因组稳定性

C11 炎性疾病代谢调控及药理学干预

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（1）肠道微生物群失调与类风湿性关节炎（RA）的发病机制密切相关。我们的目的是确定潜在的益生菌肠道微生物，可以改善 RA 的发展。结果显示新发 RA 患者和有病史的 RA 患者中 *P. distasonis* 的相对丰度下调，这种下降与疾病活动评分-28（DAS28）呈负相关。用活的 *P. distasonis*（LPD）口服治疗关节炎小鼠显著改善了 RA 的发病机制。LPD 衍生的石胆酸（LCA）、脱氧胆酸（DCA）、异石胆酸（isoLCA）和 3-氧代石胆酸（3-oxoLCA）对 RA 的治疗具有相似的协同作用。除了直接抑制 Th17 细胞的分化外，3-氧代 LCA 和异 LCA 被鉴定为促进巨噬细胞 M2 极化的 TGR5 激动剂。胆汁盐水解酶的一种特异性合成抑制剂通过减少这四种胆汁酸的产生来减弱 LPD 的抗关节炎作用。天然产物人参皂苷 Rg2 通过促进远志的生长而表现出抗 RA 的作用。*P.distasonis* 和人参皂苷 Rg2 可能是治疗 RA 的益生菌和益生元制剂。（2）到目前为止，溃疡性结肠炎（UC）的治疗由于其复杂的病因而具有挑战性。在这里，非靶向/靶向代谢组学和蛋白质组学分析显示，UC 患者的血清精氨酸水平和限速合成酶精氨酸琥珀酸合成酶 1（ASS1）显著较高。外源性精氨酸输注和 ASS1 过表达加重了小鼠结肠炎的病理特征。抑制和沉默 ASS1 可预防实验性结肠炎。ASS1 的诱导与乙酰化 H3 和三甲基化 H3K4 的上调以及 ASS1 启动子周围的二甲基 H3K9 的下调平行，这表明结肠炎中 ASS1 的表观遗传学激活。ASS1/精氨酸轴诱导 mTOR 的异常激活，从而导致结肠炎症。我们进一步从 160 万个对 ASS1 具有良好结合亲和力的化合物中筛选出新的化合物 C-01，并且低剂量的 C-01 显著改善结肠炎。我们的研究结果表明，ASS1 可能是 UC 治疗的新靶点。

关键词：关节炎；益生菌；益生元；胆汁酸；结肠炎；代谢组学；精氨酸

Metabolic regulation and pharmacological intervention in inflammatory diseases

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(1) Gut microbiota dysbiosis is closely linked to the pathogenesis of rheumatoid arthritis (RA). We aimed to identify potential probiotic gut microbes that can ameliorate the development of RA. The relative abundance of *P. distasonis* in new-onset patients with RA and patients with RA with history of the disease was downregulated and this decrease was negatively correlated with Disease Activity Score-28 (DAS28). Oral treatment of arthritic mice with live *P. distasonis* (LPD) considerably ameliorated RA pathogenesis. LPD-derived lithocholic acid (LCA), deoxycholic acid (DCA), isolithocholic acid (isoLCA) and 3-oxolithocholic acid (3-oxoLCA) had similar and synergistic effects on the treatment of RA. In addition to directly inhibiting the differentiation of Th17 cells, 3-oxoLCA and isoLCA were identified as TGR5 agonists that promoted the M2 polarisation of macrophages. A specific synthetic inhibitor of bile salt hydrolase attenuated the antiarthritic effects of LPD by reducing the production of these four bile acids. The natural product ginsenoside Rg2 exhibited its anti-RA effects by promoting the growth of *P. distasonis*. *P. distasonis* and ginsenoside Rg2 might represent probiotic and prebiotic agents in the treatment of RA. (2) To date, the current treatment for ulcerative colitis (UC) has been challenging due to its complicated aetiology. Here, untargeted/targeted metabolomics and proteomics analyses reveal that serum arginine levels and the rate-limiting synthetase argininosuccinate synthetase 1 (ASS1) are significantly higher in UC patients. Exogenous arginine infusion and ASS1 overexpression aggravate the pathological features of colitis in mice. Inhibiting and silencing ASS1 protects against experimental colitis. Induction of ASS1 is paralleled by upregulations of acetylated H3 and trimethylated H3K4, and downregulation of dimethyl H3K9 surrounding the ASS1 promoters, indicative of epigenetic activation of ASS1 in colitis. The ASS1/arginine axis induces aberrant activation of mTOR, thus leading to colonic inflammation. We further screen the novel compound C-01 from 1.6 million compounds with favorable binding affinity to ASS1, and a low dose of C-01 substantially improves colitis. Our findings indicate that ASS1 might be a novel target for UC treatment.

Keywords: Arthritis; Probiotics; Prebiotics; Bile acids; Colitis; Metabolomics; Arginine

C12 血管稳态转录因子对肺动脉高压血管功能调控机制的研究

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肺动脉高压 (Pulmonary arterial hypertension，PAH) 是由多种病因和不同发病机制所致的肺动脉结构和功能改变，引起肺血管阻力升高和氧气运输受限的临床和病理生理综合征，继而发展成右心衰竭甚至死亡。PAH 也被称为恶性心血管疾病，尚无有效治疗方法。本人系列工作在离体微血管和动物模型中解析了血管稳态转录因子对PAH微小血管功能紊乱的分子信号转导调控机制，为 PAH 的治疗提出新的策略。

过氧化物增殖子激活受体γ（PPARγ）作为糖脂代谢关键调控因子，近年来被证明在心血管系统中具有抗炎、抗氧化和抗增殖等多种作用，与心血管稳态直接相关。PAH患者和动物模型中，循环5-羟色胺（5-HT）显著增高，并通过其受体5-HT2BR诱发肺动脉的高收缩性。本人在野百合碱（monocrotaline，MCT）和慢性缺氧（chronic hypoxia）诱导的PAH大鼠中分别以长时程（4周）预处理和短时程（3天）治疗形式给与PPARγ激动剂噻唑烷二酮药物（TZD）。应用离体微血管张力测定方法，发现PPARγ的激活抑制肺动脉平滑肌细胞5-HT2BR的表达及其介导的血管收缩功能，改善了肺动脉功能，其中TZD长时程处理可以抑制肺动脉病理重构和右心室肥厚。在此基础上，研究首次报道5-HT对5-HT2BR表达的正反馈调节及其转录调节方式。该工作发表于*Hypertension*，并被选作当期封面。

此外本人也关注了肺动脉中PPARγ对于PAH疾病过程中关键诱导和致病因子内皮素-1（ET-1）的调控作用，临床上认为ET-1作用于平滑肌细胞内皮素受体A（ETAR），导致其异常激活，与PAH发病密切相关。本人发现在PAH动物模型中，PPARγ可以在抑制ETAR的同时上调肺动脉内皮细胞中ET-1另一类内皮素受体ETBR，通过ETBR介导的一氧化氮的释放而促进肺动脉舒张，改善血管功能（*PPAR Research*）。

Krüppel like factor 4（KLF4）是锌指转录因子，在多种生理活动包括生长、分化和正常组织稳态的维持中具有重要作用。近期研究表明 KLF4 在 PAH、动脉粥样硬化、冠脉介入后再狭窄及糖尿病等疾病中具有重要的血管稳态调节作用。KLF4 自身的功能受到多种化学修饰的调控，如泛素化、乙酰化和磷酸化等。亚硝基化是一氧化氮及其衍生物对蛋白质半胱氨酸巯基的氧化还原修饰，蛋白的亚硝基化广泛参与调控心血管系统功能和介导心血管疾病过程。本人研究发现氮化应激在内皮细胞中引起 KLF4 的亚硝基化修饰，利用液相色谱串联质谱确定 KLF4 第 437 位半胱氨酸是亚硝基化的主要位点。KLF4 的亚硝基化修饰通过抑制 KLF4 蛋白的核转位显著抑制其转录活性。氮化应激与缺氧环境密切相关，我们在缺氧诱导 PAH 大鼠模型中发现 KLF4 亚硝基化水平明显增加，核定位减少，同时 KLF4 下游靶基因转录活性明显抑制。此外，在内皮细胞中，PAH 致病因子 ET-1 诱导了 KLF4 蛋白亚硝基化修

饰，而这种修饰可以被 PAH 治疗药物内皮素受体拮抗剂 Bosentan 所逆转。小鼠离体肺动脉中 KLF4 的亚硝基化明显抑制其介导的血管舒张作用，参与 PAH 的发生发展(Redox Biology)。

上述系列研究针对肺动脉血管功能改变和血管重构过程，探讨了血管稳态核受体的在 PAH 中的作用和转录调控机制，取得了一系列创新性结果。研究不仅对 PAH 的发病机理和防治提供理论基础，也具有一定的临床转化潜能及应用价值。

关键词：转录因子，血管稳态，肺动脉高压，血管功能，转录调控

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C13 突触发育及小胶质细胞功能研究

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斑马鱼幼鱼的视网膜-视顶盖系统是经典的研究神经形态发育和感觉-运动转导的脊椎动物模型。我们应用此模型探究了神经联接（突触）的发育规律和小胶质细胞的生理功能。

突触是神经联接建立的部位，突触的定位和数量决定着全脑神经元之间的联接关系和联接权重，因此突触发育是全脑神经联接网络形成的基本和关键过程。为研究中枢神经系统突触的在体发育，我们应用 GAL4-UAS 系统建立了转基因斑马鱼品系，将融合 EGFP 的突触前蛋白 Synaptophysin 表达在视网膜神经节细胞（RGC）中，从而稳定标记视网膜-视顶盖突触的突触前位点。利用 GAL4-UAS 转基因的位置效应，我们发现即使在转基因中，也可以产生对单个到几个 RGC 嵌合标记的效果，这使得我们可以通过在体长时程成像，跨不同发育阶段地对单个 RGC 轴突上完整的突触前发育过程进行追踪。我们首先探究了突触的发育过程是否受到昼夜节律的调节。通过连续两个昼夜周期的较高时间分辨率的长时程成像，我们发现，发育早期突触数量的增长速率呈现白天快、夜晚慢的昼夜节律性，此节律主要由突触形成而非突触消除速率的昼夜差异造成，且受到下丘脑食欲素能神经系统的调节；损害生物钟或下丘脑系统，会影响突触在 RGC 轴突上的排布以及突触后视顶盖神经元感受野的精细化。这些研究结果为神经联接发育规律提供了系统维度的解析，也为生物钟调节发育过程提供了重要证据。

小胶质细胞是大脑中主要的免疫细胞。在生理状态下，它们通常处于“静息”状态，其分枝不断地向周围神经组织延伸和收缩。这种高度动态性的静息态小胶质细胞是否以及如何与周围神经元进行功能性交互并不清楚。通过对斑马鱼视顶盖的小胶质细胞形态和神经元 Ca^{2+} 活动同步进行长时程成像，我们发现神经元电活动可以掌舵静息态小胶质细胞分枝的朝向，促进它们与电活动高的神经元接触。反过来，这种静息态小胶质细胞对神经元的接触减少了被接触神经元的自发和视觉诱发电活动。这些研究结果揭示了神经元电活动对静息态小胶质

细胞分枝动态性的指导作用，并暗示了静息态小胶质细胞在健康大脑中调节神经元电活动稳态的功能。

综上，从神经细胞角度，我们发现了神经联接形成的昼夜节律性规律和神经电活动稳态的胶质细胞调节机制；从小胶质细胞角度，我们发现了小胶质细胞参与生理功能调节—神经元电活动稳态，这些发现为理解神经联接发育规律以及神经元和胶质细胞互作在大脑生理功能中的重要性提供了实验依据和理论基础。

关键词：斑马鱼，突触发生，小胶质细胞，神经元电活动稳态，生物钟，食欲素，视顶盖，长时程成像

Research on synaptic development and microglial cell function

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The larval zebrafish retinotectal system is a classic model for studying neural morphogenesis and sensorimotor transformation in vertebrates. We have applied this model to explore the developmental rules of neuronal connection (synapse) formation and physiological functions of microglia.

Synapses are the sites of neuronal connections, and the location and number of synapses determine the connection relationship and connection strength between neurons in the whole brain. Therefore, synapse development (synaptogenesis) is the basic and key process for the formation of the whole-brain neural connectome network. To study the development of central synapses in vivo, using the GAL4-UAS methodology, we established stable transgenic lines, which express the synaptic vesicle protein synaptophysin fused with EGFP in retinal ganglion cells (RGCs), to reliably label the presynaptic sites of retinotectal synapses. Taking advantage of the position-effect variegation of GAL4-UAS transgenes, we found that even in transgenic fish, only single to several RGCs can be labeled, which enables us to track the complete process of presynaptic development on single RGC axons across different developmental stages by in vivo long-term time-lapse imaging. We first explored whether the development of synapses is regulated by the circadian clock. Through continuous time-lapse imaging with relatively high temporal resolution for two circadian cycles, we found that the rate of increase in the number of synapses at early developmental stages showed a rhythm of faster in the day and slower at night. This rhythmicity arises primarily from the synapse formation rather than elimination and requires the

hypocretinergic neural system. Disruption of this synaptogenic rhythm, by impairing either the circadian clock or the hypocretinergic system, affects the arrangement of the retinotectal synapses on axon arbors and the refinement of the postsynaptic tectal neuron's receptive field. These results provide both a systemic mechanism for the development of neuronal connections, and important evidence for the circadian regulation of developmental processes.

Microglia are the primary immune cells in the brain. Under physiological conditions, they typically stay in a ‘‘resting’’ state, with ramified processes continuously extending to and retracting from surrounding neural tissues. Whether and how such highly dynamic resting microglia functionally interact with surrounding neurons are still unclear. Using in vivo time-lapse imaging of both microglial cell morphology and neuronal activity in the optic tectum of larval zebrafish, we found that neuronal activity steers resting microglial processes and facilitates their contact with highly active neurons. Reciprocally, such resting microglia-neuron contact reduces both spontaneous and visually evoked activities of contacted neurons. Our findings reveal an instructive role for the neuronal activity in resting microglial cell motility and suggest the function for microglia in the homeostatic regulation of neuronal activity in the healthy brain.

Taken together, from the perspective of neurons, we have found the circadian rhythm of neuronal connection formation and the microglial regulation of neuronal activity homeostasis; from the perspective of microglia, we have found that microglia participate in the physiological function regulation of neuronal activity homeostasis. These findings provide experimental evidence and theoretical basis for understanding the rules of neuronal connectivity development and the importance of the neuron-glia interactions in brain physiological functions.

Keywords: Zebrafish, Synaptogenesis, Microglia, Neuronal activity homeostasis, Circadian clock, Hypocretin/Orexin, Optic tectum, Time-lapse imaging

C14 系列微生理系统的构建及生理活性物质的纳米酶电化学传感测定

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微生理系统（microphysiological systems，MPS），也称为器官芯片（organs-on-a-chip），是指在体外构建三维（3D）人体器官或组织微环境，模拟其结构和生理功能特征。近十年来，MPS 发展十分迅速，在组织工程、再生医学、药物筛选、体外实验模型等研究领域已经广泛应用，为生物医学领域带来一场技术性革命。

巨噬细胞与成纤维细胞在皮肤伤口愈合的过程中有着非常重要的作用，研究它们的互作

对于探索伤口愈合机制和药物开发具有重要的意义。基于此研究目的，本课题组根据皮肤生理学或病理生理学特征，开展了系列多种细胞共培养芯片的研究。我们设计了双层式微流控芯片，采用空气阀将成纤维细胞分离，模拟创面愈合微环境，然后采用光刻技术制备的微通道将 M2 型巨噬细胞和成纤维细胞分离。微通道不允许细胞通过，只允许含有信号分子的溶液通过。利用该芯片我们研究了不同巨噬细胞在共培养体系中对成纤维细胞融合率的影响，以反映不同巨噬细胞在创面愈合中的作用，该研究为细胞共培养及互作的研究提供了新平台[1]。三维异质多细胞球体模型在伤口愈合增殖和重塑阶段的研究中具有重要的潜在价值。我们采用 NIH-3T3 成纤维细胞和 M2 型巨噬细胞，开发了一种坐滴式芯片来培养三维球体并模拟体外创面愈合阶段。借助表面张力和重力的偏移，固定式液滴阵列能够通过每个微孔的超疏水表面将细胞悬浮液形成球体，同时微孔底部的圆孔为球体提供足够的氧气。结果表明，NIH-3T3/M2 异质多细胞微球可在 9 天内形成并维持其生理活性。基于纳米抗体三维免疫染色法，分析了细胞的增殖和分化特征。结果发现，M2 型巨噬细胞能促进 NIH-3T3 成纤维细胞微球的良性分化。该研究为类器官培养提供了新方法和新技术 [2]。生理活性物质的精准、原位、快速测定对于微生理系统的构建以及其它生理学相关的研究至关重要。我们的早期研究实现了细菌生物膜的三维培养及电化学原位检测，为细菌生物膜的机制研究及相关抑制剂的筛选提供了新工具与新平台；[3]。近两年，我们开发了基于激光诱导石墨烯（LIG）的电化学传感芯片，结合自行研发的纳米酶 Au@CuO，实现了葡萄糖的快速测定，检测响应时间为 1.5 s，检测限（LOD）为 1.8 μM。检测线性范围为 0.005 ~ 5.0 mM，灵敏度为 1.124 $\times 10^{6}$ μA mM^{-1} cm^{-2}。该传感器具有良好的选择性和稳定性，6 周后仍保持 84.12%的活性 [4]。我们利用体内新冠病毒侵袭宿主细胞时 ACE2 与 S 蛋白的选择性识别机制，创新性的发明糖基化外囊泡样识别受体，并用于新冠病毒抗原的检测 [5]。通过分子克隆技术构建过表达 ACE2 的 HEK-293T 稳转细胞系，提取富含 ACE2 的生物膜，增强识别受体与 S 蛋白的结合亲和力和特异性捕获效率。再通过化学工程技术手段实现细胞膜的糖基化修饰，使其形成副结合位点，进一步增强识别受体与分析物的结合亲和力和选择性。该识别受体易于在磁性电极表面固定和释放，避免了传统生物传感界面构建需要多个步骤的弊端，提高了生物传感器的稳定性和可重复性。其响应时间为 20 min，检测限为 1 pg/mL，线性范围为 1 pg/mL ~ 1 ng/mL。神经化学物质和生殖激素的纳米酶电化学传感测定新方法和新技术正在开发中。

关键词：微生理系统，器官芯片，纳米酶，电化学传感器，生理活性物质

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Development of a series of microphysiological systems and nanoenzyme-based electrochemical sensing of physiologically active substances

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Microphysiological systems (MPS), also known as organs-on-a-chip, refer to the construction of three-dimensional (3D) human organ or tissue microenvironment in- vitro. It is a technological revolution in the field of biomedicine. In the past years, the development of MPS was rapid, and research topics have gradually shifted to tissue engineering, regenerative medicine, drug screening, and in-vitro experimental models. Based on the physiological or pathophysiological characteristics of the skin, our team has developed a chip for co-culture of multiple cells. In the process of skin wound healing, macrophages and fibroblasts play an important role, and study of their interactions is of great significance for exploring wound healing mechanisms and drug development. We designed a double-layers microfluidic chip and using air valves to separate fibroblasts. It can mimic the microenvironment of wound healing. Microchannels prepared by photolithography separated M2 macrophages from fibroblasts. The microchannels do not allow the passage of cells, only the solution containing signaling molecules. The microfluidic chip can be used to explore the confluence rate of fibroblasts in the co-culture system, so as to reflect the role of different macrophages in wound healing. The study provided a new platform for the study of cell co-cultures and cells interactions [1]. 3D heterogeneous multicellular spheroid models have important potential value in the study of proliferation and remodeling phases of wound healing. Based on NIH-3T3 fibroblasts and M2 macrophages, we developed a sessile drop chip for developing 3D spheroids and mimic wound healing stages in-vitro. By the aid of the offset of surface tension and gravity, the sessile drop array is able to transfer cell suspensions to spheroids via the superhydrophobic surface of each microwell. Meanwhile, each microwell has a cylinder hole at its bottom that provides adequate oxygen to the spheroid. It demonstrated that the NIH-3T3 fibroblast spheroid and the 3T3 fibroblast/M2-type macrophage heterotypic multicellular spheroid can form and maintain physiological activities within nine days. In order to further investigate the structure without destroying the entire spheroid, we reconstructed its 3D morphology using transparent processing technology and the Z-stack function of confocal microscopy. Additionally, a nano antibody-based 3D immunostaining assay was used to analyze the proliferation and differentiation characteristics of these cells. It found that M2-type macrophages were capable of

promoting the differentiation of 3T3 fibroblast spheroid. In this study, a novel, inexpensive platform was constructed for developing spheroids, as well as a 3D immunofluorescence method for investigating the macrophage-associated wound healing microenvironment [2].

Accurate, in-situ and rapid determination of physiologically active substances is crucial for the construction of MPS and other physiologically related research. Our previous research achieved 3D culture and in-situ detection of bacterial biofilms, providing new tools and platforms for the study of bacterial biofilm forming mechanisms and the screening of inhibitors [3]. In the past two years, we have developed an electrochemical sensing chip based on laser-induced graphene (LIG). Combined with the self-developed nanozyme Au@CuO, it was used for rapid glucose test. The response time was 1.5 s and the limit of detection (LOD) was 1.8 μM. The detection linear range was 0.005 ~ 5.0 mM, and the sensitivity was 1.124×10^6 μA mM^{-1} cm^{-2}. The sensor exhibited good selectivity and stability, maintaining 84.12% activity after 6 weeks [4]. In addition, we developed a glycosylated extracellular vesicle-like receptor (GlycoEVLR) for the rapid detection of virus antigens by mimicking the selective recognition mechanism of ACE2 and S protein [5]. We used molecular cloning technology to construct a HEK-293T cell line that overexpresses ACE2, and then extracted ACE2-rich cell membrane. It can enhance the binding affinity and specific capture efficiency of GlycoEVLR to the S protein. Then, chemical engineering techniques were used to achieve glycosylation modification of the cell membrane to form a secondary binding site, further enhancing the binding affinity and selectivity. The GlycoEVLR was easy to be fixed on and released from the surface of the magnetic electrode. It avoided multiple steps required to construct a traditional biosensing interface, and improving the stability and repeatability of the biosensor. At the same time, the method enables the electrodes to be reused, which can reduce costs. The response time was 20 min, the LOD was 1 pg/mL, and the linear range was 1 pg/mL ~ 1 ng/mL. New methods and technologies are being developed for nanoenzyme-based electrochemical sensing of neurotransmitters and reproductive hormones.

Keywords: Microphysiological systems (MPS), organs-on-a-chip, nanozymes, electrochemical sensors, physiologically active substances

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C15 Convergent adaptations counteracting aging and cancer in subterranean mammals

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Aging is a major risk factor for multiple diseases including cancer. Naturally long-lived and cancer-resistant animals provide powerful models to uncover novel anticancer mechanisms that are potentially applicable to humans. The blind mole rat (BMR, *Spalax*) is a group of subterranean rodent species of the Muroidea superfamily, characterized by long maximum lifespan (> 21 years) and resistance to cancer. We recently reported the mechanism of cancer resistance of the BMR. The cells and tissues of BMR have naturally weak DNMT1. Rapidly proliferating cells in BMR lose global DNA methylation, which derepresses retrotransposons. Activated retrotransposons form RNA/DNA hybrids in the cytoplasm and trigger cGAS-STING-interferon pathway to eliminate the overproliferated cells. Similar mechanism also works against tumorigenesis in mice

and human cancer cells. We propose that retrotransposons are a double-edged sword, acting as a tumor suppressor in young age but later contributing to inflammaging.

We hypothesize that some anti-cancer mechanisms may have convergently evolved in subterranean mammals during adaptation to underground habitats. It has been reported that the cells and tissues of the subterranean naked mole rat (NMR, *Heterocephalus glaber*) secreted large amount of high-molecular-mass hyaluronic acid (HMM-HA), which contributed to its cancer resistance. But why HMM-HA has evolved in the NMR was not clear. We found that HMM-HA is secreted by six phylogenetically distant species of subterranean mammals, including NMR, BMR, Damaraland mole rat (DMR, *Fukomys damarensis*), Eastern mole (EM, *Scalopus aquaticus*), star-nosed mole (SNM, *Condylura cristata*), and Transcaucasian mole vole (TMV, *Ellobius lutescens*). The HMM-HA from these species resulted from different expression and mutations of enzymes involved in HA synthesis and degradation. We propose that HMM-HA has coevolved with subterranean lifestyle by providing flexible skins needed for life in narrow underground tunnels, and by protecting from hypoxia-induced oxidative stress. This adaptation was coopted to contribute to cancer resistance and longevity of subterranean species.

Furthermore, we found that in human cancer cells, retrotransposons were repressed by tumoral hypoxia, which may explain the malignancy of solid tumor resulted from hypoxic microenvironment. However, in the NMR and plateau zokor (*Myospalax baileyi*), another subterranean rodent species in China, retrotransposons including LINE1 and SINE B1 were activated by hypoxia. This may contribute to potential cancer resistance of the NMR and plateau zokor.

It has been proposed that species living in protected environments tend to live longer. The currently known long-lived species include NMRs, BMRs, whales, elephants, and bats. Whales and elephants have large body sizes, protecting them from nonhuman predators. Bats' flight capability warrants them to escape from predators. NMRs and BMRs live in subterranean tunnels, exposing to far fewer predators than above ground rodents. Therefore, it is interesting to research mechanisms of longevity and cancer resistance in a broad spectrum of subterranean species.

Overall, our study points to subterranean species as a natural model of aging and cancer research. We propose that cancer resistance may be a common phenotype shared by subterranean mammals, and exploring a wider range of non-model subterranean mammals will reveal numerous antiaging and anticancer mechanisms that are potentially applicable to humans.

Keywords: Aging, Cancer, Subterranean species, Retrotransposons, Hyaluronic acid

C16 小胶质细胞乳酸代谢紊乱在阿尔茨海默病中的作用与机制

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阿尔茨海默病（Alzheimer's disease, AD）是老年人群中最为常见的神经退行性疾病，目前发病机制不清楚，临床上缺乏安全有效的治疗药物。小胶质细胞激活及其介导的神经炎症是 AD 重要的病理特征，在炎性激活的过程中，小胶质细胞会发生代谢重编程，从线粒体氧化磷酸化（OXPHOS）向无氧糖酵解转变，但具体的分子调控机制尚不清楚。我们发现糖酵解终产物乳酸及其介导的组蛋白乳酸化在 AD 模型小鼠和 AD 患者脑中显著升高，其中 H4K12la 在 Aβ 斑块周围的小胶质细胞中特异性升高。进一步研究发现，H4K12la 可以结合到小胶质细胞 PKM2、LDHA 等糖酵解相关基因的启动子区，促进这些基因的转录激活，进而形成糖酵解/H4K12la/PKM2 正向反馈调控循环，该循环加剧了小胶质细胞的代谢紊乱和神经炎症。通过特异靶向小胶质细胞 PKM2 破坏该正向反馈调控循环，可以恢复小胶质细胞的代谢与功能稳态，改善 AD 的认知和病理。该工作揭示了小胶质细胞代谢紊乱驱动 AD 发生发展的表观遗传调控机制，阐明了靶向调控糖酵解/H4K12la/PKM2 正向反馈循环干预 AD 病理进程的作用机理，为临床干预 AD 提供了理论基础和治疗靶点。

根据上述研究发现，我们利用前期构建的天然小分子化合物库，靶向筛选能够重编程小胶质细胞代谢方式的小分子。结果发现，黄酮类小分子化合物—芦丁钠能够显著重编程炎性激活小胶质细胞的能量代谢方式，使小胶质细胞从无氧糖酵解向 OXPHOS 转变，促进小胶质细胞 ATP 产生，提高小胶质细胞对 Aβ 的吞噬和清除功能。同时，我们在不同的 AD 动物模型上（APP/PS1 和 5XFAD）口服给与芦丁钠，结果发现芦丁钠能够显著提高 AD 模型小鼠的认知功能，减轻脑中的 Aβ 斑块沉积、胶质细胞的异常激活以及神经炎症相关因子的表达，对 AD 认知和相关病理具有明显的改善作用，为 AD 的防治提供潜在候选药物。

此外，我们还发现非药物干预方式—间歇性禁食可以显著改善 AD 模型小鼠小胶质细胞的乳酸代谢紊乱现象，进而缓解 AD 模型小鼠的认知功能障碍和病理进程。进一步利用宏基因组学和代谢组学联合分析，我们发现肠道菌群-代谢物-脑轴在间歇性禁食干预 AD 过程中发挥重要作用，其中肌氨酸和二甲基甘氨酸在间歇性禁食处理的 AD 小鼠盲肠内容物和血清中显著升高。通过腹腔注射连续 3 个月给与 AD 模型小鼠肌氨酸和二甲基甘氨酸后，发现补充肌氨酸或二甲基甘氨酸均可以模拟间歇性禁食改善 AD 小鼠认知和病理的作用效果，提示间歇性禁食可能通过重塑肠道菌群稳态及其相关代谢产物水平，进而改善小胶质细胞的代谢紊乱和 AD 病理进程。

综上，我们的系列研究结果表明，小胶质细胞乳酸代谢紊乱可能是驱动 AD 发生发展的

重要因素，改善小胶质细胞乳酸代谢紊乱可能是防治 AD 的新策略。

关键词：阿尔茨海默病，小胶质细胞，乳酸代谢，乳酸化，代谢重编程，神经炎症，芦丁钠，间歇性禁食

Microglial lactate metabolism disorder in Alzheimer's disease

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Alzheimer's disease (AD) is the most common form of neurodegenerative disease without effective clinical treatment due to the unknown pathogenesis. The pro-inflammatory activation of microglia is a hallmark of AD, and this process involves a switch from oxidative phosphorylation (OXPHOS) toward glycolysis. Here, we show how a positive feedback loop in microglia drives AD pathogenesis, and we demonstrate that inhibiting this cycle in microglia can ameliorate Ab burden and cognitive deficits in an AD mouse model (5XFAD). After first detecting elevated histone lactylation in brain samples from both 5XFAD mice and individuals with AD, we observed that H4K12la levels are elevated in Aβ plaque-adjacent microglia. This lactate-dependent histone modification is enriched at the promoters of glycolytic genes and activates transcription, thereby increasing glycolytic activity. Ultimately, the glycolysis/H4K12la/PKM2 positive feedback loop exacerbates microglial dysfunction in AD. Pharmacologic inhibition of PKM2 attenuated microglial activation, and microglia-specific ablation of *Pkm2* improved spatial learning and memory in AD mice.

Based on our above findings, we used the natural small molecule compound library to screen candidate(s) that can reprogram the metabolism of microglia. We identified sodium rutin (NaR) as a potent candidate that could promote a metabolic switch from anaerobic glycolysis to mitochondrial OXPHOS in pro-inflammatory activation of microglia, which could provide microglia with sufficient energy (ATP) for Aβ clearance. Thus, NaR administration could attenuate neuroinflammation and enhance mitochondrial OXPHOS and microglia-mediated Aβ clearance, ameliorating synaptic plasticity impairment and eventually reversing spatial learning and memory deficits in AD mice.

Additionally, we identified a non-drug treatment strategy—intermittent fasting (IF) could improve microglial lactate metabolism disorder, thus ameliorated cognitive functions and AD-like pathology in 5XFAD mice. IF alters gut microbial composition with a significant enrichment in probiotics such as *Lactobacillus*. The changes in the composition of the gut microbiota affect

metabolic activities and metabolite production. Metabolomic profiling analysis of cecal contents revealed IF leads to a decreased carbohydrate metabolism and an increased abundance in amino acids (for example, sarcosine and dimethylglycine). Interestingly, we found that the administration of IF-elevated sarcosine or dimethylglycine mimics the protective effects of IF in 5XFAD mice, including the amelioration of cognitive decline, amyloid-β (Aβ) burden and glial overactivation.

In summary, our series studies demonstrate that microglial lactate metabolism disorder might drive the development and progression of AD, and improving lactate metabolism disorder of microglia may be a potential therapeutic approach for the treatment of AD.

Keywords: Alzheimer's disease, Microglia, Lactate metabolism, Lactylation, Metabolic reprogramming, Neuroinflammation, Sodium rutin, Intermittent fasting

C17 星形胶质细胞在记忆维持中的生理病理作用及替代干预机制

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星形胶质细胞通过其胞内"钙活动"不仅可在微观尺度调控神经突触形成和可塑性，也可在宏观尺度调控群体神经元活动。星形胶质细胞对神经环路进行多尺度调控的这一特性，决定了其在记忆维持过程中可能起到重要的生理和病理作用。

实现自由清醒动物星形胶质细胞钙活动记录是解析其在大脑认知功能中生理作用的关键，但长期以来缺乏稳定且特异地记录其钙活动的技术手段。以上技术主要面临：1.钙信号运动噪声大；2.长期慢性记录难；3.细胞特异性低等难点。我们通过建立自由清醒动物星形胶质细胞钙活动光纤和双光子活体成像等多尺度功能记录技术，实时记录了皮层星形胶质细胞在记忆获取，维持及提取过程中的钙活动。将光纤记录技术与星形胶质细胞特异标记的基因编码钙指示剂（Genetically encoded calcium indicators，GECIs）相结合，实现了自由清醒小鼠大脑星形胶质细胞特异性钙活动记录。该工作为实现自由清醒动物大脑皮层及皮层下部位，稳定、长期、特异地记录星形胶质细胞钙活动提供了有力的技术方法。

采用以上自主研发的自由清醒动物星形胶质细胞钙活动光纤记录技术及活体双光子成像技术，以恐惧记忆为模型，对记忆形成和维持过程中星形胶质细胞钙活动变化特征进行了实时解析。首先，我们在大脑皮层星形胶质细胞中发现了尼古丁受体介导的学习诱导钙信号。在活体单细胞尺度和自由清醒动物中，我们发现恐惧学习训练过程可逐步诱导表达尼古丁受体的大脑皮层星形胶质细胞产生学习相关钙信号。阻断或敲除尼古丁受体，此学习相关钙信号则消失。其次，研究显示大脑皮层星形胶质细胞学习相关钙信号与恐惧记忆行为同步维持

或消退。人为消除动物恐惧记忆行为，大脑皮层星形胶质细胞学习相关钙信号也出现同步降低或消失。最后，我们发现大脑皮层星形胶质细胞尼古丁受体介导恐惧记忆行为维持过程。实验结果表明敲除小鼠大脑皮层星形胶质细胞尼古丁受体可明显降低其恐惧记忆行为。 此工作直接证实了恐惧学习过程可诱导星形胶质细胞产生新的钙信号，该信号由尼古丁受体介导，是恐惧记忆维持的重要细胞机制。

此外，我们结合高分辨率活体双光子钙成像技术和星形胶质细胞特异标记的基因编码钙指示剂（GCaMP6f）技术，对衰老过程中星形胶质细胞各亚细胞结构的“钙活动”变化进行了细致研究。结果显示，衰老过程可改变大脑星形胶质细胞与周围环境相互交流的“语言”---“胞内钙活动”。其次，研究者将胶质前体细胞移植入小鼠大脑皮层，进而研究移植星形胶质细胞的形态和功能整合，及其对老年动物感知功能的影响。结果显示，移植星形胶质细胞可在成年和老年动物脑内正常存活、迁移，并整合入宿主动物大脑神经网络。更令人惊喜的是，移植星形胶质细胞可在老年动物脑内长期保持年轻健康形态，并改善老年动物感知能力。

关键词：星形胶质细胞，基因编码钙指示剂，钙成像，学习记忆，移植

C18 胃肠稳态与机体糖脂代谢紊乱及相关疾病

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慢性代谢性疾病如肥胖和糖尿病及相关肿瘤，与肠道细菌组成改变和肠道黏膜完整性缺陷有关。我们的前期研究以及文献报道发现肠道菌群多样性下降和革兰氏阳性厚壁菌门的细菌增加是糖脂代谢紊乱的关键因素。

肠道中革兰氏阳性细菌的细胞壁成分肽聚糖（PGN）入血后引起循环系统和脂肪组织慢性炎症，PGN 在胰岛素抵抗和代谢性炎症中发挥重要作用。我们的研究发现 PGN 在饮食诱导的肥胖小鼠中显著升高，PGN 处理使小鼠在寒冷暴露下产热减少、体温降低。PGN 抑制瘦小鼠受寒冷诱导的皮下脂肪组织米色化，表现为脂肪细胞体积增大和 UCP1 表达降低。这种改变同时伴随着皮下白色脂肪组织中 F4/80 阳性巨噬细胞和细胞因子增加。PGN 处理巨噬细胞的条件培养基转移给前脂肪细胞之后显著抑制其米色化。从 *AdipoQ-Tlr2*$^{-/-}$（*Adiponectin-cre×Tlr2-flox*）小鼠的皮下脂肪组织中分离敲除 TLR2 的 SVF 细胞，PGN 不影响特异性敲除 TLR2 的 SVF 细胞米色化。本研究表明**PGN 通过 TLR2 抑制脂肪组织米色化，减少机体产热。干预 PGN-TLR2 能为肥胖治疗提供潜在策略**（***Acta Pharm Sin B* 2022**）。

母体菌群是新生儿微生物群定植过程中最重要的菌群来源。间断禁食是否会改变后代肠道菌群稳态，目前尚不清楚。我们的研究表明，**母体长期间断禁食导致子代代谢障碍可能是通过减少有益的菌群、破坏肠道屏障实现的**（***COMMUN BIOL* 2023**）。怀孕前 12 周的隔日间断禁

食减少其子代成年后有益的肠道菌群，如肠道乳杆菌（*L. intestinalis*）；抑制子代肠道紧密连接蛋白 Claudin-1 的表达，增加循环系统 LPS 和炎症因子导致肠道屏障受损；子代小肠绒毛高度显著缩短。补充肠道乳杆菌或与健康小鼠同笼饲养恢复了肠壁功能和代谢表型。母体间断禁食同时还抑制子代肝脏 DNA 甲基转移酶的表达。DNA 甲基化修饰与 mTORC1 信号通路相关的分子显著改变，导致 mTORC1 信号的抑制。过表达 S6K1 激活肝脏 mTORC1 信号逆转了间断禁食子代的代谢损害。**长期的孕前间断禁食增加子代成年后肝脏脂肪变性、脂肪堆积和糖代谢恶化的风险，这是通过抑制 DNA 甲基化依赖的肝脏 mTORC1 信号实现的（*FASEB J* 2023）。**

Roux-en-Y 胃旁路手术（Roux-en-Y gastric bypass，RYGB）因其能持久地改善体重和血糖而广泛用于治疗肥胖和 2 型糖尿病，术后还能恢复紊乱的肠道菌群。我们的研究发现 RYGB 手术不仅改善糖脂代谢，还可预防胰腺腺泡细胞癌的发生。*Ngn3-Tsc1*$^{-/-}$（*Neurogenin3-cre*×*Tsc1-flox*）小鼠胰腺特异性缺失 TSC1 基因可诱导胰腺腺泡细胞癌的发生。假手术 *Ngn3-Tsc1*$^{-/-}$小鼠 300 日龄肿瘤发生率 96.7±3.35%，存活率 67.0±1.4%，肝转移率 69.7±9.7%，肾转移率 44.3±8.01%。在 16 周龄进行 RYGB 的动物 300 日龄时全部存活，无肝肾转移。RYGB 显著减弱胰腺腺泡细胞癌中 mTORC1 信号的激活并增加抑癌基因 p21、p27 和 p53 表达。本研究表明**减肥手术可能通过抑制胰腺 mTORC1 信号来防治胰腺腺泡细胞癌。显示了 RYGB 对代谢障碍和癌症的干预前景（*Nat Commun* 2018）**。

关键词： Roux-en-Y 胃旁路手术；肽聚糖；脂肪组织米色化；间断禁食；mTORC1

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C19 前列腺素 E_2 系统与血管结构和功能稳态调控

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血管功能和结构稳态失衡与重构是包括主动脉瘤/夹层、高血压及血管再狭窄等重大心血管疾病的病生理基础。多不饱和脂肪酸花生四烯酸代谢产物前列腺素 E_2（PGE_2）通过 4 种 G 蛋白偶联受体 EP1-4 发挥其功能作用。大量证据表明 PGE_2 系统与血管结构和功能稳态的维持有密切关系。过去十年，我们对 PGE_2 受体 EP4 在主动脉夹层、高血压及血管再狭窄中的作用及机制做了大量研究，包括：

1）、EP4 与主动脉夹层：我们发现接受慢性持续 Ang II 处理的血管平滑肌细胞特异性 EP4 基因敲除小鼠频繁发生主动脉夹层，伴有严重的弹性纤维降解和血管平滑肌细胞去分化。进一步研究表明，敲除血管平滑肌细胞 EP4 可增加血管炎症、上调基质金属蛋白酶-2/9 水平并促进活性氧产生。机制研究表明，血管平滑肌细胞 EP4 通过抑制 MCP-1 和 NOX1 表达而改善血管炎症及氧化应激，并通过促进血清反应因子（SRF）转录活性维持血管平滑肌收缩

表型。本研究阐明了血管平滑肌细胞 EP4 对血管结构稳态维持的重要作用，提示 EP4 可能是主动脉夹层的潜在治疗靶点（PNAS，2019）。

2）、EP4 与高血压：我们发现，血管平滑肌细胞特异性敲除 EP4 的小鼠在基础和 Ang II 缓释条件下均表现出更高的血压，而在血管平滑肌过表达人 EP4 则可改善 Ang II 诱导的高血压。离体和体外研究表明，血管平滑肌细胞 EP4 基因敲除通过增加细胞内钙离子而促进 Ang II 引起的阻力血管收缩反应。此外，血管内皮细胞特异性敲除 EP4 同样引起小鼠血压升高，而血管内皮细胞特异性过表达人 EP4 有效降低小鼠血压。进一步研究表明，一氧化氮合成抑制剂 L-NAME 可消除这种血压差异；其机制是 EP4 通过 AMPK 通路促进 eNOS 的 Ser1177 位点磷酸化继而激活 eNOS。上述结果表明 EP4 可能作为一种临床防治高血压的新靶点（PNAS，2019；JCI Insight，2020；生理学报，2021）。

3）、EP4 与血管再狭窄：研究表明，血管平滑肌细胞特异性敲除 EP4 可减轻股动脉导丝拉伤及颈动脉结扎诱导的血管内膜新生；相反，特异性过表达人 EP4 可加重血管内膜的形成。机制研究表明，EP4 通过 cAMP/PKA/ mTORC1/rpS6 通路在翻译水平调控细胞外基质蛋白 Tenascin C 的表达，从而控制血管平滑肌细胞的增殖和迁移，最终参与血管再狭窄的发生发展。该研究为以 EP4 为靶点的血管再狭窄的防治提供了实验依据（Cells，2022）。

综上，我们的系列研究集中阐释了血管组织 EP4 在血管结构和功能稳态中的作用，阐明了 EP4 在主动脉夹层、高血压和血管再狭窄中的作用及机制，为防治上述重大心血管疾病提供了新的靶点。

关键词：前列腺素 E_2，EP4 受体，主动脉瘤/夹层，高血压，血管再狭窄

C20 脂滴蛋白 17β-HSD13：肝脏脂代谢稳态的重要调控因子

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脂滴蛋白的异常蓄积是 NAFLD 发生的重要病理基础。我们前期通过分离纯化正常肝脏和 NAFLD 病人肝脏脂滴，鉴定了一系列人类脂肪肝中表达显著改变的脂滴相关蛋白，并率先发现 17β-HSD13 参与了 NAFLD 的发生发展过程，是 NAFLD 的重要致病因子。随后我们对其展开了系统的研究，并获得如下重要成果：

1、17β-HSD13 促进脂肪肝的发生发展。我们发现，17β-HSD13 特异性高表达于人和小鼠肝脏，并选择性的定位于脂滴表面。在正常 C57Bl/6 小鼠肝脏过表达重组人 17β-HSD13 腺病毒可诱导典型小鼠脂肪肝表型，并显著上调脂质合成关键蛋白 SREBP-1c 和 FAS 的表达水平，上述结果提示 17β-HSD13 可能通过上调 SREBP-1c 的活性从而促进脂肪肝的发生与发展，靶向 17β-HSD13 的药物有望成为 NAFLD 治疗的新靶点（*Proc Natl Acad Sci U S A.*, 2014；*Mol Cell Endo.,* 2019；发明专利 CN201310503889.0）。

2、17β-HSD13 是 SREBP-1 的直接靶基因。LXR/SREBP-1c 通路是调控肝脏脂质代谢的关键通路，在 NAFLD 中处于激活状态。我们的研究发现 LXR 泛激动剂 T0901317 可以通过 LXRα 依赖的机制上调 17β-HSD13 的表达从而促进肝脂滴蓄积，而在细胞上沉默 17β-HSD13 可以显著减轻油酸诱导的肝细胞脂肪变。该研究不仅为开发针对 17β-HSD13 的 NAFLD 治疗药物提供了实验基础，也阐明了 LXR 激动剂导致肝脏脂质沉积的可能机制，为联合靶向 LXR 和 17β-HSD13 治疗 NAFLD 提供了理论基础（*Am J Physiol Endocrinol Metab.*，2017）。

3、17β-HSD13 翻译后修饰在肝脏脂滴代谢稳态维持中发挥重要作用。我们发现 17β-HSD13 蛋白在不同物种中存在一个高度保守的 Ser33 PKA 磷酸化位点并可被 PKA 磷酸化；机制研究证实，17β-HSD13 是一个新的 PKA 磷酸化底物，其 Ser33 位点可被 PKA 磷酸化。该位点的失活（S33A knock-in）的小鼠表现为显著的脂肪肝表型，伴随肝脏甘油三酯显著增加，血 ALT 和 AST 的明显升高、血胰岛素水平的增加和血游离脂肪酸的降低。机制研究发现 17β-HSD13 可以结合肝细胞脂滴水解关键因子 ATGL，而 S33A 竞争性阻断了 ATGL 和 CGI-58 的结合，进而抑制了 ATGL 酶活性，导致脂滴水解障碍和脂滴的大量蓄积。此外，S33A 小鼠显著加剧了高脂诱导的 NASH 进程和肝功能损伤。进一步研究发现，FDA 批准的治疗哮喘的药物瑞普特罗（β2 受体激动剂）可靶向磷酸化 17β-HSD13 并显著抑制小鼠 NAFLD 的进展，提示靶向 17β-HSD13 Ser33 磷酸化可能是干预 NAFLD 的一种新的手段（*Nat commun..*, 2022; 发明专利 CN201710342106.3）。

综上所述，17β-HSD13 因其肝脏表达的特异性和肝脂滴代谢的重要性使其成为一个非常有前景的代谢病治疗靶点。目前，国内外多个大规模的人群研究中已证实 17β-HSD13 的一个常见单核苷酸位点多态性（SNP）-rs72613567 与人群中的慢性肝病导致的肝损伤负相关。基于小核苷酸的 si-HSD17B13 药物Ⅰ/Ⅱ临床试验结果，人体内沉默 17β-HSD13 在脂肪肝病人展示出优良的降 ALT 和 AST 的效果和极小的副作用，提示 17β-HSD13 是一个有前景的脂肪肝治疗靶点。目前 17β-HSD13 的细胞生物学功能和酶学底物尚不清楚，对其结构的解析和生化功能的深入了解将为药物研发提供新的方向。

关键词：17β-HSD13，脂滴，非酒精性脂肪肝，糖脂代谢

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C21 代谢手术改善机体代谢内分泌及生殖内分泌紊乱的相关研究

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代谢紊乱性疾病严重威胁人类健康，不仅缩短患者预期寿命，降低患者生活品质，还是

多种其他疾病的发病基础，尽管已有的药物可以针对单一代谢紊乱进行管理,但复杂顽固性代谢紊乱并没有良好的综合治疗手段。代谢手术最早被欧美国家临床用于治疗肥胖，至今已在全球普遍应用于肥胖、T2DM 的治疗，我国亦有多家三甲医院大力开展及应用。本人近些年的研究主要围绕在应用小鼠动物模型模拟人类代谢性疾病，并通过对动物模型实施胃旁路手术等代谢手术，验证手术改善效果并研究其作用机制研究，以期找出代谢手术发挥作用的靶点，针对靶点进行干预，发现新的药物，以期不需要手术就可以获得胃旁路手术对代谢性疾病的综合治疗效果，最终实现“药物性胃旁路手术”。系列论文包括以下方面：

1. 成功建立显微镜下胃旁路手术（RYGB）小鼠模型，并创建新型小鼠胃旁路手术：食管-十二指肠胃旁路手术(EDGB)，通过与小鼠经典胃旁路手术 RYGB 对照研究，揭示胃肠激素 Nesfatin-1 在胃旁路手术改善糖脂代谢中的关键作用，有力佐证了“胃中心学说”。

2. 发现胃旁路手术对胰腺癌的防治作用，创新性提出并验证胃旁路手术应用于癌症预防及治疗的可能性，为癌症的病因研究及治疗方式的探索提供新思路。

3.将胃旁路手术对代谢异常疾病的机制研究拓展到生殖内分泌领域，从胃肠激素和肠道菌群两方面入手，开展胃肠—生殖轴的研究，探索代谢手术改善代谢紊乱和生殖紊乱的作用及机制。

胃旷置性代谢性手术可以阻止必然会发生的癌症，可以在不减少进食量的同时有效改善胰岛素抵抗、控制血糖血脂，并且 RYGB 胃旁路手术及其上调的胃肠激素 Nesfatin-1 能够改善高脂及高雄激素所致小鼠 PCOS、改善高脂小鼠睾丸生精功能的作用，那么，代谢手术所展现的胃中心学说将打开一个探究胃肠—生殖轴的良好领域。对其作用机制及靶点的研究，可筛选出“药物性胃旁路手术”的药物，达到与代谢手术治愈代谢异常疾病的相同目的。

因此，本人在前期研究的基础上，跨领域提出代谢手术对代谢障碍引起的男女性生殖障碍有改善作用，利用多囊卵巢综合征及肥胖 2 型糖尿病伴有生精功能障碍小鼠模型，通过代谢手术进行干预，研究代谢手术调控代谢内分泌及生殖内分泌的作用，并进一步探讨其深入机制，为临床预防和治疗生育障碍提供新的策略。

关键词：代谢手术、代谢内分泌紊乱、生殖内分泌紊乱；

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Study on the improvement of metabolic endocrine and reproductive endocrine disorders by metabolic surgery

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Abstract

Disruptive disease poses a great threat to human health, short life expectancy of patients with short stature, declining patient quality of life, various underlying causes of disease, and many other morbid causes of disease. A good comprehensive treatment. Treatment for obesity in the first European countries, and now universally applied for obesity, T2DM treatment, we have developed a large number of three-tier hospitals in the country. In recent years, he has been conducting major research on animal models of rats for human generational diseases, and has also conducted gastrointestinal surgery on animal models. Initiating point, point-to-point progressing problem, innovative drug, non-essential gastrointestinal surgery available for alternative disease comprehensive treatment effect, the latest practical "physical gastrointestinal surgery". Series of comprehensive theories below:

1. Successful RYGB gastrointestinal tract surgery small mouse model, jointly constructed new mouse gastrointestinal tract surgery: esophageal tube-twelve finger gastrointestinal tract surgery EDGB, through-and-through small rat gastrointestinal tract surgery RYGB comparative study, showing Gastrointestinal stimulant Nesfatin-1 is effective in improving glycogen metabolism in gastrointestinal tract surgery, and has been shown to be a powerful "stomach-centered study."

2. Developed gastrointestinal therapy for prevention of adenocarcinoma, presenting the novelty and proving the possibility of gastrointestinal therapy application for cancer prevention and treatment, providing a new way to research the etiology of cancer and to explore the therapeutic modalities.

3. Exploring the reproductive endocrine area, access to the gastrointestinal tract bacteria complex from the gastrointestinal tract, development of gastrointestinal-reproductive pathway research, exploratory genetic surgery improvement, reproductive disorder Disruptive effects and mechanisms.

Gastric replacement surgery is possible, but it is possible to prevent inevitably occurring

cancers, but it is possible to reduce the amount of food intake and simultaneously improve insulin resistance, control blood sugar and lipids, and RYGB gastrointestinal surgery and improve gastrointestinal hypertension Nesfatin-1 ability. High-fat and high-fat mouse PCOS, improvement of high-fat mouse testicles vitality function, China, replacement surgery to expand the study of the stomach center, explore the gastrointestinal tract-good area of the reproductive system. For the study of its mechanism of action and its purpose, it is possible to select "physical gastrointestinal surgery" drug, which has a similar purpose to the treatment of abnormal diseases.

Due to this, based on research during my early years, I submitted a cross-regional therapeutic procedure to improve male-female reproductive disorders caused by dysregulation. With the progress of the replacement therapy, the research replacement therapy controls the effects of endocrine and reproductive endocrinology, along with a step-by-step exploration of its in-depth mechanism, providing a new strategy for the prevention and treatment of growth disorders.

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C22 TIP60 在急慢性应激反应中的调节作用

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基因和环境是精神疾病的常见影响因素，环境（应激刺激）因素异常所导致的应激障碍在新冠期间引起研究热潮。慢性应激对认知和情绪的损伤为大家所熟知，病理机制尚不完全清楚。急性应激（单次刺激）对于机体行为带来的影响是多方面的，与个体暴露在急性应激环境下的时间相关联。不同应激刺激对动物行为影响不一，此处我们首先使用慢性应激因子建立时间梯度的急性束缚应激模型，以评估不同时间的单次束缚应激刺激对动物行为的影响。结果发现，2 小时（2h）急性束缚应激（Acute restraint stress, ARS）合并 30 分钟应激后休息，增强小鼠在面对负面刺激（电击足底，冷水游泳和悬尾）时的逃跑行为，对个体自主探索行为无影响。应用 2h/日的束缚应激，持续 21 日，以建立慢性束缚应激（Chronic restraint stress, CRS）模型，发现 CRS 可诱发显著的抑郁行为和认知损害，伴随突触分子的转录抑制。

广谱的组蛋白去乙酰化酶（Histone deacetylase，HDAC）抑制剂在动物实验中被证实可

以缓解抑郁发生。然而，大多数 HDAC 抑制剂对特定 HDAC 亚型的选择性很低，限制了其临床应用。Tat-interacting 蛋白 60（TIP60）作为组蛋白乙酰转移酶的一种，与 HDAC 共同维持着细胞乙酰化水平的平衡，TIP60 是否可为抗抑郁的潜在靶点？TIP60 作为核受体的辅助调节因子，调节基因转录进程，对肿瘤和阿尔兹海默症的发生具有一定的抑制作用，但在应激反应中的作用尚未见报道。

我们首先检测了 ARS 小鼠海马 TIP60 的表达，发现 2h-ARS 显著上调 TIP60 水平，伴随突触分子（PSD95、NR2B 和 NR1 等）基因转录的激活；应用 TIP60 抑制剂 MG149 可阻断 2h-ARS 对转录和行为的易化作用。随后我们发现 CRS 诱发转录抑制和行为损伤时显著下调海马 TIP60 蛋白表达，应用慢病毒提前过表达 TIP60 可激活突触分子基因转录，缓解 CRS 的损害效应，呈现抑郁行为和认知功能的改善。此外，我们通过体外实验发现 TIP60 亦同向调节突触分子蛋白和 mRNA 的表达，此过程可被 MG149 所阻断。

TIP60 作为核受体的调节因子，需激活相应的核受体以调节基因转录。我们通过体外干预 TIP60 表达，发现 TIP60 可同向改变核受体 PPARγ 的表达，TIP60 对突触分子转录的调控需要与 PPARγ 形成复合体而发挥作用。相应的，体内实验发现 PPARγ 拮抗剂 GW9662 腹腔应用，可阻断过表达 TIP60 对 CRS 损伤效应的保护作用。综上所述，我们认为 TIP60 是一个新的且有力的急性应激反应调节因子，CRS 诱发 TIP60 表达缺失和过表达 TIP60 可对抗 CRS 损伤效应进一步表明 TIP60 可能为抗抑郁药物研发的新颖靶点。

关键词：急性应激，慢性应激，抑郁，组蛋白乙酰转移酶，基因转录

第十五届全国青年生理学工作者学术会议

The 15th Young Physiologist Symposium

Y1 心肌细胞特异性的体内基因递送

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目的：腺相关病毒（AAV）是 FDA 批准的体内基因治疗载体，在心血管研究中被广泛应用。AAV 血清型 9（AAV9）可递送心脏肌钙蛋白 T (Tnnt2, 又称 cTNT)启动子驱动的转基因，通常被认为在体内心肌细胞中特异性表达。然而，这种 AAV9-Tnnt2 系统的组织特异性尚未在心血管研究中用高灵敏度的检测手段进行严格评估。这个问题给应用 AAV9-Tnnt2

递送系统的心血管研究带来技术隐患。本研究的目的是对 AAV9-Tnnt2 体内基因递送系统的组织特异性进行更严格的评估和优化。

方法：本研究利用 Cre-LoxP、CRISPR/Cas9 和腺嘌呤单碱基编辑器（ABE）等高灵敏度的 DNA 标记技术在小鼠体内评估 AAV9-Tnnt2 系统的组织特异性。通过改造 AAV9-Tnnt2 系统携带转基因的 3'UTR，本研究提高心肌基因递送的组织特异性。

结果：传统的 GFP 报告基因检测手段显示 AAV9-Tnnt2 系统具有心肌细胞特异性，然而 Cre-LoxP、CRISPR/Cas9 和腺嘌呤单碱基编辑器（ABE）等高灵敏度的 DNA 标记技术能检测到 AAV9-Tnnt2 系统在约 50%的肝脏细胞中存在基因表达泄露情况。尤其在 CRISPR/Cas9 的应用中，肝脏泄露的基因编辑导致 AAV 的 DNA 整合到肝脏基因组中，带来额外安全隐患。本研究向 AAV9-Tnnt2 递送的转基因的 3'UTR 中引入 miR-122 的靶序列（miR122TS），减少了超过 90%的肝脏泄露情况，同时维持了 AAV9-Tnnt2 系统在心脏中的正常表达。在 CRISPR/Cas9 相关应用中，miR122TS 避免了 AAV DNA 定向整合肝脏基因组的情况。RNA-Seq 分析显示 miR122TS 显著降低了 AAV9-Tnnt2 系统递送基因在肝脏中的表达，同时基本不造成内源基因表达的变化。

结论：AAV9-Tnnt2 系统在肝脏中存在较低水平的基因表达,在 Cre-LoxP、CRISPR/Cas9 和 ABE 等高灵敏度的应用场景中会造成严重的肝脏泄露情况。在 AAV 转基因的 3'UTR 中引入 miR122TS 可以有效消除 AAV9-Tnnt2 系统的肝脏泄露缺陷，是实现心肌细胞特异性的体内基因递送、基因编辑和基因治疗的关键技术。

关键词：腺相关病毒（AAV），心肌细胞特异性，体内基因编辑，miR122TS

Y2 A putative loop connection between VTA dopamine neurons and nucleus accumbens encodes positive valence to compensate for hunger

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Abstract

Dopamine (DA) signal play pivotal roles in regulating motivated behaviors, including feeding behavior, but the role of midbrain DA neurons in modulating food intake and neural circuitry mechanisms remain largely unknown. Here, we found that activating but not inhibiting ventral tegmental area (VTA) DA neurons reduces mouse food intake. Furthermore, DA neurons in ventral VTA, especially neurons projecting to the medial nucleus accumbens (NAc), are activated by refeeding in the 24 h fasted mice. Combing neural circuitry tracing, optogenetic,

chemogenetic, and pharmacological manipulations, we established that the VTA→medial NAc→VTA loop circuit is critical for the VTA DA neurons activation-induced food intake reduction. Moreover, activating either VTA DA neurons or dopaminergic axons in medial NAc elevates positive valence, which will compensate for the hungry-induced food intake. Thus, our study identifies a subset of positive valence-encoded VTA DA neurons forming possible loop connections with medial NAc that are anorexigenic.

Methods

The role of VTA DA neurons in regulating food intake was examined by optogenetic and chemogenetic tools. Mouse VTA neuronal activities and neural circuits were evaluated by c-Fos immunostaining combined with anterograde and retrograde tracing methods. Relying on Cre-loxp and Flp-FRT systems, the involvement of VTA DA-related pathways in regulating fasting food intake was investigated by applying different virus strategies. Real-time place preference behavioral test was used to evaluate positive valence.

Results

(1) Activation of VTA DA neurons reduces food intake, but silencing DA neurons has little effect.

We first used both chemogenetic and optogenetic methods to directly manipulate the activity of VTA DA neurons with DAT-Cre transgenic mice and measured the food intake in different conditions. Activation of VTA DA neurons reduced food intake, but silencing DA neurons had little effect. Besides, long-term activating VTA DA neurons significantly decreased mouse body weight and the food intake relative to body weight.

(2) DA neurons in ventral VTA are involved in reducing food intake in fasted mice.

We then investigated the activity change of VTA DA neurons after 2 h refeeding in 24 h fasted mice. The cFos expression in VTA was detected in the fasting and refeeding conditions. The number of the TH and cFos double-positive neurons tended to increase in the refeeding condition, especially those distributed in the medial and ventral VTA subregions, i.e. the paranigral nucleus (PN) and interfascicular nucleus (IF), while GABA and cFos double-positive neurons was reduced. Optogenetic activating VTA GABA neurons significantly increased mouse food intake.

(3) Ventral VTA DA neurons may form a positive loop with medial NAc in reducing food intake in the 24 h fasted mice.

To investigate the neural-circuit mechanisms of VTA DA neurons regulating food intake, we determined the candidate target regions of VTA DA neurons, medial NAc, LH, LS, by combing Fluoro-Gold (FG) and immunohistochemical staining of cFos. Further, activating VTA DA neurons projecting to the medial NAc, or activating dopaminergic axons in medial NAc reduced food intake. We inferred that ventral VTA DA neurons may form loop connection with medial

NAc neurons to reduce mouse food intake. After verifying the VTA→medial NAc→VTA loop circuit, we found activating the VTA→medial NAc→VTA loop circuit decreased feeding behavior.

(4) Positive valence induced by activating the connections of ventral VTA DA neurons with medial NAc circuit compensates for the hunger-induced food intake.

Combined optogenetic stimulation and the real-time place preference behavioral test, we found that activation of VTA DA neurons, dopaminergic axons in medial NAc or VTA-medial NAc-VTA loop circuit induced place preference in both normal feeding mice and 24 h fasted mice, which was sufficient to compensate for the hunger-induced food intake.

Conclusion

In this study, we dissected the anorexigenic effect of the VTA→medial NAc→VTA loop circuit and proved the positive valence encoded by this circuit can compensate for food intake in hungry mice. These findings not only uncover a new DA circuit in regulating food intake but also suggest the possible translational value of elevating VTA DA-related positive valence in losing weight.

Keywords: Dopamine, Ventral tegmental area, Feeding behavior, Neural circuit, Positive valence

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Y3 内皮细胞 BRD4 参与狼疮性肾炎的机制研究

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狼疮性肾炎（Lupus nephritis, LN）是常见且致死的免疫相关肾病，内皮细胞损伤是 LN 的核心发病环节，但其分子调控机制不明。BET 家族成员的溴结构域蛋白 4（Bromodomain Containing protein 4, BRD4）是表观遗传阅读器，参与调控炎症和增殖。研究表明 BRD4 抑制剂 JQ1 可部分缓解 LN 小鼠疾病进展，但 BRD4 在 LN 中的作用机制尚不明确。

首先，我们在 LN 患者和小鼠肾脏中发现，BRD4 是 BET 家族中 mRNA 升高最显著的成员，其高表达与肾小球滤过率呈负相关；在肾脏固有细胞中，BRD4 在 LN 患者和小鼠肾脏的内皮细胞中的表达较正常对照组显著增高。进而，我们构建了内皮细胞特异性敲低

BRD4 腺病毒（BRD4$^{\Delta EC}$-shRNA-AAV）处理 MRL/lpr 狼疮小鼠，验证显示该 AAV 具有较好内皮靶向性；与对照病毒组相比，BRD4$^{\Delta EC}$-shRNA-AAV 显著改善了小鼠肾脏损伤（蛋白尿、基底膜致密物和 IgG 沉积、线粒体异常、三级淋巴结构、$CD3^{+}$T 细胞浸润）、淋巴器官增殖、血清抗体产生和心脏损伤。同时，我们也使用 BRD4 新型抑制剂 NHWD870 处理 MRL/lpr 和 R848 两种狼疮小鼠，均获得较好肾损伤缓解的疗效。其次，在人肾小球内皮细胞（Hrgec）中过表达 BRD4 行 RNA-seq 和验证发现，促炎因子 CXCL10、内皮损伤指标 PECAM1 等的表达以及 T 细胞和巨噬细胞的粘附显著增加，内皮细胞呈向高静脉内皮转化；在干扰素（IFN）刺激模拟患者高干扰素血症后进一步发现，BRD4 的过表达显著加重了 IFN 诱导的以上内皮损伤；反之，BRD4 抑制剂显著改善内皮损伤。最后，在 Hrgec 中，抗体下拉 BRD4 行蛋白质谱和 ChIP-seq 联合测序及验证发现，Fli-1 是与 BRD4 相互结合并作用的关键转录因子；过表达 Fli-1 出现内皮损伤加重，反之抑制 Fli-1 可改善内皮损伤；BRD4 与 Fli-1 核蛋白相互结合形成转录复合物，且在启动子区域调控 CXCL10 和 PECAM1 的转录表达，进而促进内皮细胞损伤。

本研究表明，内皮细胞高表达的 BRD4 参与 LN 的发生发展；其机制可能与 BRD4 激活 Fli-1 的转录活性，促进内皮细胞 CXCL10 和 PECAM1 的转录表达、向高静脉内皮转化，并增加肾脏 T 细胞的浸润相关；提示 BRD4 是 LN 有效治疗靶点。

关键词：内皮细胞，BRD4，Fli-1，狼疮性肾炎

Y4 Inner nuclear membrane protein LEMD3 stabilizes 3D chromatin architecture and controls vascular smooth muscle cell identity

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The contractile phenotype of vascular smooth muscle cells (VSMCs) is essential for maintaining vascular homeostasis. In response to pathological factors, contractile VSMCs can undergo phenotypic transition to a dedifferentiated state, participating in the pathogenesis of multiple vascular diseases. To date, it has been recognized that transcription factors, growth factors, extracellular matrix, oxidative stress, metabolism and epigenetic modification participate in phenotypic transition of VSMCs. Recent studies have shown that 3D chromatin architecture plays an important role in cell differentiation and tumorigenesis. However, the role of 3D chromatin architecture in maintaining the contractile phenotype of VSMCs and vascular

homeostasis remains unclear.

In this study, we established stable MOVAS cell line with the fusion of green fluorescent protein (GFP) to the C terminus of α-SMA (α-smooth muscle actin) by CRISPR/Cas9-mediated knock-in technology. A genome-scale CRISPR screen was performed based on the dual-vector lentiviral GeCKO system, and VSMCs with reduced GFP fluorescence intensity (reduced α-SMA expression level) were sorted by flow cytometry. High-throughput genome sequencing found that LEMD3, a nuclear membrane protein, may be involved in maintaining the contractile phenotype of VSMCs. Western blot and immunohistochemistry results showed that LEMD3 was highly expressed in arteries and localized in the nucleus of VSMCs. Knockdown of LEMD3 in VSMCs reduced the expression levels of smooth muscle contractile proteins, changed the cell morphology from long spindle shape to polygonal shape, decreased the contraction ability, and enhanced the proliferation ability of VSMCs. Overexpression of LEMD3 inhibited PDGF-BB-induced phenotypic transition. Knockout of LEMD3 in the mouse model of carotid artery wire injury aggravated neointima formation.

Mechanistically, we combined RNA-seq with ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) to find out differentially expressed genes and altered chromatin accessibility. By overlapping down-regulated genes and genes located in less accessible chromatin regions, we identified 143 genes including VSMCs contractile genes such as *Acta2*, *Cnn1*, *Tagln*, and key transcription factor *Srf*, suggesting that LEMD3 maintains VSMCs contractile phenotype by regulating chromatin accessibility. LEMD3 as an inner nuclear membrane protein is spatially close to heterochromatin. Knockdown of LEMD3 increased the distribution of H3K9me3 inside the nucleus of VSMCs, suggesting that the spatial localization of heterochromatin changed from near the nuclear membrane to inside the nucleus. Protein interactome assay showed that LEMD3 interacted with the heterochromatin protein CBX3, which specifically recognized histone H3K9me3 modification. Co-immunoprecipitation assay further demonstrated that the C-terminal RRM domain of LEMD3 interacted with CBX3. These results suggested that LEMD3 mediated perinuclear anchoring of heterochromatin by interacting with CBX3. The change of chromatin spatial distribution could result in the alteration of 3D chromatin architecture and further alter gene expression. High-throughput chromatin conformation capture (HiC) sequencing showed that LEMD3 knockdown in VSMCs resulted in changes in chromatin compartment composition and interactions between topologically associated domains (TADs). Inter-TAD interactions between the TADs, in which *Tagln* or *Acta2* genes locate, and adjacent TADs were changed, associated with alterations in smooth muscle contractile genes expression.

In conclusion, we found that LEMD3 played a vital role in maintaining the contractile phenotype of VSMCs through CRISPR genome-wide screening. Combined with high-throughput

sequencing analysis such as RNA-seq, ATAC-seq, ChIP-seq and HiC, we revealed that inner nuclear membrane protein LEMD3 mediated the perinuclear anchoring of heterochromatin by binding to heterochromatin protein CBX3, maintaining 3D chromatin architecture, which further regulated the expression of contractile genes and maintained VSMCs contractile phenotype and vascular homeostasis. This study first revealed the significant role of inner nuclear membrane proteins in maintaining the contractile phenotype of VSMCs by regulating 3D chromatin architecture, and provided a potential intervention target for the treatment of vascular diseases such as vascular restenosis and atherosclerosis.

Keywords: Vascular smooth muscle cell, Phenotypic transition, Nuclear membrane protein, 3D chromatin architecture

Y5 Gastrodin acts on presynaptic $GABA_B$ receptors to ameliorate vestibular disorders

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Gastrodin, a traditional Chinese medicine monomer compound extracted from *Gastrodia elata Blume*, has been used as a first-line medication for vestibular disorders in clinical practice. However, the precise mechanism of gastrodin in the amelioration of vestibular symptoms, such as vertigo, disequilibrium, postural instability, and nystagmus, remains unknown. Here, by using the methods of the transmission electron microscope (TEM), whole-cell patch-clamp recording as well as chemogenetic manipulation, we report for the first time that gastrodin facilitates vestibular compensation, a homeostatic process that occurs in the central nervous system in response to peripheral vestibular dysfunction, by targeting $GABA_B$ receptors, and thereby ameliorates vestibular symptoms. Our results show that gastrodin treatment significantly improves both static and dynamic vestibular deficits after unilateral labyrinthectomy (UL). Furthermore, TEM data reveal an elevation of vesicles docking in the presynaptic active zone at inhibitory synapses in the ipsilateral medial vestibular nucleus (MVN) after UL, which can be reversed by gastrodin

treatment. Accordingly, gastrodin decreases both mIPSCs and evoked IPSCs in the ipsilateral MVN neurons after UL, by antagonizing $GABA_B$ receptors selectively located in the inhibitory commissural pathways. Either chemogenetic inhibition of the inhibitory commissural pathways or knockdown of the MVN $GABA_B$ receptors totally blocks the gastrodin-induced facilitation of vestibular compensation. These results reveal a key role of $GABA_B$ receptors in gastrodin amelioration of vestibular dysfunction. The findings provide not only new insight into the mechanism of gastrodin treatment, but also a novel potential therapeutic target for vestibular disorders. (*Supported by NSFC grants 31961160724, 32030044, and 32171012; National Key R&D Program of China 2021ZD0202805; JSNSF grant BK20190008; and Fundamental Research Funds for the Central Universities, China*)

Keywords: gastrodin; vestibular compensation; medial vestibular nucleus; synaptic transmission; $GABA_B$ receptor

Y6 精子核周层蛋白的生理功能及其与男性不育的关联

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研究目的：精子核周层是紧紧包裹精子细胞核的一薄层特殊细胞骨架结构，分为顶体下层板和顶体后区域两个连续的组成部分。虽然精子核周层的结构、蛋白组成和组装方式已被报道，但是其生理功能及其缺陷与男性不育的关联尚不十分清楚。我们前期工作揭示了精子核周层蛋白 calicin 和 Actrt1 分别具有保护精子细胞核和介导顶体锚定的生理功能（Zhang XZ *et al. Cell Reports*, 2022; Zhang XZ *et al., Development*, 2022）。本研究拟围绕实验室特色工作并基础紧密联系临床，探究精子核周层蛋白 cylicin-1 功能缺陷导致人和小鼠顶体脱落和精子头部畸形的机理。

材料与方法：我们首先利用 CRISPR/Cas9 基因编辑技术构建了 *Cylc1* 基因敲除小鼠并进行了生育力分析和精子超微结构观察；我们还开展了 332 例精子头部畸形和体外受精率低下的男性不育患者的全外显子测序和 Sanger 测序验证；我们继而建立了 *Cylc1* 基因点突变小鼠用以探究突变对 cylicin 蛋白功能的影响；我们最后综合利用分子生化手段用以揭示 cylicin-1 介导顶体锚定的潜在分子机制。

结果：*Cylc1* 基因敲除小鼠雄性生育力降低，其精子头部畸形和顶体脱落比例显著升高。位于顶体下层板的 cylicin-1 蛋白可能通过与顶体内膜蛋白 Spaca1 和核膜蛋白 Fam209 相互作用的方式将发育中的顶体锚定在精子核膜上。我们发现 14 例精子头部畸形和体外受精率低下的男性不育患者携带 *CYLC1* 基因半合子突变。*Cylc1* 基因点突变小鼠（与病人携带突变

位点同源）同样表现为精子顶体脱落、精子头部畸形和雄性生育力降低。我们开展了 14 例携带 *CYLC1* 基因突变患者的辅助生殖治疗并发现卵胞浆内单精子注射（ICSI）是 *CYLC1* 基因突变患者可行的辅助生殖治疗手段。

结论：精子核周层蛋白 cylicin-1 具有介导顶体锚定的生理功能，其编码基因突变可能是男性不育或生育力降低潜在的致病机理。

关键字：男性不育，精子，精子核周层，基因敲除小鼠，Cylc1

Y7 孕期糖皮质激素暴露通过抑制 FTO/GLUT3 影响小鼠胎盘发育的机制研究

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目的 探究孕期糖皮质激素暴露通过 RNA m6A 甲基化修饰影响小鼠胎盘发育的机制。**方法** 构建孕期糖皮质激素暴露的动物和细胞模型，检测胎盘、胎鼠重量及胎盘结构变化、RNA m6A 甲基化水平和 FTO 表达水平。随后在胎盘滋养层细胞系 HTR8/SVNeo 和 JEG-3 中过表达或敲低 FTO，检测其对细胞的增殖、凋亡和迁移的影响及相关营养转运体的表达变化。**结果** 与对照组（NS）相比，地塞米松（DEX，人工合成的糖皮质激素）暴露组中胎盘及胎鼠重量显著降低，胎盘中 RNA m6A 甲基化水平升高、m6A 去甲基化酶 FTO 表达水平降低；与 PBS 组相比，FTO 在 DEX 处理的 HTR8/SVNeo 和 JEG-3 细胞系中表达降低，使用糖皮质激素受体（GR）拮抗剂 RU486 预处理，能显著逆转这一现象；在 HTR8/SVNeo 和 JEG-3 细胞系中敲低 FTO 的表达，显著抑制细胞的增殖和迁移能力及葡萄糖转运体 GLUT3 的表达，尤其是细胞膜上 GLUT3 的表达降低；而在 HTR8/SVNeo 和 JEG-3 细胞系中过表达 FTO，能够显著增强 GLUT3 的表达。**结论** 孕期糖皮质激素暴露通过 GR 介导的作用抑制胎盘滋养层细胞 FTO 表达，进而下调 GLUT3 表达从而影响小鼠胎盘发育。本研究为糖皮质激素过度暴露所致的胎盘发育异常的防治提供了理论基础和干预靶点。

关键词：糖皮质激素、胎盘发育、FTO、RNA m6A methylation、GLUT3

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Y8 The specific roles of renal macrophages in monitoring and cleaning off intratubular particles

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Background: During the filtrate of the glomerulus flows through the renal tubular system, various microscopic sediment particles, including mineral crystals resulting from urine concentration, are generated. Dislodging these particles in the intratubular compartment is critical to ensure free flow of filtrate and the final formation of urine. However, the underlying mechanism for the clearance is unclear.

Objectives: This study aims to investigate whether there is an inherent cellular mechanism for the removal of sedimentary particles and to study the roles of resident macrophages (MØ) in maintaining the homeostasis of kidney.

Materials and methods: We used super high-resolution microscopy and immune electron microscopy to investigate the anatomic relationship between renal resident MØ and tubular epithelium. We also employed two-photon microscopy to visualize dynamic interactions between MØ and tubules in real time. Urine was examined by flow cytometry to analyze the cellular components. Hyperoxaluria nephrolithiasis model was applied to study the role of renal MØ in disposing intratubular particles.

Results: The juxtatubular MØ in the kidney constitutively formed transepithelial protrusions which were exposed to the lumen of tubules in steady state. There was spatial disparity in the density of transepithelial protrusions, as this structure was prominent in the medulla over the cortex. These MØ-derived protrusions penetrate the renal epithelium in a very special way, i.e., through a transcellular route (through cell body) instead of a paracellular route (between epithelial cells), which was confirmed by both confocal microscopy and electron microscopy. Thus, the formation of transepithelial protrusion did not disrupt the sealing capacity of tubular epithelium. Two-photon microscope observation of live renal medulla slice revealed that these transepithelial protrusions in the medulla were constantly making extension-and-retraction movements, sampling the urine contents and probing intratubular environment. This sampling-like movement would expedite during nephrolithiasis (development of kidney stones). By function, these transepithelial protrusions were efficient in sequestering and phagocytosing intraluminal particles. Moreover, the juxtatubular MØ in the medulla would made transmigration to the tubule lumen to escort the removal of intratubular particles. This unique behavior was live recorded by two-photon microscopy, and was also manifested by the detection of insertion of MØ nucleus into the

epithelial monolayer in fixed slices (indicative of transmigration) and the detection of MØ in the normal urine. In particular, MØ, when present in the urine, are generally associated with urine-borne particles, and their number in the urine would significantly increase during nephrolithiasis, further supporting their particle-escorting role. Selective depletion of renal medullary MØ by delivery of DT into the bladder of *Cx3cr1*$^{CreERT2/+}$:iDTR mice significantly aggravated stone formation and the associated renal inflammation in a hyperoxaluria nephrolithiasis model. The physiological impact of renal MØ in dislodging tubular sediments was further highlighted in our longitudinal studies: with both genetic and pharmacological approaches, we demonstrated that a long-term deficiency of renal MØ would result in rampant deposition of diverse urine sediments in the medullary tubules. Thus, our data strongly suggest that urine flushing alone is not enough to keep the tubules unobstructed in both normal and pathological situations, and a routine "plumber" work executed by renal MØ is additionally required.

Conclusion: Our results showed that renal medullary MØ constitutively extend transcellular protrusions through tubular epithelial monolayer, whereby MØ were sampling and monitoring urine contents. More importantly, these innate behaviors of MØ were crucial for keeping tubules unobstructed by facilitating the removal of particles in the luminal space.

Keywords: kidney; macrophages; renal tubules; epithelium; kidney stone

Y9 Role of dopamine receptor D1/D2 neurons in mPFC in mediating CSDS-induced anxiety-like behavior and chronicity of postoperative pain

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Postoperative pain is a kind of pain that occurs in clinical patients after surgery. Due to the effect of different factors on perioperative period (including preoperative, intraoperative and postoperative stages), acute postoperative pain in some patients after surgery often develops into chronic postoperative pain. Among the factors that affect the transition from acute postoperative pain to chronic postoperative pain, chronic stress has been widely concerned in recent years. More and more studies have shown that a variety of chronic stress in perioperative period can prolong or aggravate postoperative pain, and cause persistent postoperative hyperalgesia. However, few

studies explored the brain mechanism of chronic stress-induced persistent postoperative pain. Previous studies by our group have shown that perioperative social defeat stress is a key risk factor for development of chronic postoperative pain. In this study, wild-type C57BL/6J mice, D1-Cre and D2-Cre transgenic mice were used. Combined with mechanical pain and anxiety-like behavioral evaluation, a mouse model of chronic postoperative pain induced by chronic social defeat stress (CSDS) was established, and HE staining, immunohistochemical staining, Western blotting, immunofluorescence staining, chemical damage, chemogenetics and optogenetics were conducted to investigate the role of dopamine receptor D1/D2 neurons in mPFC in CSDS-induced anxiety-like behavior and chronic postoperative pain. Our results showed that preoperative CSDS significantly prolonged postoperative pain caused by plantar incision (lasting at least 15 days), and there is no significant correlation between chronic postoperative pain induced by CSDS and plantar wound tissue inflammation; Further studies showed that chemical damage of mPFC or chemogenetic inhibition of dopamine receptor neurons in mPFC could induce anxiety-like behavior and persistent postoperative pain after surgery. In addition, specific activation of dopamine receptor D1 neurons but not D2 neurons in mPFC by chemogenetic or optogenetic techniques can significantly improve CSDS-induced anxiety-like behavior and postoperative hyperalgesia. In conclusion, this study suggests that the abnormal activity of dopamine receptor neurons in mPFC is one of the vital mechanisms of anxiety-like behavior and chronic postoperative pain induced by CSDS, and specific activation of dopamine receptor D1 neurons in mPFC can significantly alleviate the above behavioral deficits.

Keywords: Chronic social defeat stress, chronicity of postoperative pain, anxiety, dopamine receptor, optogenetics, chemogenetics

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Y10 SERCA2 is an essential regulator of cardiomyocyte maturation

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Heart failure is a severe pathological end stage of many cardiovascular diseases.

Sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) is a key player in cardiomyocyte calcium handling and also a classic target in the gene therapy for heart failure. Cardiac function is largely determined by the Ca^{2+} homeostasis of cardiomyocytes. During cardiac development, the regulatory capacity of Ca^{2+} in cardiomyocytes is gradually established during cardiomyocyte maturation. SERCA2 expression also progressively increases during cardiomyocyte maturation in the postnatal phase of heart development. Based on the intimate relationship between SERCA2 and cardiomyocyte maturation, we hypothesized that SERCA2 might be involved in the regulation of cardiomyocyte maturation. Here, we performed Cas9/AAV9-mediated somatic mutagenesis (CASAAV) in mice and achieved cardiomyocyte-specific knockout of *Atp2a2*, the gene coding SERCA2. Cardiac echocardiograms and electrocardiograms confirmed the impairment of cardiac function in *Atp2a2* knockout mice. Through a cardiac genetic mosaic analysis, we demonstrated the cell-autonomous role of SERCA2 in building key ultrastructures of mature ventricular cardiomyocytes, including transverse-tubules and sarcomeres. RNA-seq analysis of FACS-sorted cardiomyocytes from genetic mosaic hearts revealed that SERCA2 also exerted a profound cell-autonomous impact on oxidative respiration gene expression and sarcomere isoform switching from *Myh7/ Tnni1* to *Myh6/ Tnni3*, which are transcriptional hallmarks of cardiomyocyte maturation. Heart failure can activate the gene expression signature of the embryonic heart and reduce the gene expression signature of cardiomyocyte maturation at the transcriptome level. Therefore, the regulation of SERCA2 on the cardiomyocyte maturation would provide a new mechanism by which SERCA2 mitigates heart failure. Together, this study uncovered a pivotal role of SERCA2 in cardiomyocyte maturation and provided new insights regarding SERCA2-based cardiac gene therapy.

Keywords: Heart failure, SERCA2, CASAAV, genetic mosaic analysis, cardiomyocyte maturation

Y11 胆固醇调控溶酶体稳态在模拟失重大鼠脑动脉重塑中的机制研究

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失重条件下，脑血管的结构和功能重塑是影响航天员身体健康和工作效能的重要因素，也是航天医学领域的重点研究问题。探索失重/模拟失重致脑血管重塑的机制，对于解决脑血流灌注异常对航天员造成的不良影响有着重要的指导意义。多项研究表明，胆固醇代谢紊乱可导致脑卒中、血管性痴呆等多种脑血管疾病。本研究表明，胆固醇耗竭不仅可导致大鼠

脑动脉的肌源性紧张度显著降低，且模拟失重大鼠对此更为敏感，提示胆固醇可能在调控模拟失重下脑动脉的结构和功能重塑中发挥重要作用。溶酶体在血管稳态调控中扮演重要角色，维持溶酶体稳态已成为干预血管疾病相关机制的新思路。本研究证实，模拟失重大鼠血管平滑肌细胞中的溶酶体数量减少，向细胞膜转移；溶酶体相关分子蛋白表达均降低，基因表达升高；自噬体与溶酶体融合受到阻碍。此外，在体外培养的血管平滑肌细胞系中发现，胆固醇耗竭均可导致溶酶体向细胞膜转移、与膜融合增多，因此推测：胆固醇可能参与调控微管介导的溶酶体外泌过程。为验证该猜想，本课题观察了胆固醇耗竭对微管聚合程度的影响。结果表明，胆固醇耗竭可增加微管的聚合程度，而使用微管解聚药物 Nocodazole 成功干预微管后，胆固醇耗竭引起的溶酶体数量减少、向胞膜移动可被抑制，提示微管介导的溶酶体外泌过程可能受到胆固醇代谢的调控。综上，本课题聚焦航天员在失重环境下发生脑血管重塑这一前沿问题，针对目前血管平滑肌细胞功能改变的具体机制不清，仍需寻找关键机制和分子这一需求，通过多种先进实验手段，探究胆固醇调控溶酶体稳态在血管平滑肌细胞功能改变中的作用。

关键词：胆固醇；溶酶体；模拟失重；脑动脉重塑

Y12 Activating a collaborative innate-adaptive immune response to enhance anti-tumor activity of human pluripotent stem cell-derived CAR-macrophages

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Generation of chimeric antigen receptor macrophages (CAR-M) from human pluripotent stem cells (hPSCs) offers new prospects for cancer immunotherapy, but is currently challenged by low differentiation efficiency and limited function. Here, we develop a highly efficient monolayer-based system that can produce around 6,000 macrophages from a single hPSC within 3 weeks. Based on screens of modified structures, we identify macrophage-compatible CAR structures with optimized ability to generate hPSC-CAR-M with stable CAR expression and potent tumoricidal activity *in vitro*. To overcome the loss of tumoricidal activity of hPSC-CAR-M that acquire an anti-inflammatory phenotype after infusion *in vivo*, we use interferon-γ and

monophosphoryl lipid A to activate an innate immune response *in vivo* to repolarize the infused hPSC-CAR-M to tumoricidal macrophages. Moreover, through combined activation of T cells by hPSC-CAR-M to initiate an adaptive immune response, we demonstrate that activating a collaborative innate-adaptive immune response can further enhance the anti-tumor effect of hPSC-CAR-M in both liquid and solid tumor xenograft models. Collectively, our study provides feasible methodologies that significantly improve the production and function of hPSC-CAR-M to support the translation of hPSC-based "off-the-shelf" immunotherapies into clinical applications.

Keywords: cancer immunotherapy, human pluripotent stem cells, macrophages, innate immune, adaptive immune

S13：比较生理学新进展——基因、行为、环境

S13-1 从 SARS 到 COVID-19：传统中草药是否是对抗新兴病毒的解方？

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COVID-19 的新型冠状病毒(SARS-CoV-2)与蝙蝠冠状病毒相似度高达 96%，而 SARS 的冠状病毒(SARS-CoV)与蝙蝠冠状病毒的相似度则高达 79%。由于蝙蝠特殊的生物特征和生态习性以及病毒易感染性等特性，使其成为病毒和其他疾病媒介非常合适的重要宿主，目前已知狂犬病病毒(Rabies virus)、亨德拉病毒(Hendra virus)、尼帕病毒(Nipah virus)、梅南高病毒(Menangle virus)、刁曼病毒(Tioman virus)、伊波拉病毒(Ebola virus)、SARS 冠状病毒、MERS 冠状病毒、以及新型冠状病毒，多藉由蝙蝠作为宿主并且引起人类和其他脊椎动物疾病。由于中国历史上曾经发生几次严重的流行性瘟疫，感染症状与 COVID-19 有着许多相似之处，而东汉张仲景《伤寒杂病论》及明朝吴又可《瘟疫论》曾为后人留下珍贵的流行性传染病医学理论与实务经验。2003 年亚洲部分地区爆发严重急性呼吸系统综合症(SARS)，造成人类高染病性与致死率，而 2019 年 COVID-19 则引爆全球更多的人类感染与死亡，甚至重创全球的经济发展。为此，卫生福利部国家中医药研究所依据中医典籍文献，以明代张时彻所辑《摄生众妙方》中之荆防败毒散为处方基础，重新组成十味药材之新复方，研发「台湾清冠一号」，在临床上显著降低新冠患者转重症及减少死亡风险，而让传统中医药受到国际认可。中医典籍文献提及诸多传统汉方草药可以有效预防或是抑制病毒感染，例如金银花对流感病毒、疱疹病毒有抑制作用，能抑制病毒的复制，延缓病毒所致细胞病变的发生，并有一定的抗炎解热、抗内毒素作用；而连翘具有抗病原微生物、解热、抗发炎效果，临床上常用于治疗流行性感冒、肺炎、急性传染性肝炎等；此外，板蓝根的提取物对出血热病毒、

单纯疱疹病毒有明显的破坏作用，对流感病毒、腮腺炎病毒也有明显的抑制作用。在 SARS 期间，鱼腥草的萃取物也因为能够百分之百杀死 SARS 病毒，而被广泛应用在 SARS 病人的替代治疗上，鱼腥草抗病毒的功效目前也广泛应用在治疗上呼吸道感染、慢性支气管炎、肺炎等疾病；而柴胡多用于流行性感冒、病毒性肝炎、腮腺炎的替代治疗；另外，甘草素对人体艾滋病病毒、肝炎病毒、腺病毒、单纯疱疹病毒、牛痘病毒等也有明显的抑制作用。由于传统汉方草药富含许多抗病毒活性成分，如黄酮类、萜类、蒽醌类、多酚类、多醣体、生物碱等，这种有效成分的多元化，使得病毒难以对其产生抗药性。此外，传统汉方草药与现有抗病毒药的并用，也能够降低抗病毒药物的使用量，进而减少副作用的产生，同时增加抗病毒的效果。综合上述，如能萃取汉方草药中具有疗效并且可以作为食物原料的内容，研制开发成为保健食品，对于人类未来对抗新兴病毒引发的疾病，应该是极具商业潜力。

S13-2 Genetic and epigenetic evidence for non-estrogenic disruption of otolith development by bisphenol A in zebrafish

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Bisphenol A (BPA) is a well-known endocrine-disrupting chemical (EDC) with estrogenic activities. In addition to disrupting reproductive development and function via estrogenic signaling pathways, BPA can also interfere with non-reproductive functions through non-estrogenic pathways; however, the mechanisms underlying such non-estrogenic activities remain largely unknown. In this study, we demonstrated that BPA could disrupt otolith formation during early development of zebrafish with long-lasting ethological effects. Using multiple mutants of estrogen receptors (nERs: *esr1*$^{-/-}$, *esr2a*$^{-/-}$ and *esr2b*$^{-/-}$; mER: *gper1*$^{-/-}$), we provided strong genetic evidence that the BPA-induced otolith malformation was independent of estrogen signaling. Immunofluorescent staining ruled out the possibility that the abnormalities in hair cells and tethered cilia caused otolith malformation after BPA exposure. Transcriptome analysis revealed that two genes related to otolith development, otopetrin1 (*otop1*) and starmaker (*stm*), decreased their expression significantly after BPA exposure. Knockout of *otop1* and *stm* could phenocopy the BPA-induced otolith malformation, while microinjection of their mRNAs could rescue the BPA-induced abnormalities of otolith formation. Further experiments showed that BPA inhibited the expression of *otop1* and *stm* through histone methylation, but not DNA methylation, in their promoter regions. BPA exposure increased the trimethylation of H3K27 in the promoter regions of *otop1* and *stm*, and it worked by activating the MEK/ERK pathway, which in turn increased the expression of H3K27 methyltransferase (EZH2). Taken together, our study provided

comprehensive genetic and molecular evidence that BPA induced the otolith malformation through non-estrogenic pathway during zebrafish early development and its activities involved epigenetic control of key genes (*e.g.*, *otop1* and *stm*) participating in otolith formation.

S13-3 裸鼹鼠 cGAS 调控基因组稳定性的机制研究

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维持高效且精确的 DNA 双链断裂修复对于延缓衰老十分关键，裸鼹鼠寿命可达 30 年，其 DNA 修复效率和精确性提升是长寿的重要原因。在前期以人细胞和小鼠为模型的研究中，我们发现胞内 DNA 识别受体 cGAS 具有独立于固有免疫的新功能，其在 DNA 损伤时入核抑制 DNA 双链断裂修复从而促进肿瘤发生。而肿瘤发生概率极低的裸鼹鼠是否抑制了 cGAS 在人和小鼠中的这一功能尚未被研究。我们通过比较生物学、分子生物学以及其他多种研究手段，解析了裸鼹鼠 cGAS 促进 DNA 修复的分子机制，并且发现裸鼹鼠 cGAS 可以通过提升基因组稳定性延缓衰老发生。这为后续靶向 cGAS 延缓衰老奠定了理论基础。

S13-4 基于 CRISPR/Cas9 技术构建基因编辑动物疾病模型

于鸿浩
桂林医学院

CRISPR/Cas9 是广泛应用于生物医药研究的基因编辑技术。我们以小型猪为研究对象，制备了的 *GHR* 和 *DMD* 基因敲除猪模型，两种动物模型可以模拟人类原发性生长激素不敏感综合征以及杜氏营养不良综合征。此外，也制备了 *GGTA1*、*B2M* 和 *CIITA* 三基因同时敲除猪模型，该模型表现出更好异种器官移植耐受力；以小鼠为研究对象，制备了 *Galt* 和 *Ext1* 基因编辑小鼠。*Galt* 基因编辑小鼠表现为较小的体型、严重的肝损伤和肺损伤，部分个体表现为白内障症状，可以模拟人半乳糖血症。*Ext1* 基因编辑小鼠表现为尾骨增生，而且我们通过杂交选育得到了 *Ext1* 基因敲除纯合子小鼠，突破了传统对 *Ext1* 基因完全敲除致死型的理解。通过以上研究，丰富了我们对基因功能的认识，为深入研究遗传病的机制提供了实验动物基础，具有一定的理论和实际意义。

S13-5 高原视觉皮层损伤和适应的环境和基因机制

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人类脑急性高原反应和慢性适应的机制一直不清楚。本研究基于人脑磁共振成像和脑电图研究显示高原移居和世居人群脑的结构和功能变化主要在视觉、运动和岛叶皮层，而影像-遗传学研究显示低氧诱导因子通路 EPAS1、EGLN1 和 PPARA 基因突变都会重塑视觉皮层及其结构和功能网络。模拟高原低氧小鼠脑结构和分子影像证实了视觉皮层的改变，并基于双光子成像及代谢组学显示脑内视觉皮层细胞活动、血管反应和代谢对低氧的反应最显著，且小胶质的激活介导了这些反应。总之，高原环境低氧和基因突变共同作用于视觉皮层，该发现有助于理解高原人类的行为特征。

关键词：脑；视觉皮层；低氧；高原

S13-6 Dissecting aging and disease from non-model subterranean mammals

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Aging is a major risk factor for multiple diseases including cancer. Naturally long-lived and cancer-resistant animals provide powerful models to uncover novel anticancer mechanisms that are potentially applicable to humans. We have previously discovered that the blind mole rat (BMR, *Spalax galili*), a subterranean rodent species, is extremely resistant to both spontaneous and induced tumorigenesis. The fibroblasts isolated from BMR have a unique anti-cancer phenotype termed concerted cell death (CCD), during which the cells spontaneously undergo a massive necrotic cell death upon over-proliferation. The onset of CCD is coupled with the activation of type I interferon pathway. We found that the BMR cells and tissues have naturally weak DNMT1. In rapidly proliferating cells, the weak DNMT1 fails to maintain DNA methylation, resulting in loss of methylation and overexpression of retrotransposons including L1 and SINE families. The retrotransposons then trigger the interferon pathway via cytoplasmic DNA sensing cGAS-STING pathway. Mimicking this mechanism on human cancer cells and mouse tumorigenesis models yielded similar results, suggesting that this mechanism is broadly applicable to other species. We propose that retrotransposons are a double-edged sword, serving as a tumor suppressor in young age but later contributing to inflammaging.

Another known mechanism responsible for the cancer resistance of the subterranean naked

mole rat (NMR, *Heterocephalus glaber*) is by secreting large amount of high-molecular-mass hyaluronic acid (HMM-HA). We recently found that HMM-HA is secreted by six different species of subterranean mammals, including NMR, BMR, Damaraland mole rat (DMR, *Fukomys damarensis*), Eastern mole (EM, *Scalopus aquaticus*), star-nose mole (SNM, *Condylura cristata*), and Transcaucasian mole vole (TMV, *Ellobius lutescens*). The HMM-HA from these species resulted from different expression and mutations of enzymes involved in HA synthesis and degradation. We propose that HMM-HA has coevolved with subterranean lifestyle, and that cancer resistance may be a common phenotype shared by subterranean mammals. Exploring a wider range of non-model subterranean mammals will reveal numerous antiaging and anticancer mechanisms that are potentially applicable to humans.

S13-7 青藏高原上的蛙类对紫外辐射的适应机制

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气候变暖和平流层臭氧消耗所导致的紫外辐射增加是目前全球尺度下突出的两个环境问题，也是导致两栖动物种群数量下降或灭绝的主要驱动因素。这两个环境因子通常在高海拔地区的变化更为显著，温度升高和 UVBR 水平增加可能会改变生物机体的热适应性，对高原两栖动物的生命活动产生不利影响。近年来，课题组以我国特有且分布较广的无尾两栖类动物高原林蛙为研究对象，分别从蝌蚪和成体两个层面探究紫外辐射和温度变化对高原两栖动物发育不同阶段以及不同种群造成的影响。结果表明，UVBR 对蝌蚪存在负面影响可能是 UVBR 诱导的生物分子损伤、能量可利用性降低的结果，但在一定范围内升高的温度可以通过提高蝌蚪的热耐受范围、热偏好温度、运动能力及抗氧化酶的热敏感性来补偿 UVBR 带来的负面影响。由此，我们推测在一定范围内温度升高可能会增加机体对环境变化的适应能力，从而对生活在高海拔地区的两栖动物产生一定的积极影响。此外，通过高原林蛙高低海拔两种群间比较发现，高海拔种群对强紫外辐射有着强大的适应机制。对这种适应性的研究，有助于揭示高原物种的紫外适应规律和机制，为其它两栖动物的研究和保护策略提供科学依据，同时也为人类的紫外损伤医疗提供线索。

S13-8 White and brown adipose tissues: the fuel for hibernation

邢昕
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Hibernation is the most effective energy saving strategies for small mammals. To survive the hibernation season, some hibernators store body fat as the main fuel of hibernation during fattening period. There are 2 types of adipose tissue with opposite functions, the white adipose tissue (WAT) is the energy storing organ and the brown adipose tissue (BAT) burn the lipid through thermogenesis. WAT accumulation affects the survive rate and hibernation expression. WAT dramatically increased by about 10-fold in 2-3 months fattening period with on evidence of obesity-related diseases. However, the underlying mechanism of this impressive adaptation is still unknown. The distribution of WAT is crucial for metabolic health, the visceral fat accumulation is closely related with metabolic disorders. Our recent study shows that, Daurian ground squirrel (*Spermophilus dauricus*), a typical fat-storing hibernator, accumulate subcutaneous WAT before visceral WAT during fattening, the visceral WAT showed hyperplasia rather than hypertrophy during fattening period. This adipogensis pattern provide the insights into metabolic health during fattening. According to our previous observation, the hibernation varies among individuals, some animals just express very shallow torpors during the whole hibernation season. Since BAT is the the most important thermogenic organ and mitochondria is crucial organelle for the thermogenic capacity, we observed the morphological differences of mitochondria among hibernating, euthermia and arousal Daurian gound squirrels. We found that the euthermia squirrels showed decrased mitochondrial cristae density comparing with hibernating and arousal squirrels. Besides, the lipid droplet area is significantly smaller in euthermia squirrels' BAT. These results might be indicating the relationship between BAT mitochondrial morphology and hibernation expression. Above all, as the fuel of hibernation, the accumulation and physiological changes of adipose tissue affect the hibernation profoundly, the underling mechanisms might provide evidences of hibernation initiation and maintenance.

Key words: hibernation, white adipose tissue, brown adipose tissue, Daurian ground squirrel

S14：认识衰老-机制探索与应对策略

特邀嘉宾报告

S14-1 衰老的编程和重编程（Programming and reprogramming of aging）

刘光慧
中国科学院动物研究所

S14-2 线粒体表观遗传学与衰老及代谢综合征（Mitoepigenetics in aging and metabolic syndrome）

刘健康
西安交通大学

S14-3 衰老导致血管平滑肌表型转化的作用和机制

黄恺
华中科技大学协和医院

S14-4 器官对话与系统衰老（Organ cross-talks and systemic aging）

刘宝华
深圳大学

衰老与健康专业委员会专题报告

S14-5 血管衰老与认知障碍的队列研究

曹丰
中国人民解放军总医院

S14-6 幼年期运动促进小鼠中老年期脂肪酸代谢及健康

张星
中国人民解放军空军军医大学

S14-7 组蛋白去乙酰化酶 SIRT2 在老年心血管疾病中的保护作用

陈厚早
中国医学科学院北京协和医学院

S14-8 琥珀酸脱氢酶组装异常对肝脏胰岛素敏感性的影响及其在扩张型心肌病中的作用

冯智辉
西安交通大学

S14-9 衰老肝脏的内皮分区

王琳
中国人民解放军空军军医大学西京医院

S14-10 酮体代谢与老年肌少症

向阳
南昌大学

S15：神经免疫内稳态与疾病

S15-1 Neuroimmune regulation in tumor microenvironment

杨竞
北京大学

Lung cancer is a significant threat to human health despite recent developments in therapeutic strategies. Notably, clinical evidence has implicated that psychological stresses such as anxiety

and depression, which cause chronic activation of the body's sympathetic signals, may result in a poor prognosis of lung cancer. However, cellular and molecular mechanisms underlying this sympathetic modulation remain mostly unknown. Here, we exploit advanced whole-tissue 3D imaging to reveal the frequent presence of sympathetic innervations in human lung tumors. Also, similar spatial engagement of sympathetic inputs and tumors is observed with lung metastases in the mouse PyMT model. We then show that the ablation of local sympathetic innervations inhibits tumor growth in the lungs of PyMT mice. Mechanistically, the sympathetic neurotransmitter norepinephrine directly stimulates the cancer cell expression of CXCL1 and CXCL2, the central chemokines recruiting neutrophils into lung tumors. At the same time, norepinephrine acts via the b2-adrenergic receptor to trigger the immunosuppressive function of those recruited neutrophils. Moreover, we demonstrate that the b2-adrenergic receptor antagonist can potentiate the anti-PD-L1 immunotherapy of lung cancer in mice. Together, these results have elucidated the sympathetic modulation of the immune microenvironment in lung cancer, providing a novel target for effective treatments.

S15-2 骨髓免疫与神经炎症

刘强
天津医科大学总医院

视神经脊髓炎谱系疾病 (NMOSD) 是中枢神经系统炎性疾病，特征为免疫介导的严重脱髓鞘及轴突损伤，主要累及视神经和脊髓。NMOSD 是造成我国青壮年残疾的重要原因，但当前仍缺乏特效疗法。B 细胞驱动 NMOSD 的免疫病理，大约 75% 的 NMOSD 患者具有抗水通道蛋白-4 （AQP4-IgG） 的自身抗体。AQP4-IgG 主要累及星形胶质细胞，导致中枢神经系统炎症、脱髓鞘和组织损伤。骨髓造血系统可感知免疫系统激活，生成各类免疫细胞影响炎症反应的演变。然而，NMOSD 中骨髓造血细胞的改变及其对疾病进展的影响仍然未知。申请人率先通过 NMOSD 患者骨髓样本的单细胞测序，发现骨髓造血前体细胞异常激活，发生以中性粒细胞为主的髓系增生，且高表达 B 细胞刺激因子（BAFF），并伴有骨髓内 B 细胞克隆扩增。此外，NMOSD 患者骨髓中性粒细胞可刺激 B 细胞分化，从而产生抗体分泌细胞和产生 AQP4-IgG。BAFF 中和抗体（贝利尤单抗）可减少 NMOSD 患者复发和 AQP4-IgG。这些发现表明，骨髓造血系统发生的异常中性粒细胞过度增殖，可驱动 B 细胞介导的自身免疫反应和中枢神经系统炎症损伤。明确骨髓这一中枢免疫器官在 NMOSD 免疫病理中的作用，有助于找到靶向骨髓免疫，回归机体免疫稳态，减轻神经炎性损伤的新途径。从而为实现靶向骨髓免疫，治疗 NMOSD 等神经免疫病的创新治疗提供临床依据，并推动神经免疫疾病的新药研发。

S15-3 Diverse roles of microglia in the brain

高志华
浙江大学

Microglia, the primary brain immune cells, have been shown to be involved in multiple process in the physiological regulation of brain activity and brain pathology. We have explored how different nucleotide metabolism and glucose metabolism pathway in regulating microglia function in the brain. We have founded that regulators in nucleotide and glucose metabolic pathways are critical for microglial surveillance, chemotaxis and immune responses in ischemic and degenerative diseases. We also found that microglia modulate the process of general anesthesia, further expanding the role of microglia in the brain.

S15-4 Hypertension and microglia, a sensor bridges the CNS and periphery

史鹏
浙江大学

高血压被称为“沉默性杀手”，是引起致死性心血管疾病的首要独立危险因素。在我国乃至全球范围内成年人群的发病率高达 30%以上，极大的增加了老龄化进程中的医疗和社会负担。临床 90%以上高血压病因不明，但普遍存在交感神经活性升高的病理现象。本课题组既往的研究发现高血压导致脑内自主神经核团出现慢性炎症，脑内固有免疫细胞小胶质细胞的激活是导致这一炎症状态的主要因素。通过综合心血管、神经、免疫的技术手段，我们的研究进一步揭示：小胶质细胞通过旁分泌的方式直接调控交感神经元兴奋性，进而影响交感输出和血压；干扰这一旁分泌通路导致了交感高张，血压升高。本研究为以交感高张为病理特征的心血管疾病提供了新的细胞分子机制，同时也为治疗此类疾病提供了潜在靶点。

S15-5 Vessel-mediated immune surveillance at the boundary of central nervous system

罗金才
北京大学

S15-6 Enteric GABAergic neuron-intestinal muscle unit promotes gut defense

刘军强
湖南大学

γ-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the nervous system and plays critical roles in balancing between excitation and inhibition in neural communications, while the role of GABAergic signaling in intestinal immunity remain unknown. Here, we show that deficiency in GABAergic transmission between enteric AVL/DVB neurons and the intestinal muscles of *C. elegans* results in enhanced sensitivity to pathogenic *Pseudomonas aeruginosa* PA14 infection, which requires the conserved PMK-1/p38 MAPK, but not IIS/DAF-16 or DBL-1/TGF-b pathway. Based on transcriptome profiling, we identified that an intestinal muscle-derived FMRFamide neuropeptide FLP-6 is regulated by enteric GABAergic signaling from AVL/DVB neurons. FLP-6 acted as a paracrine molecule to suppress the transcription factors (TFs) ZIP-10 and KLF-1 in the intestine and contribute to gut defense through the PMK-1/p38 pathway. Our findings uncovered a novel enteric neuron-muscle-epithelium axis that may be evolutionarily conserved in higher organisms.

S16：细胞微环境在生理与病理中的功能与机制

S16-1 肝脏内皮细胞微环境与肝脏疾病

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Here, we showed that aging-induced liver sinusoidal endothelial cell (LSEC) senescence accelerated liver sinusoid capillarization and promoted steatohepatitis by reprogramming liver endothelial zonation and inactivating pericentral endothelium-derived C-kit. Abrogation of endothelial C-kit triggered cellular senescence which disturbed LSEC homeostasis. During diet-induced NASH development, C-kit deletion aggravated hepatic steatosis and exacerbated NASH-associated fibrosis and inflammation. Mechanistically, CXCR4/SDF-1 signaling was inhibited by C-kit. Blocking CXCR4/SDF-1 signaling by AMD3100 abolished LSEC-macrophage crosstalk and recovered the aggravated NASH in C-kit deficient mice. For therapeutic purpose, C-kit+ LSECs were implanted into NASH or aged mice, which counteracted LSEC senescence

and improved diet or aging-induced NASH by restoring the homeostasis of pericentral liver endothelium.

S16-2 细胞感应微环境配体分布的机制

魏强
四川大学

细胞微环境的配体分布参与调控细胞粘附、迁移、分化等众多功能。然而，细胞感应配体在界面微纳米尺度与分子尺度分布的机制尚待深入探索。我们通过材料化学手段，构筑了从微米尺度到分子尺度的一系列模拟细胞外基质配体分布的材料模型，提取出单一的配体分布的信息，从细胞力传递与信号转导角度理解细胞行为机制。发现细胞通过黏着斑-机动球蛋白骨架-核纤层蛋白骨架组成的分子链感应界面物理力学信号，并调控染色质重塑以及 YAP/TAZ 转录调节子的活性，进而参与基因转录过程。界面配体分布通过影响整合素间距与流动性，调控分子链的组装及细胞内牵引力的产生，令细胞以伪足或应力纤维等不同粘附方式适应多样化的界面结构。而细胞应力纤维不仅会匹配界面形貌变化，且能够利用牵引力，重塑界面结构，优化细胞与微环境的界面相互作用力。总而言之，配体分布与细胞相互适应，通过力平衡的方式调控细胞内牵引力，进而影响细胞行为与功能。

S16-3 力学微环境与动脉硬化

周菁
北京大学

动脉（粥样）硬化是诱发心肌梗死、缺血性脑卒中等重大心血管疾病的病理基础，是糖尿病、慢性肾脏病、高血脂的严重并发症，对人类健康构成极大威胁，需要我们深入理解其病生理机制以提高预防和诊疗水平。血管壁细胞功能稳态与失衡决定了血管的健康与否，其失衡是动脉（粥样）硬化重要发病机制。这种稳态与失衡是管壁细胞对来自于循环和血管外膜中生化性损伤因子的反应及与血管局部机械力学微环境（血流剪切力、机械牵张、细胞外基质刚度和拓扑等）相互作用的结果。血管内皮和平滑肌细胞表达的机械力信号传感器作为受体分子将力学信号转化为化学信号，决定细胞增殖、迁移、凋亡、分化、分泌和代谢。细胞膜表面特殊受体（如整合素、骨形态发生蛋白受体、盘状结构域受体等）与细胞核（如核骨架和细胞骨架复合物的连接体等）均可充当力信号传感器，介导血管内皮和平滑肌细胞对力学信号的应答，影响血管功能并参与疾病发生发展。改善血管局部力学微环境或者靶向力信号传感器及下游信号途径已在实验研究中展示出对动脉（粥样）硬化防治的转化和应用前景。

S16-4 温度微环境与免疫监视

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同济大学

免疫细胞的粘附与迁移是机体免疫与宿主防御的关键环节。免疫细胞表面的整合素与细胞所处微环境之间的交互作用对于调控免疫细胞的粘附与迁移至关重要。发热是机体受到病原体感染、产生损伤或者炎症后的一种复杂的生理应激反应，是一种重要的细胞微环境刺激。发热可以促进免疫细胞迁移到次级淋巴器官或者炎症部位而调控免疫稳态维持和免疫监视，但是发热所产生的高温物理信号如何调控生物信号（如：免疫细胞的粘附与迁移）的机制还不清楚。我们猜想：热休克蛋白作为响应温度变化最迅速的一类蛋白，可能是连接高温物理信号和生物信号之间的桥梁。通过一系列实验研究发现：发热通过热休克蛋白 90（Heat shock protein 90, Hsp90）-α4 整合素热感应信号轴，将高温物理信号转化为细胞内生物信号，诱导 α4 整合素在细胞膜上活化并聚簇，并向内传递信号引发下游细胞骨架重排，最终促进了免疫细胞迁移到次级淋巴结与感染部位。该项发现对临床上发热处理现存的误区具有重要指导意义：在身体条件允许情况下，体温维持在 38.5 ℃以上一段时间将有效促进免疫细胞的迁移和对感染的清除。本研究成果开辟了温度等微环境调控免疫监视的新思路，深入探究 Hsp90-α4 整合素信号轴介导的免疫细胞定向迁移，将为炎症和癌症等免疫相关疾病的治疗提供了新方向。

S17：生殖科学与生殖健康

S17-1 双胎生长不一致的分子机制探讨

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选择性生长受限（sIUGR）是单绒毛膜双胎妊娠中的一种特殊妊娠并发症，通常 sIUGR 胎盘在两胎儿中的分配显著失常，小胎儿侧的胎盘具有出血流供应不足、浸润能力下降等表现。因其遗传学背景与母体环境完全一致，sIUGR 双胎生长不一致的病理学起因很大程度上来源于胎盘功能不全。已有研究表明血管生成、氧化应激、表观修饰异常等均与 sIUGR 发病相关。本研究中，利用 sIUGR 两胎儿胎盘的高通量蛋白组学检测，发现血管生成通路被显著富集，其中血管生成蛋白 MTDH 在生长受限胎儿胎盘的表达水平显著低于生长正常胎儿。体内外细胞实验证实敲低 MTDH 能够显著促进滋养层细胞的功能。深入挖掘后发现

嗜碱性粒细胞前体蛋白（proMBP）在两胎儿间的表达也呈现出极强差异。利用冷冻电镜技术解析了 proMBP 和 STC2 两个抑制剂分别与妊娠相关血浆蛋白 A(PAPP-A)结合的空间结构，阐释了共价键介导的外位结合的结构基础，探索了其在调控 sIUGR 胎盘功能和引发双胎生长不一致的分子机制。

S17-2 RNF17-ADAD2 复合物介导 P-body 生成调控 piRNA 通路及精子发生

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Pachytene piRNA 的生物合成是生殖细胞发育的一个标志性事件，与 pre-pachytene piRNA 生物合成不同，Pachytene piRNA 合成缺乏一个被称为 Ping-pong 循环的二次扩增过程。然而，这种 Ping-pong 循环的抑制和发生的场所仍然不清楚。在这个研究里，我们发现一种睾丸特异性蛋白 ADAD2 与 TDRD 家族成员蛋白 RNF17 相互作用，并与 P-body 相关。重要的是，我们发现 ADAD2 可指导 RNF17 抑制生殖细胞中 Pachytene piRNA 生物合成过程中的 Ping-pong 循环活性。有趣的是，我们还发现 Adad2 或 Rnf17 的缺失会导致彼此定位错误，导致 Ping-pong 循环活性减弱，次级 piRNA 过度产生，减数分裂阶段的 P-体完整性被破坏，最终引起精子发生阻滞在圆精子阶段被。总之，我们研究揭示了 P-体在抑制 Pachytene piRNA 生物合成中的 Ping-pong 循环活性的新机制。

S17-3 Redox homeostasis in the uterine epithelium is critical to embryo implantation

袁佳
山东大学

The uterine epithelium undergoes a dramatic spatiotemporal transformation to enter a receptive state, involving a complex interaction between ovarian hormones and signals from stromal and epithelial cells. Redox homeostasis is critical for cellular physiological steady state; emerging evidence reveals that excessive lipid peroxides derail redox homeostasis, causing various diseases. However, the role of redox homeostasis in early pregnancy remains largely unknown. We found that uterine deletion of Glutathione peroxidase 4 (GPX4), a key factor in repairing oxidative damage to lipids, confers aberrant receptivity and defective implantation, leading to infertility. To further pinpoint Gpx4's role in different cell types, uterine epithelial-specific Gpx4 was deleted by a Ltf-Cre driver; the resultant females were infertile, suggesting unbalanced redox homeostasis in the uterine epithelium compromises receptivity and

implantation. Our study reveals the pernicious impact of unbalanced redox signaling on embryo implantation and suggests the obliteration of lipid peroxides as a possible therapeutic approach to prevent implantation defects.

S17-4 子痫前期发生中的“矛”与“盾”

王广
暨南大学

妊娠早期出现的胎盘滋养细胞侵袭不足导致子宫螺旋动脉重铸障碍是子痫前期发生发展的重要机制之一，而滋养细胞的侵袭与子宫螺旋动脉平滑肌细胞的被替换恰如“矛与盾”的关系。我们通过 DIA 蛋白质组学和临床样本发现子痫前期胎盘组织中 FTL 表达水平显著低于正常胎盘组织，通过免疫组化等方法证实该蛋白主要表达在滋养细胞（矛）中，为了进一步探讨 FTL 与子痫前期的因果关系，本研究团队使用腺病毒载体作为工具，敲低孕鼠胎盘滋养细胞 FTL 表达，结果发现敲低孕鼠胎盘滋养细胞 FTL 可诱导孕鼠出现子痫前期样表型，这可能与滋养细胞的铁死亡密切相关；我们又发现 α2 巨球蛋白（A2M）在人螺旋动脉平滑肌（盾）上有显著表达，且在 PE 孕妇血浆及螺旋动脉平滑肌中均表达升高，过表达 A2M 后的孕鼠也可出现子痫前期样症状，体外实验显示 A2M 的高表达显著维持了螺旋动脉平滑肌的存活，使得子宫螺旋动脉重铸障碍发生。以上研究从螺旋动脉重铸的角度揭示了子痫前期发生中“矛与盾”的重要性，为子痫前期的发生机制提供了一定的理论和实验依据。

S17-5 内源性逆转录病毒衍生增强子调控滋养层细胞谱系分化的机制

曹彬
厦门大学

滋养层干细胞沿不同路径分化为结构及功能迥异的滋养层细胞亚型，是胎盘发育及功能维持的重要细胞生物学基础。合体化是人类滋养层细胞的主要分化途径之一，即单核滋养层细胞通过细胞融合形成巨大多核合体滋养层细胞（Syncytiotrophoblast，STB）。但目前对人类滋养层干细胞（Human trophoblast stem cell, hTSC）分化为 STB 的调控机制的认识仍然十分有限。人类基因组的重要组成部分内源性逆转录病毒（Endogenous retrovirus, ERV）序列，可作为编码蛋白及顺式调控元件等深刻影响着基因组的结构及基因表达。我们利用 hTSC 及胎盘类器官等体外分化研究模型，描绘了 hTSC 向 STB 分化过程中代表性组蛋白修饰在基因组的动态分布及变化特征。发现部分 ERV 衍生增强子在 hTSC 中兼具 H3K27ac 和 H3K9me3 的双价修饰特征，并在合体化过程中失去抑制型的 H3K9me3 修饰转变为转录激

活状态。其中，灵长类动物特有的MER50双价修饰增强子富集于STB分化调控基因的附近，从而促进基因的转录激活。在转录活跃的MER50增强子临近基因中，寻找并鉴定到TNFAIP2及 RAI14 等一系列新型合体化调控基因。我们的研究工作揭示了内源性逆转录病毒衍生增强子通过促进关键合体化基因表达调控滋养层细胞谱系分化的表观遗传学机制。

S17-6 Haploid-genetic screening of trophectoderm specification identifies

帅领
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Trophectoderm (TE) and the inner cell mass (ICM) are the first two lineages in murine embryogenesis and cannot naturally transit to each other. The barriers between them are unclear and fascinating. Embryonic stem cells (ESCs) and trophoblast stem cells (TSCs) retain the identities of ICM and TE, respectively, and thus are ideal platforms to investigate these lineages in vitro. Here, we develop a loss-of-function genetic screening in haploid ESCs and reveal many mutations involved in the conversion of TSCs. The disruption of either Catip or Dyrk1a (candidates) in ESCs facilitates the conversion of TSCs. According to transcriptome analysis, we find that the repression of Dyrk1a activates totipotency, which is a possible reason for TE specification. Dyrk1a-null ESCs can contribute to embryonic and extraembryonic tissues in chimeras and can efficiently form blastocyst-like structures, indicating their totipotent developmental abilities. These findings provide insights into the mechanisms underlying cell fate alternation in embryogenesis.

S18：神经退行性疾病：从发病机制到实验治疗

S18-1 Integration of stress by transcriptional factors in aging and aging-related diseases

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细胞衰老是细胞在应答一系列内、外源性应激时出现的复制阻滞状态，是一种独特的细胞命运。衰老细胞数目的增加是机体衰老和年龄相关疾病发生的基础，因此，深入探究细胞衰老演进的分子机制并揭示关键调控分子，将为延缓衰老及防治年龄相关性疾病提供新的策略。转录因子是细胞命运决定中发挥重要作用的核心蛋白，通过与基因组中的特定序列结合，

改变基因表达水平，从而驱动细胞代谢等状态变化，对转录因子活性的精细调节是触发或阻止细胞衰老的基本调节方式之一。我们课题组发现：（1）应激通过调节转录因子 TFEB 调控自噬-溶酶体介导的细胞分解代谢；（2）应激通过调节转录因子 MEF2 调控 mTORC1 激酶介导的细胞合成代谢。MEF2 和 TFEB 活性的变化控制不同应激条件下细胞“合成”及“分解”代谢状态的适应性改变，决定了不同的细胞命运。研究显示：（1）转录因子 TFEB 是调节溶酶体生成和细胞自噬活性的关键分子。我们发现伴侣分子 HSP90AA1 与转录因子 TFEB 结合，协同 TFEB 入核和下游基因转录，从而促进溶酶体生成；HSP90AA1-TFEB 通路在细胞营养缺乏时活化，并调节卡路里限制诱导的线虫寿命延长；蛋白激酶 Cdk5 在多种应激条件下活化，通过磷酸化 HSP90AA1 第 595 位丝氨酸阻断其与 TFEB 的结合，抑制营养缺乏时 TFEB 的转录活性和细胞溶酶体生成，从而促进细胞衰老，使线虫寿命缩短（Autophagy, 2022）。（2）既往研究证实 mTORC1 信号通路是代谢和衰老的主要调节器，mTORC1 过度活化与细胞衰老和肿瘤发生密切相关。我们发现转录因子 MEF2A/D 通过调节 FNIP1/2 表达水平控制 mTORC1 对营养物质和生长信号的感知及活化，进而影响细胞蛋白与脂质合成和自噬活性等系列稳态调控过程；生长因子信号刺激可以活化酪氨酸激酶 c-Src，c-Src 通过直接磷酸化 MEF2D 增强其转录活性和 FNIP1/2 表达，使 mTORC1 过度活化，参与细胞衰老调节和肿瘤发生（Autophagy, revised）。此外，我们还发现分子伴侣介导的自噬（CMA）直接降解 Nrf2 的负调控因子 Keap1；慢性氧化应激时 CMA 活性增加以维持 Nrf2 功能和细胞存活，并且 Nrf2 可以转录 CMA 的主要限速分子 LAMP2A 以提高细胞 CMA 活性，形成抗氧化应激的正反馈调节环路（Aging Cell，2022）。上述研究系统揭示了在细胞响应不同应激过程中关键转录因子活性变化调节细胞衰老的具体机制，可能为理解衰老和年龄相关疾病发生提供新的理论基础。

S18-2 小胶质细胞代谢紊乱在阿尔茨海默病发生中的作用机理

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老年痴呆（Alzheimer’s Disease, AD）是一种以进行性认知功能障碍为主要特征的神经退行性疾病，其发病机制尚需进一步探究。我们的研究发现小胶质细胞代谢紊乱驱动了 AD 的发生发展，同时靶向小胶质细胞代谢重编程可以改善 AD 模型的病理和认知障碍。

S18-3 神经退行性疾病大脑中一种新的小胶质细胞亚型的鉴别

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在帕金森病和阿尔茨海默病等神经退行性疾病的发生发展中，小胶质细胞始终扮演着至关重要的角色。神经退行性病变过程中，具有免疫监视功能的小胶质细胞被激活并且转变为过度活跃的病理响应状态。传统观点认为，在此过程中，激活的小胶质细胞可原位增殖，使激活的小胶质细胞群得到扩增。我们在神经退行性疾病大脑中发现一种表达硫酸软骨素蛋白聚糖 4（*Cspg4* 或 NG2）的小胶质细胞亚群，这类细胞具有增殖能力。在多种帕金森病的小鼠动物模型大脑中，*Cspg4*$^{+}$小胶质细胞的比例均显著增加。单细胞转录组分析结果显示，在 *Cspg4*$^{+}$小胶质细胞中，高表达 *Cspg4*（*Cspg4*^{high}）的细胞亚群呈现独特的转录组特征，与已知的神经退行性疾病相关的小胶质细胞亚群相比，它们细胞周期相关基因的表达丰度较高，而神经炎症与吞噬作用相关基因的表达水平较低。在脑内删除小胶质细胞后，这类小胶质细胞亚型的再生速度也远高于不表达 *Cspg4* 的小胶质细胞。在阿尔茨海默病患者脑内，我们也检测到了这一群高表达 *Cspg4* 的小胶质细胞。综上所述，我们的研究表明，在神经退行性病变的过程中， *Cspg4*^{high} 小胶质细胞是增殖的小胶质细胞的新的来源。该研究在一定程度上解析了神经退行性疾病中增殖性小胶质细胞的特征与功能，为这类疾病的干预提供了新的思路。

S18-4 神经退行性疾病的感知觉机制

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神经退行性疾病及慢性疼痛相关的疾病已成为重要的社会问题，因此全面了解神经退行性疾病感知觉的生理心理机制和调节机理显得尤为重要，对更有效地开发针对性治疗方法具有关键意义。近年来我们运用多模态磁共振成像技术，聚焦于脑皮层-脑干-脊髓的痛觉上行传递和下行抑制环路以及疼痛慢性化的神经机制研究。本次报告将介绍我们基于脑脊髓成像的神经通路和神经调控研究以及在神经退行性和脱髓鞘神经疾病等相关的临床研究。

S18-5 阿尔茨海默病非人灵长类动物模型的建立及干细胞治疗探索

景乃禾
广州实验室（生物岛实验室）

阿尔茨海默病（Alzheimer's disease, AD）是一种与衰老相关的进行性神经退行性疾病。AD 动物模型在研究 AD 发病机制、药物开发、AD 治疗策略等方面都至关重要。非人灵长类动物与人类在进化上最为相近，是用来模拟 AD 的最佳动物。通过脑立体定向手术，我们将合成的人源 β 淀粉样蛋白寡聚体（Amyloid-$\beta_{1\text{-}42}$ oligomers，AβOs）注射到老年非人灵长类食蟹猴脑实质中，可以诱发形成与 AD 相关的多种神经病理特征：大量的 Aβ 斑、Tau 神经纤维缠结、神经炎症和神经元的退行性病变以及突触的丢失等。同时，我们在模型动物脑中还检测到 Aβ 斑和 Tau 缠结共存的神经炎症斑（Neurotic plaque），提示在非人灵长类脑中可以真实再现 AD 的发病过程。此外，我们发现 AβOs 注射到中年食蟹猴脑实质，并不能诱导出与老年食蟹猴脑中相似的 AD 病理特征，提示衰老脑环境对 AβOs 诱导非人灵长类 AD 模型的重要性。目前，临床上还没有可以治愈 AD 或者阻止、延缓 AD 发病的药物或者其它有效的治疗策略。近年来，随着干细胞和重编程技术的发展，使得从人体细胞中诱导建立神经干细胞/祖细胞（human induced neural stem/progenitor cells, hiNPCs）成为可能。我们将人外周血单核细胞来源的 hiNPCs 移植到 AD 小鼠海马区，可以有效改善 AD 小鼠的认知功能，提示人源 hiNPCs 在干细胞替代治疗 AD 上是一种极具应用前景的供体细胞。进一步，我们发现人源 hiNPCs 在非人灵长类动物脑内可以长期存活，并分化为功能成熟的神经元；长期进行免疫抑制剂治疗可以有效抑制 hiNPCs 在非人灵长类脑中引起的免疫排斥反应。这些结果为开发安全有效的、基于人源神经干细胞的细胞替代治疗策略的建立，及其在神经退行性疾病治疗中的应用提供了宝贵的线索。

S19：神经调控能量代谢和平衡

S19-1 中枢神经调控代谢的机制研究

刘铁民
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大脑在调节能量代谢和糖代谢中的重要作用。目前市场主要上的减肥药物的作用机理主要是集中在两个大脑减肥通路。第一个就是通过药物激活羟色胺 2C (5-HT2CR) 受体来抑制饮食。早期最有名的减肥药物是芬氟拉明(d-fenfluramine d-Fen), 然而由于在心脏方面的副作

用，这两款药于 1997 年退出市场。在间隔 13 年后，2012 年美国食品药品管理局(FDA)正式批准了 Arena 制药公司的新减肥药盐酸氯卡色林 (lorcaserin)上市。盐酸氯卡色林的减肥作用靶点也是羟色胺2C受体。第二个就是中枢神经α-黑素细胞刺激激素/黑皮质素4受体（MC4Rs）途径在调节能量代谢和糖代谢中的作用。研究表明 α-黑素细胞刺激激素/黑皮质素 4 受体（MC4Rs）途径是最有潜力的抗肥胖途径之一。黑皮质素 4 受体缺乏动物和人类显示重度肥胖。我们对这两个大脑减肥通路的研究着眼于将基础研究中的新发现转化为新颖的药理和临床干预疾病的研究。

S19-2 摄食行为的神经机制及免疫调控

占成
中国科学技术大学

Both the hypothalamus and the brainstem contain critical neuronal populations that control feeding behavior. The nucleus of the solitary tract (NTS) in the brainstem is the first brain area of integration of gastrointestinal vagal afferents. While many studies have emphasized the importance of vagal afferents to the NTS in inducing satiation, little is known about whether and how the vagal-NTS pathway senses orexigenic signals and stimulates feeding. Our previous study discovered that a population of catecholaminergic NTS neurons coexpressing neuropeptide Y (NPY) receive vagal afferents and stimulate feeding. Interestingly, these brainstem orexigenic neurons may stimulate feeding behavior independent of the first-order orexigenic neurons (e.g., AgRP neurons) in the hypothalamic arcuate nucleus, and vice versa. We hypothesize that first-order orexigenic neurons in the brainstem and hypothalamus function independently and redundantly to maintain ad libitum feeding and body weight homeostasis.

S19-3 Diet-induced inflammation in the paraventricular thalamus controls compulsive sucrose-seeking

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Overconsumption of palatable food initiates addiction-like neuroadaptive responses in the brain reward circuitry and drives the development of compulsive eating behavior. However, how dietary excess induces hedonic eating remains elusive. Here, we reported that high-fat diet (HFD)

impeded a cue-induced suppression of sucrose seeking in adult mice. Remarkably, this HFD-induced compulsive sucrose seeking is due to enhanced cue-triggered neuronal activity in the anterior paraventricular nucleus of the thalamus (aPVT) resulting from microglia activation in this area brought about by HFD. Thus, metabolic inflammation in the aPVT produces an adaptive response to cues of threat, leading to compulsive food foraging. This diet-induced adaptive response in the aPVT may be evolutionarily important to survive a food shortage but can be hijacked by food surplus to cause obesity.

S19-4 能量稳态的神经调控机制

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生物体必须对低温环境作出适当的反应来维持机体能量稳态，从而保证生物体存活。然而，抵抗寒冷引起的能量稳态失衡的特异性神经元类型与神经环路仍然还不清楚。这里，我们在下丘脑弓状核发现了一群新型的冷敏感神经元。通过单细胞测序和原位杂交验证这群神经元与已知的神经元类型都不一样，并且有自己独特的电生理属性。随后通过体内钙成像技术发现寒冷温度可以激活这群神经元，同时炎热的温度会抑制它们。沉默这群神经元的突触输出，导致小鼠整体能量代谢下降，摄食降低，反过来化学遗传学激活会导致小鼠整体能量代谢上升，摄食增加。这表明，这群新型神经元对能量稳态的调控属于镜像不平衡模型，而不是传统的跷跷板模型。进一步，我们利用 fMost 技术对这群神经元进行全脑投射重构，发现其投射到已知的能量稳态相关脑区，后续通过神经元操纵技术确认了其调控机体的摄食和能量代谢的神经环路。总之，我们鉴定了一群新型神经元帮助我们抵抗环境压力维持机体的能量稳态。

S19-5 雌激素调节体温与代谢的神经机制

张智
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Estrogen signaling in the hypothalamus tightly regulates body temperature and metabolism while the precise neurons and their circuits remain unclear. The medial preoptic area of the hypothalamus (MPA), a key site for thermoregulation, is enriched in estrogen receptor alpha (ERα) expression. We found that chemogenetic activation of ERα+ MPA neurons dramatically reduced core body temperature with increased heat dissipation and suppressed heat production. The

reduction in temperature lasted up to 3 days and was accompanied by decreases in oxygen consumption, heart rate, respiratory rate, physical activity and brain activity, all of which resemble the key features of hibernation or torpor. Indeed, using in vivo calcium imaging we found that ERα+ neuronal activity was associated with natural torpor induced by prolonged fasting. Conversely, selective ablation of these neurons disrupted normal body temperature regulation and blocked the full expression of fasting-induced torpor. Overall, these findings suggest that estrogen-sensitive MPA neurons are required for thermoregulation and could direct thermoregulatory and metabolic responses to energy deficiency inducing a torpid state. The ability to induce a deep, persistent, and repeatable state of hypothermia and hypometabolism in non-torpor animals including humans may help in the treatment of brain injury, stroke, or cardiac arrest.

S20：教育信息化专业委员会专题研讨会

S20-1 基于 ESP 可穿戴设备的早临床教学设计与实践

羡晓辉
河北医科大学

河北医科大学病理生理学教研室遵循以“学生中心，目标导向”的教学理念，基于 ESP 可穿戴设备开展早临床教学设计。撰写临床案例剧本，设置“患者”、“医生”“患者亲友”等多种沉浸式角色，由同学进行演绎，促进学生在演绎中深刻理解相关的病理生理生理学基础和临床联系。教学实施过程分为知识储备、角色演绎、复盘拓展和形成性评价几个过程。首先通过理论课堂掌握基础理论，通过机能学动物实验观察病理现象，从而完成知识储备；基于 ESP 可穿戴设备按照临床案例剧本分角色演绎临床案例，完成“早临床”实践过程；通过思考题和病例汇报，完成复盘拓展；最后结合客观评价和师生、生生形成性评价完成综合评价考核。该教学设计为学生提供“身临其境”的沉浸式学习环境，促进教学活动的趣味性和学习主动性，将基础医学和临床医学进行有效的衔接，初步培养学生的临床思维和技能，实现从知识、能力和素质三个层面的全面提升。

S20-2 医学实践课程数字化转型的探索与实践

沈静
浙江大学

我国教育领域的数字化改革正全面迈入深度融合阶段。如何实现从起步、应用和简单融合数字技术，到真正树立数字化意识和思维、构建智慧教育发展生态、形成全要素、全流程的教育数字化体系和机制成为新的挑战。浙江大学医学院的《生理科学实验》课程旨在以优质的实践课为立足点，全面助力医学创新人才培养，进行系列信息化建设：以胜任力为导向，将智能测评数据融入课程内目标矩阵；打通在线课程、新形态教材和虚拟仿真实验平台，构建“一体化数字教学资源”；通过数字化、多维度评价聚焦学习全过程，促进学生的深度学习。课程的成效评估显示，学生在反应、学习和行为三个层次显著提升，为加快中国特色的医学实践课程数字化转型提供了重要的经验。

S20-3 基于临床前构架的基础医学虚拟仿真综合实验建设成效

张鸣号
宁夏医科大学

随着我国高等教育教学信息化的高速发展，对基础医学实验教学提出了更高要求。本文介绍了我校自 2008 年以来，基于临床前构架，针对实验教学中的痛点问题，以临床问题为中心，以主要器官典型疾病为引导，引入“虚拟仿真+人工智能”场景化教学。通过“线上线下、虚拟实体”双向结合，聚焦“课前、课中、课后”三个维度，实施“思政元素、多学科知识、经典案例、理论与实践”四项融合，创设“知识-设计-虚拟-实体-反思”五步教学法，以“革新课程考核，多元评价反馈”为保障机制，铸就了“双结合三维四融五步”的基础医学实验教学新模式，促进了基础与临床有效衔接，学生学习兴趣和岗位胜任力大幅提升。建成线上线下混合、虚拟仿真两门国家级一流本科课程，虚拟仿真联盟 2021 年度百门实验教学应用示范课程，国家级虚拟教研室；教学团队获批国家级教学团队。

关键词：教育信息化；基础医学；虚拟仿真；临床前；建设成效

S20-4 基于“三位一体”理念的生理学线上线下课程教学探索

王觉进
南京医科大学

《生理学》是培养医学人才的一门重要基础课程，也是基础医学与临床医学之间的重要桥梁课程。通过教学，不仅使学生掌握生理学的基本知识和基本实验技能，而且要培养学生积极主动的学习精神和分析思考医学问题的能力。为适应医学教育模式的改变，推进“新医科”建设，我们在生理学教学的思政教育、课程安排、教学方法、考核以及课程监管方面进行深层次的教学改革创新。在教学过程中，围绕“以学生为中心”的教学理念，研发了国内首个“功能数字人”，并构建了“三位一体”教学模式为特色的教学系统，开创了生理学教学新模式，以落实注重能力培养，强化实践，结合临床，贴近科研的基础医学教学新理念。

S21：感觉与情感障碍交互作用

S21-1 Brain control of gastric motility induced by stress

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中国科学技术大学

Psychological and physical stressors have been implicated in gastric disorders in humans, and fMRI has indicated a link between response to stress in the brain and gastric motility. The mechanism coupling the brain to the stomach underlying stress-induced gastric motility has remained elusive. Here, we show that the stomach directly receives acetylcholinergic inputs from the dorsal motor nucleus of the vagus (AChDMV), which are innervated by serotonergic neurons in the dorsal raphe nucleus (5-HTDRN). Microendoscopic calcium imaging and multi-tetrode electrophysiological recordings in freely moving mice reveal that the 5-HTDRN→AChDMV→stomach circuit is inhibited with chronic stress accompanied by hypoactivate gastric function. Artificial activation of this circuit reverses the gastric dysfunction induced by chronic stress. Our study demonstrates that this 5-HTDRN→AChDMV→stomach axis drives gastric dysfunction associated with stress, thus providing insights into the circuit basis for brain regulation of the stomach.

S21-2 Regulation of chronic pain by orphan G protein-coupled receptor

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Chronic pain is a major global health problem that affects approximately one quarter of the world's population. At present, the mechanism of chronic pain is still unclear and treatment is difficult. There is an urgent need to find new effective therapeutic targets. G protein-coupled receptor (GPCR), a seven-transmembrane protein superfamily, plays an important role in intracellular signal transduction and widely participates in physiological and pathological processes, including pain sensation. So far, one-third of the drugs approved by the FDA are targeted at GPCR, making it one of the best candidates to be a new therapeutic target. Orphan GPCR is a subtype of GPCR receptors whose functions and endogenous ligands are still unclear. We are interested in the functions of orphaned GPCR expressed in the dorsal root ganglions (DRG) and primary sensory neurons in chronic pain. We investigated the expression patterns of orphan GPCRs in DRG tissues and their role in chronic pain through multidisciplinary techniques including in situ hybridization, transgenic mice, behavior, electrophysiology, and calcium imaging. We found that orphan GPCR was selectively expressed in specific cell subtypes in DRG tissues, and conditional knockout of orphan GPCR significantly relieved chronic pain in mice. Our findings suggest that orphan GPCR plays a crucial role in regulating chronic pain and could be a potential therapeutic target for treating chronic pain.

S21-3 初探光的非成像视觉功能

任超然
暨南大学

外界光照条件的变化深刻地影响着机体的诸多生理功能。光除了影响成像视觉外，还具有调节情绪、认知、疼痛、睡眠等非成像视觉功能。目前非成像视觉功能的神经机制尚不明确。我实验室近年来的研究发现，位于丘脑的腹外侧膝状体及膝状体间小叶（统称：腹侧外膝体）是介导非成像视觉功能的一个关键枢纽。腹侧外膝体所传导的光信息可通过控制下游多个脑区，分别调节情绪、记忆、痛觉、睡眠。这些工作不仅初步揭示了光调节脑功能的神经环路机制，也为光疗法在抑郁症、慢性疼痛等临床疾病治疗中的应用提供了新的理论依据。在本报告中，我将就相关进展进行汇报。

S21-4 Calcitonin gene-related peptide promotes inflammatory responses of $CD8^+$T cells

王芳
中山大学

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the most severe subtypes of cutaneous adverse drug reactions. They are characterized by widespread and painful erythema, blisters, and epidermal detachment. It has been well established that themajor mechanism of this lethal entity is mediated by CD8+ T cell-driven delayed immune reactions and a cytokine storm. However, although severe pain is a typical symptom, whether any neuroimmune pathogenesis is involved remains unclarified. We detected that levels of calcitonin gene-related peptide (CGRP) are significantly elevated in the blisters of patients with SJS/TEN. Following verification of the expression of Ramp1, the receptor of CGRP, on CD8+ T cells, we set an in vitro culture system to explore the effects of CGRP on CD8+ T cells. Strikingly, CGRP is sufficient and necessary to increase the percentage of CD215+CD8+ T cells and CD218a+T cells, which may enable them to respond cytokines like IL-15 and IL-18. Taken together, our findings imply a neuroimmune pathway that may participate in survival and immune responses of CD8+ T cells underlying SJS/TEN.

S22：血液生态与疾病专题

S22-1 Engineering a soft bone marrow organoid for hematopoietic stem cell rejuvenation

岳锐
同济大学

血液系统衰老的主要特征为造血干细胞数目增加、血液重建能力减弱、克隆性造血、淋系分化降低和髓系分化增加。骨髓基质细胞作为造血干细胞的关键微环境组分，其在血液系统衰老过程中同样发生了显著功能改变。然而能否通过干预骨髓微环境逆转造血干细胞衰老却仍不清楚。我们发现骨髓基质细胞在坚硬的 2D 培养条件下剧烈下调造血维持因子，而在柔软的 3D 水凝胶中培养能够显著恢复其造血维持功能。更为重要的是，与骨髓基质细胞进行 3D 共培养不仅能够维持造血干细胞自我更新，而且可以显著促进淋系分化并逆转其衰老表型。此外，原子力显微镜实验表明小鼠骨髓基质在衰老过程中发生显著硬化。总之，我们发现骨髓基质硬度密切调控造血干细胞衰老，体外重塑柔软的骨髓微环境可以有效年轻化衰老造血干细胞。

S22-2 Bone marrow granulopoiesis in neuromyelitis optica spectrum disorder

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B cells drive the immunopathology of neuromyelitis optica spectrum disorder (NMOSD), an autoimmune neurological disease with autoantibodies to anti–aquaporin-4 (AQP4-IgG) in 75% of patients. Bone marrow niche can sense immune activation and generate hematogenous cells to orchestrate inflammation. Yet the alterations of bone marrow hematopoietic cells in NMOSD and their potential impact on disease progression remain unknown. We show remarkably augmented granulopoiesis in bone marrow of NMOSD patients, accompanied by expansion of B cell clones. This aberrant granulopoiesis was mediated by JAK-STAT pathway and led to dramatic production of BAFF that drives the production of antibody-secreting cells and AQP4-IgG, which is also observed in NMOSD patients with relapse after receiving rituximab. In an open-label, single-arm trial of belimumab, a monoclonal antibody against BAFF, in 14 NMOSD patients, belimumab reduced relapse rate, antibody-secreting cells and AQP4-IgG. Thus, targeting bone marrow niche may present a new avenue to treat NMOSD.

S22-3 肿瘤髓外红系造血调控抗瘤免疫反应

朱波
中国人民解放军陆军军医大学

造血干细胞动态有序的谱系分化是机体维持正常生命活动的重要组成部分。然而，肿瘤患者常见合并贫血和髓系发育偏移的现象，参与肿瘤发展；而具体机制尚缺乏认识。我们利用谱系示踪等手段揭示荷瘤状态下脾脏髓外造血红系前体细胞（EPCs）向红细胞发育受阻，而转向髓系细胞分化，产生一个全新的免疫抑制细胞群体---红系来源髓系细胞（EDMCs）；并通过多个临床队列发现 EDMCs 显著抑制抗瘤免疫反应，削弱免疫治疗疗效；并确立了贫血是影响免疫治疗疗效的独立因素。此外，机制探讨中我们发现荷瘤状态下脾脏髓外 EPCs 线粒体自噬障碍是其异常分化的关键原因；当采用雷帕霉素等促进线粒体自噬药物干预可部分扭转 EPCs 异常分化。总之，我们发现荷瘤状态下 EPC 线粒体自噬障碍导致红系造血紊乱，显著抑制抗瘤免疫应答。

S22-4 多组学联合解析 AML 耐药机制

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急性髓系白血病（AML）是由于骨髓中造血祖细胞异常分化、细胞增殖不受控制而导致的血液肿瘤，其进展非常迅速，同时可引起贫血、中性粒细胞减少症及血小板减少症。Fms 样酪氨酸激酶 3（FLT3）是 AML 中最常见的突变基因之一，该突变通常预示着不良预后。目前已有靶向 FLT3 的药物如 Gilteritinib 等用于 AML 的靶向治疗，但经常会发生耐药导致患者治疗效果不佳。我们利用 CRISPR-cas9 个体化文库筛选得到了 Gilteritinib 的潜在耐药靶点，随后利用以蛋白组为中心的多组学联合分析，发现敲低该靶点可引起 FLT3 及其相关信号通路 STAT5、AKT 的活化，进而导致 AML 细胞的耐药。利用激动剂激活该靶点能增强 AML 对 Gilteritinib 的敏感性，促进细胞凋亡并减少克隆形成能力。体内实验也表明激动剂与 Gilteritinib 联合用药能减轻 AML 对 Gilteritinib 的耐药作用。总之，我们发现了导致 AML 对 Gilteritinib 耐药的一个新的潜在靶点，靶向该靶点联合 Gilteritinib 为 AML 的临床治疗提供了新的思路。

S22-5 造血干细胞移植重建规律解析及临床应用

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造血干细胞移植是恶性血液病、造血功能衰竭性疾病、遗传性血液病和代谢性疾病的重要治疗方式，是最为经典和成熟的干细胞临床应用方案。患者在接受移植后的重建过程同时受到供受者、原发疾病及移植物等多因素影响，而目前对移植后特别是早期造血重建相关研究仍十分匮乏。我们以再生障碍性贫血作为背景，对患者移植后一年内多个时间点的骨髓和周血样本进行单细胞转录组测序。首先对接受动员外干移植的患者数据进行了全面分析，描述移植后的重建规律，发现并验证了对急性移植物抗宿主病具有指示作用的粒祖细胞亚群。针对临床上脐血移植重建延迟的现象，我们对接受脐血移植和外干移植后患者样本的单细胞转录组数据进行比较，从移植物差异、移植后细胞成分变化、干祖细胞谱系偏好等多方面解释了脐血移植后的重建延迟，为移植后临床的早期介入提供了依据。总之，我们的研究是对造血干细胞移植后规律的全面解析，为临床治疗提供了重要的参考。

S22-6 显微镜下的骨髓造血：从多能干细胞到成熟血细胞

张济舟
中国科学技术大学

S23：内分泌学和代谢分会专题

S23-1 A new role of MDM2-p53 axis in metabolic diseases

郑竞业
香港理工大学

S23-2 代谢手术调控代谢内分泌及生殖内分泌

何瑞
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Abstract：Polycystic ovary syndrome (PCOS) is a common metabolic disorder among women of reproductive age, with increased risk of diabetes, overweight/obesity, and insulin resistance. Roux-en-Y gastric bypass (RYGB) has been shown to be an effective treatment for PCOS and related metabolic diseases, but its specific mechanism of action remains unclear. Ferroptosis is a newly discovered form of programmed cell death, iron-dependent and distinct from apoptosis, necrosis, and autophagy, which has been associated with metabolic diseases such as obesity and type 2 diabetes. This study aimed to investigate the potential role of ferroptosis-related pathways in the improvement of PCOS by RYGB surgery in mice. C57 BL/6J female mice were fed a high-fat diet and letrozole (200 μg/mouse/day, ig) for 21 days to induce insulin resistance and PCOS. The mice underwent RYGB surgery, and changes in body weight, glucose tolerance, and insulin resistance were monitored. Histomorphological and molecular biology experiments were conducted to assess changes in ovarian morphology and expression of ferroptosis-related signals. Results as following: RYGB surgery significantly reduced body weight of PCOS mice, improved glucose tolerance and insulin resistance, and enhanced ovarian morphology. Results of SIRT3 immunohistochemistry, Western blotting for p-AMPK/AMPK, p-mTOR/mTOR, and GPX4 showed that RYGB surgery may improve PCOS through the SIRT3-regulated AMPK/mTOR ferroptosis pathway. RYGB surgery improved PCOS in mice, potentially via the SIRT3-regulated

AMPK/mTOR ferroptosis pathway. This study confirms the efficacy of RYGB surgery in improving PCOS in mice and provides new insights into the underlying mechanisms involving ferroptosis-related pathways.

S23-3 Increased angiocrine factor R-spondin3 contributes to aerobic exercise-induced protection against acute kidney injury

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Abstract：Exercise training exerts protective effects against sepsis-associated multiple organ dysfunction. As a secreted protein highly expressed in endothelial cells, R-spondin 3 (RSPO3) has been reported to exert biological functions in regulation of vascular endothelial function. We found that aerobic exercise restored the lipopolysaccharide (LPS)-induced downregulation of RSPO3 in the kidney. Exercise training or RSPO3 supplementation attenuated, whereas inducible endothelial cell-specific RSPO3 knockout exacerbated LPS-induced renal glycocalyx loss, endothelial hyperpermeability, inflammation and acute kidney injury (AKI). Bioinformatics analysis results revealed significant increases in matrix metalloproteinases (MMPs) expression in kidney tissues of mice exposed to sepsis or endotoxemia, which was validated in renal tissue from LPS-exposed mice and LPS-treated human microvascular endothelial cells (HMVECs). Both RSPO3 and MMP inhibitor restored LPS-induced downregulation of tight junction protein ZO-1, adherens junction protein vascular endothelial (VE)-cadherin, and glycocalyx components syndecan (SDC)-1 and SDC-4, thus ameliorating LPS-induced endothelial cell leakage. Aerobic exercise or RSPO3 supplementation reversed LPS-induced upregulation of MMPs in renal tissues. Collectively, increased angiocrine factor RSPO3 may contribute to aerobic exercise-induced protection against LPS-induced renal endothelial hyperpermeability and AKI by suppressing MMPs-mediated disruption of glycocalyx and tight and adherens junctions. Our findings reveal a novel endogenous exerkine for renoprotection.

S23-4 白细胞介素 17 家族在胰岛发育和糖尿病中的作用及其机制研究

童攒
武汉大学

免疫细胞因子在糖尿病的胰岛 beta 细胞损伤中发挥重要的作用。白细胞介素 17 家族包

括 6 个成员(IL-17A-F)，可以结合 5 个不同受体(IL-17RA-E)，在抗感染免疫中发挥重要的作用，同时是多种自身免疫性疾病发病机制的核心因素。IL-17A 主要在免疫细胞中表达，招募中心粒细胞、促进炎症反应，在胰岛的免疫浸润和 beta 细胞损伤中发挥重要作用。与 IL-17A 高同源且结合相同受体的 IL-17F 在 beta 细胞中低表达，影响胰岛的生长发育和糖尿病的发生发展。靶向拮抗 IL-17A、IL-17F 的药物已获批上市用于治疗中重度斑块型银屑病和强直性脊柱炎。深入研究 IL-17A 和 IL-17F 在糖尿病中的功能可以为精准靶向治疗提供科学依据。

S23-5 生长激素促进脂肪细胞线粒体生物形成及改变其代谢的研究

王向东
山东大学

线粒体的数量和功能对脂肪细胞储存脂肪的量影响巨大。业已证明生长激素（GH）在发育成熟后具有降低体脂比率的效应，但其机制不明。我们的研究结果显示，GH 促进脂肪细胞线粒体密度增高；深入研究发现 GH 促进线粒体生物形成相关基因（PGC-1α，TFAM，POLG 在脂肪）在脂肪细胞中的表达。高脂饮食所致肥胖动物经 GH 干预，其内脏和皮下脂肪细胞中 PGC-1α，TFAM，POLG 的表达也显著升高。我们对 GH 调控这三种基因表达的机制进行了研究，发现 GH 三条信号途径对 PGC-1α， POLG 表达的调控具有协同作用。我们还发现 GH 通过调控 Cidea 进而调控 UCP1 表达的通路。研究具理论和实际意义。

S23-6 Effects of peptidoglycan on the development of lean NAFLD

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Abstract:Peptidoglycan (PGN) derives mainly from gram-positive bacteria. Elevating evidences suggested roles of PGN for the insulin resistance, metabolic inflammation and liver disorders. But, whether PGN affects the occurrence of non-alcoholic fatty liver disease (NAFLD) remains unclear. Among patients with NAFLD, 19.2% showed normal or lean body size (BMI<25kg/m^2), and 40.8% did not develop obesity (BMI<30kg/m^2). There is still a lack of research on the pathogenesis and physiological mechanism of lean NAFLD development, which is a key scientific problem that needs to be solved urgently. Here, we reported that subcutaneous infusion of purified PGN for 4 eeks significantly increased hepatic levels of triglyceride, inflammation and fibrosis in lean mice fed normal chow. These alterations were associated with

raise in circulating triglyceride, cholesterol, insulin content and inflammatory cytokines. PGN significantly increased triglyceride contents and lipogenesis related genes in primary hepatocytes or LO2 cells, either in basal or oleic acid treated conditions. Administration of PGN stimulated the expression of NOD2, as well as phosphorylation of p65 and IκBα, leading to subsequent nuclear translocation of p65. Over-expression of NOD2 significantly enhanced the phosphorylation of p65, levels of nuclear PPARγ and SREBP1, followed by increase in triglyceride contents in LO2 cells treated with or without oleic acid. Further, over-expression of NOD2 significantly augmented the up-regulation of PPARγ induced by rosiglitazone. Inhibition of NFκB blocked the effect of NOD2 on the upregulation of PPARγ. Our study demonstrates that PGN stimulates hepatic lipogenesis by NOD2-NFκB-PPARγ signaling. PGN from intestinal microbiota is thus sufficient to induce the progression of lean NAFLD.

S24：肠道微生态与神经相关疾病

S24-1 肠道微生物组学在帕金森病中的研究进展

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近年来研究发现肠道微生物紊乱与帕金森病密切相关,而肠道微生物组学的研究

方法已被用于帕金森病的研究,包括基因组学、代谢组学和药物微生物组学等。通过肠道微生物基因组学研究发现，帕金森病疾病状态影响肠道微生物构成，肠道微生物基因检测可作为帕金森病可靠的诊断新方法。肠道微生物代谢组学研究揭示帕金森病患者粪便及血浆中肠道菌群代谢产物含量发生变化，而且部分代谢物可作为帕金森病诊断的标志物，肠道菌群代谢产物可能介导肠道菌群与帕金森病发病的复杂联系。药物微生物组学研究发现，肠道微生物能够影响帕金森病患者左旋多巴疗效，而帕金森病药物也能影响肠道菌群构成，药物微生物组学研究将为提高帕金森病药物疗效提供新靶点。

S24-2 Ghrelin 合成调控及其在机体糖脂代谢中的作用

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胃体 X/A 样内分泌细胞是循环中 ghrelin 的主要来源，其合成分泌与机体的能量状态密

切相关，我们的系列研究发现长期能量过剩显著减少 ghrelin、尤其是辛酰化 ghrelin 的产生。相反，饥饿引起的能量缺乏明显增加 ghrelin、辛酰化 ghrelin 的含量。其机制是能量过剩激活、能量缺乏抑制 X/A 样细胞内雷帕霉素靶蛋白（mTOR）活性，进而分别减少或抑制 ghrelin 的合成分泌。组蛋白去乙酰化酶 5（HDAC5）通过减少 Raptor 蛋白乙酰化、激活 mTOR、进而抑制 ghrelin 的合成分泌。此外，mTOR 激活明显增加 ETV5 核转录因子的降解，而 ETV5 具有明显促进 ghrelin 辛酰化调节酶 GOAT 表达的作用，因此 mTOR 通过抑制 ETV5 进而降低辛酰化 ghrelin 产生。进一步研究发现，在敲除 X/A 样细胞内 mTOR 上游抑制分子 TSC1 激活 mTOR、明显减少 ghrelin 产生，改善高脂喂养诱导的肥胖及其糖脂代谢紊乱，相反敲除 mTOR 则显著增加 ghrelin 产生，恶化高脂喂养诱导的肥胖及其糖脂代谢紊乱。这些研究提示 X/A 样细胞内 mTOR 可以感知机体能量状态、调节 ghrelin 的合成分泌、从而调节机体糖脂代谢。

S24-3 肠道微生物菌与“脑-肠轴”：探索基于作用机制的因果关系

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肠道中定植了庞大的微生物群落—肠道菌群（肠道微生物组）。肠道菌群与健康和疾病密切相关，参与宿主生理活动和病理过程。肠道菌群与神经系统疾病的因果关系以及宿主互作机制，成为生命科学领域的研究热点，既有肯定“肠-脑轴”的实验证据，也有研究指出，肠道菌群和神经系统疾病例如自闭症，仅仅是一种统计学意义上的关联关系。“科赫法则“是验证因果关系、鉴定致病菌的金标准，然而，由于仍有超半数肠道菌种还没有在实验室成功培养，加上肠道菌株功能的冗余，针对肠道菌群这样的复杂系统，科赫法则本身也遇到了挑战。没有菌株资源，难以验证肠菌和疾病的因果关系，更无法研究肠菌-宿主互作机制。我们认为，在肠道菌群-宿主健康/疾病研究中，基于作用机制的肠菌-宿主互作关系，才有可能揭示肠道微生物对宿主健康或者疾病的真正影响。报告将介绍我们实验室构建的肠菌菌株资源库，以及基于菌株库资源开展的肠道菌群-宿主“肠-脑轴”研究结果，包括针对阿尔茨海默病患者和自闭症儿童的肠道微生物-宿主互作的研究结果。

S24-4 高原低氧诱导肠道激惹综合症 IBS 的 CRF 机制

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Irritable bowel syndromes (IBS) commonly induced by stresses have been the focus of

researches in recent years. However, IBS-like during high altitude hypoxia stress

(hypoxia) and the role played by corticotropin releasing hormone (CRF) in this disorder is not well understood. Here, we showed that hypoxia can produce constipation symptoms (IBS-C-like) with decreased in pain threshold, food intake, water intake and body weight in mice. A neural CRF brain-gut axis originating from periaqueductal gray (PAG) that modulates colon physiological function was identified. We showed that hypoxia stimulated CRF neural activity from the vlPAG brain-gut axis. Chemogenetic inhibition of the vlPAG-gut CRF neurons causes a decrease of fecal pellet output and body weight in both normoxia and hypoxia. Transcriptomic analysis showed that downregulated colon Tac1 expression from inactive colon provoked by hypoxia and isoflurane anesthesia, indicating that Tac1 gene was involved in hypoxia induced IBSC like. This was further validated by substance P antagonist (Aprepitant, ig) and immunohistochemistry (IHC) experiments. Hypoxia was shown to lead to a significant reduction the number of mast cells and trypase release, gene expression of proinflammatory cytokines and chemokines. A 5-HT4 receptor agonist (Prucalopride, ig) successfully improved fecal pellet output and food intake during hypoxia IBS-C-like. These findings proposed that CRF-SP-mast cells in brain-gut axis are involved in hypoxia IBS-C like and prucalopride has a potential role in alleviating constipation and improving appetite during hypoxia. This study highlights the mechanism of brain-gut in health and translation medicine.

S24-5 The central regulatory mechanisms of GI dysfunction in Parkinson's disease

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Gastrointestinal (GI) dysfunction is one of the commonest premotor symptoms reported in Parkinson’s disease (PD) patients. Ghrelin, a brain-gut peptide, contributes to the communication between brain and GI tract. In this study, we try to clarify the

neuroprotective effects of ghrelin on dopaminergic neuron and the reason for the

decreased plasma ghrelin levels and GI dysfunction in PD. Our studies showed both

decreased ghrelin levels and functional GI disorders are early events in PD patients and animal models. The subcutaneous administration of low-dose ghrelin via mini-osmotic pumps on α-synuclein A53T transgenic mice for 4 or 8 weeks could rescue the decrease levels ghrelin in plasma. What is even more exciting is that exogenous ghrelin treatment attenuated the loss of dopaminergic neuron by inhibiting oxidative stress and neuroinflammation. Impairment of cholinergic neurons in DMV is accompanied by GI disorders, including decreased stool wet

weight, stool dry weight, small intestine advancing rate, and gastric emptying rate, while exogenous ghrelin treatment can partially ameliorate GI dysfunction of α-synuclein A53T transgenic mice. Using pseudorabies virus retrograde trace method, the existence of a direct pathway from the stomach fundus to the DMV is shown. Taken together, we identified that the reduction in plasma ghrelin levels in the early stages of PD was caused by the lesion of cholinergic neurons in the dorsal motor nucleus of the DMV. Ghrelin established the communications between neurodegeneration and GI dysfunction in PD, and also provide a possible targets for the early diagnosis and therapy of PD.

S25：脂滴蛋白和生物活性脂质在代谢性疾病中的作用

S25-1 Alox15/15-HpETE 通过促进心肌细胞的铁死亡加重心肌缺血再灌注损伤

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心肌缺血再灌注(I/R)损伤导致的心肌细胞死亡是造成心功能障碍的重要原因。研究表明 I/R 可能导致的心肌细胞的铁死亡，然而其发生的时间窗口和调控机制仍不清楚。为了阐述上述问题，我们利用左前降支冠状动脉结扎小鼠模型进行了研究。我们发现，铁死亡是 I/R 后期主要的细胞死亡形式。针对生物活性脂质分子的靶向代谢组学分析表明，脂氧合酶 15（Alox15）的代谢产物在铁死亡的心肌组织中积累。免疫荧光实验证实 Alox15 特异性地在缝线下的左心室受伤区域内表达增加，并与心肌细胞共定位。在小鼠的心肌中特异性地敲除 Alox15，能够减轻 I/R 损伤并恢复了心功能。我们发现一种 Alox15 氧化花生四烯酸产生的中间代谢产物 15-羟过氧化四烯酸(15-HpETE)，是触发心肌细胞铁死亡的关键分子。我们探索了其作用的潜在机制，发现 15-HpETE 促进了转录辅因子 Pgc-1α 与 E3 泛素连接酶 RNF34 的结合，导致其被泛素化降解，进而造成线粒体生物合成减弱和形态异常。Alox15 的特异性抑制剂 ML351 可提高 Pgc-1α 蛋白水平，抑制心肌细胞铁死亡，保护受损心肌，促进心功能恢复。我们的结果证实了 Alox15/15-HpETE 介导的心肌细胞铁死亡在 I/R 损伤道德后期起着重要作用。

S25-2 亚油酸代谢产物 13-HODE 在年龄相关肝脏脂质沉积中的作用

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非酒精性脂肪性肝病（non-alcoholic fatty liver disease, NAFLD）是世界范围内的重大慢性疾病。除了遗传因素，饮食、年龄、环境等因素与 NAFLD 的发生发展密切相关。衰老是多种代谢性疾病的重要危险因素，其中包括 NAFLD。年龄因素影响肝脏脂代谢的机制还不清楚。衰老细胞通过分泌相应的物质影响组织的微环境是衰老相关疾病发生的重要机制。多不饱和脂肪酸可代谢为数量众多的生物活性脂质，这些活性代谢产物可作为信号分子影响细胞功能，但其在年龄相关肝脏脂代谢紊乱中的作用还未知。我们发现中年小鼠肝脏中衰老肝细胞和衰老肝细胞周围的肝细胞均出现更多的脂滴；衰老肝细胞的条件培养液可促进正常肝细胞出现脂质聚积。通过靶向脂质组学，我们发现肝脏中亚油酸的代谢产物 9-HODE 和 13-HODE 增加是中年小鼠 PUFA 代谢谱的特征性改变。9-HODE 和 13-HODE 的混合物显著增加了肝脏甘油三酯含量。转录组数据表明 9-HODE 和 13-HODE 影响一系列脂代谢相关基因的表达。我们进一步在原代肝细胞中发现 13-HODE 而非 9-HODE 激活了 SREBP1。为了探索其中的机制，我们通过 pull down 联合蛋白质组学鉴定出可以与 13-HODE 结合的蛋白，再通过分子对接以及表面等离子技术，发现 13-HODE 可与维持氧化还原平衡的关键酶过氧化氢酶（Catalase, CAT）直接结合。原代肝细胞中敲低 CAT 促进了肝细胞脂质沉积并增加剪切形式 SREBP1 的水平；肝细胞特异性过表达 CAT 则在细胞水平和动物水平均改善了 13-HODE 引起的肝脏脂质沉积。并且 CAT 过表达显著减少了中年小鼠肝脏中甘油三酯水平。综上，衰老的肝细胞通过产生更多的 9-HODE 和 13-HODE，影响肝脏微环境，其中 13-HODE 通过直接与 CAT 结合抑制其活性，引起肝细胞代谢紊乱，导致年龄相关的肝脏脂代谢紊乱发生。

S25-3 脂滴蛋白 17β-HSD13 及其磷酸化在 NAFLD 中的作用及机制

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脂滴蛋白的异常蓄积是 NAFLD 发生的重要病理基础。我们前期通过分离纯化正常肝脏和 NAFLD 病人肝脏脂滴，鉴定了一系列人类脂肪肝中表达显著改变的脂滴相关蛋白，并发现 17β-HSD13 参与了 NAFLD 的发生发展过程。我们对其展开了长期的研究，发现其翻译后修饰对蛋白功能和脂滴代谢至关重要。我们利用生物信息学方法分析，检测到 17β-HSD13 在不同物种中存在一个高度保守的 PKA 磷酸化位点；机制研究证实，17β-HSD13 是一个新

的 PKA 磷酸化底物，其 Ser33 位点可被 PKA 磷酸化。我们发现，在 17β-HSD13 Ser33 失活点突变敲入（S33A）的小鼠，其基础状态下表现为显著的脂肪肝表型，肝脏甘油三酯显著增加，伴随血 ALT 和 AST 的明显升高、血胰岛素水平的增加和血游离脂肪酸的降低。通过检测脂滴表面的一系列脂滴相关蛋白，我们发现脂滴水解的重要蛋白甘油三酯水解酶（ATGL）虽然在 S33A 小鼠中增加，但其辅因子 CGI-58 在 S33A 小鼠肝脏脂滴表面的表达显著降低。通过分子动力学模拟、confocal 共定位和 IP 等实验，发现 17β-HSD13-S33A 相比 17β-HSD13-WT 和 ATGL 结合更紧密，S33A 竞争性阻断了 ATGL 和 CGI-58 的结合，进而抑制了 ATGL 酶活性，导致脂滴水解的障碍和脂滴的大量蓄积。此外，S33A 小鼠显著加剧了高脂诱导的 NASH 进程和肝功能损伤。上述结果提示 17β-HSD13 蛋白 Ser33 的磷酸化在调节脂滴代谢平衡中发挥重要作用，也提示促进 Ser33 磷酸化的手段有可能改善 NAFLD 的发生和发展。我们进一步用计算机辅助药物设计及分子动力学模拟技术寻找到一个 FDA 批准的治疗哮喘的药物瑞普特罗（β2 受体激动剂）可靶向磷酸化 17β-HSD13，在原代肝细胞实验和小鼠体内均确认该药物可以通过激活 PKA 信号通路磷酸化 17β-HSD13 Ser33 位点，从而促进肝脂滴 ATGL 水解酶活性。在给予 NAFLD 造模的小鼠瑞普特罗灌胃 6 周后，可以显著抑制 NAFLD 的进展，改善肝脏功能，提示靶向 17β-HSD13 Ser33 磷酸化是干预 NAFLD 的一种新的手段。

S25-4 前列腺素合酶 mPGES-2 在 NAFLD 中的作用及机制

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在糖脂代谢紊乱的疾病中，非酒精性脂肪肝（Non-alcoholic fatty liver disease，NAFLD）是最为常见并棘手的代谢性疾病，目前在我国 NAFLD 患者人群近 2.5 亿人，未来将会成为终末期肝病的最主要原因。NAFLD 的最主要驱动因素是肥胖和糖尿病，其也会加快糖尿病的发生发展。申请人的研究发现小鼠全身性敲除 mPGES-2 在高脂饮食以及糖尿病 *db/db* 背景情况下会显著地减轻脂肪肝的发生发展。进一步探究显示小鼠敲除 mPGES-2 并不降低脂肪肝中 PGE_2 的合成，那么 mPGES-2 通过何种非 PGE_2 途径影响了肝脏脂代谢？申请人通过蛋白质组学分析发现，mPGES-2 敲除后会显著下调和脂质代谢相关的蛋白 CYP4A14，并且上调 ACOT4 最为显著。深入的机制探究发现 mPGES-2 会与 CYP4A14 上游的转录调控因子 NR1D1 竞争结合 heme，而 NR1D1 会通过抑制负性转录因子 E4BP4 的表达而升高 ACOT4 的水平，且抑制 CYP4A14 和上调 ACOT4 均可以有效地改善脂肪肝的发生发展。此外，本课题组筛选的 mPGES-2 抑制剂 SZ0232 也显示了对脂肪肝及肝炎的有效治疗作用。综上，该部分研究揭示了在肝细胞中敲除或抑制 mPGES-2 会增加细胞内游离 heme 的水平，促进 heme 与 NR1D1 的结合及其对下游 CYP4A14 和 E4BP4 的转录抑制，升高 ACOT4 的表达，

从而延缓了脂肪肝以及肝炎的发生发展。

S25-5 用于监测脂滴和脂滴-溶酶体自噬的小分子荧光探针

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脂滴-溶酶体自噬过程与神经退行性疾病、慢性炎症等疾病密切相关。因此，从生物科学和相关疾病诊断角度，监测脂滴与脂滴-溶酶体自噬过程具有重要价值。目前，鲜有能够同时监测脂滴与脂滴-溶酶体自噬动态过程的探针，无法满足进一步的实际应用。本课题组围绕着脂滴及脂滴-溶酶体自噬的监测识别展开了研究。本报告中，将着重汇报本课题组开发的“可变色”荧光分子用于监测脂滴与自噬动态过程，内容包括：（1）用于监测脂滴和脂滴-溶酶体自噬的双光子荧光探针；（2）肝纤维化病灶部位脂滴及其自噬过程的靶向识别。这类“可变色”有机小分子探针是研究脂滴与溶酶体自噬现象的理想工具，在脂滴及自噬相关代谢疾病的诊断方面具有巨大应用潜力。

S26：理论整合生理学专题研讨会

S26-1 主动健康：从理念到模式

李祥臣
国家体育科学研究所

S26-2 占比时中守恒的一元多次方程基础

刘承宜
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本文首次研究 N 个占比构成的一元 N 次方程。复杂系统的 N 个占比构成一个完备的集合。根据数学的韦达定理，N 个占比可以构成一元 N 次方程的根。该方程的系数正好是 N 个占比的多阶整合，其中 N 阶整合对应于 N 个占比的几何均值，一阶整合对应于 N 个占比的算数均值。该方程的系数是 N 个占比的对称性多项式，满足交换对称性。该方程的系数满足 Arndt-Schulz 定律，只有守恒区 Noether 定理成立。按照 Noether 定理，该方程的系数守恒，也就是 N 个占比的多阶整合守恒，构成占比时中守恒的数学基础。其中，三个占比

的情况已经获得唐璐和刘琳两个研究的证实。一个数据流如果满足时中守恒，可以经过参数调整得到健康标尺，相应的数据流可以通过参数标准化转化成占比数据流，后者的占比时中守恒，这个研究已经获得大量的证实。

S26-3 能量消耗占比时中守恒

唐璐
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本文首次研究每日能量消耗的时中守恒和占比守恒。根据 Pontzer 等人（2021）在 Science 发表的数据，本文发现三种能量消耗的时中和三种能量消耗占比的时中都满足守恒。假定两个时中守恒对于每个人成立，则可以从理论上研究三种能量消耗的变化。本文发现，基础代谢与食物热效应的和守恒。用 *a*、*b* 和 *t* 分别代表主动活动、基础代谢和食物热效应三种能量消耗在每日总能量消耗中的占比。本文发现，普通人（*a*<*b*）*t* 与 *a* 反向变化，但优秀人士（*a*>*b*）*t* 与 *a* 同向变化；普通人（*a*>*t*）*t* 与 *b* 同向变化，但低水平人士（*a*<*t*）*t* 与 *b* 反向变化；普通人（*a*>*t*）*a* 与 *b* 反向变化，但低水平（*a*<*t*）*a* 与 *b* 反向变化。以上理论预测都获得已有研究的支持，但有待设计实验的直接验证。

S26-4 钙促进分泌亲脂蛋白的清除与其在生殖道中的作用

岑慧枝
上海市生物医药技术研究院

S26-5 体成分占比时中守恒

刘琳
华南师范大学

本文首次研究体成分占比守恒。根据文献数据和有限实验，本文发现三种体成分占比的时中都满足守恒。假定时中守恒对于每个人成立，则可以从理论上研究三种体成分的变化。用 *m*、*f* 和 *o* 分别代表骨骼肌、脂肪和其它组织三种组织在身体质量中的占比。本文发现，普通人（*m*<*o*, *f*<*o*）或优秀人士（*m*>*o*, *f*>*o*）的 *f* 与 *m* 反向变化，增加 *m* 的锻炼可以降低 *f*，但运动强度降低会引起反弹；优秀人士（*m*>*o*, *f*<*o*）*f* 与 *m* 同向变化，相扑或举重等项目可以同事增加 *f* 与 *m*；肥胖人士（*m*<*o*, *f*>*o*）*f* 与 *m* 同向变化，增加 *m* 的锻炼无法降低 *f*。该理论预测获得已有研究的支持，但有待设计实验的直接验证。

S26-6 健康预期寿命

汪志胜
华南师范大学

本文首次根据能量消耗和体成分两种占比的时中守恒计算健康预期寿命。根据唐璐和刘琳的研究，假定能量消耗和体成分两种占比的时中守恒对每个人全生命周期成立，可以获得一个人一生健康标尺的变化。用某个年龄前所有健康标尺累计除以一生健康标尺的累计与一生健康标尺的几何均值的和表征健康概率，将健康概率和 1 与健康概率的差的几何均值称为健康时中，将健康时中与年龄的相关曲线称为健康曲线。根据定量差异界定健康曲线的平台区，将平台区右边与平台区最后一个健康时中定量差异刚好小于 0.805 的那个健康时中对应的年龄定义为健康预期寿命（HE）。本文发现，两个守恒的占比时中越小，HE 越长；健康时中变化越慢，HE 越长。该理论预测获得已有研究的支持，但有待设计实验的直接验证。

S27：消化与营养专题

专家组特邀报告

S27-1 The multifaceted GPER signaling in brain and gut

戎伟芳
上海交通大学

S27-2 干细胞调控肠道稳态的机制研究

于政权
中国农业大学 / 郑州大学

S27-3 营养行为干预研究探索

赵勇
重庆医科大学

S27-4 肠道巨噬细胞在稳态维持和免疫反应中的作用

胡小玉
清华大学

S27-5 The intestinal immune, microbiota, and therapy

朱书
中国科学技术大学

S27-6 神经元-肌肉信号轴调控肠道固有免疫的机制

涂海军
湖南大学

青年组专题报告

S27-7 固有淋巴样细胞谱系建立与活化调控机制研究

刘本宇
郑州大学

S27-8 Chronic stress leads to the dysfunction of intestinal stem cells

白荣盘
浙江大学医学院附属邵逸夫医院

S27-9 Novel opioid-based therapies to manage visceral pain devoid of side effects

于扬
苏州大学

S27-10 多巴胺调节肠胶质细胞释放胶质源性神经营养因子的机制研究

张晓丽
首都医科大学

S27-11 苏糖酸镁对肠易激综合征大鼠的内脏痛和情绪的作用及其机制

陈瑜
福建医科大学

S27-12 肝细胞 KLK8 通过促使巨噬细胞 M2 极化和 TGFβ1 分泌而参与肝纤维化的发生发展

伍次春
中南大学湘雅医院

S28：微生态交叉前沿与产业发展

S28-1 阴道微生态与中医药

韩月
江苏省中医院

阴道微生态是由多种阴道微生物群与局部免疫系统、宿主内分泌系统及阴道解剖之间共同形成一个相互作用、相互依赖、相互制约的阴道微生态平衡体系，在维持人体健康中发挥着不可替代的作用。研究发现：阴道微生态与宫颈癌、生殖系统感染等疾病的发生发展密切相关。中医药经典名方（完带汤等）、针灸治疗等对妇科疾病阴道微生态具有良好的调整作用，是通过恢复阴道微生态维护女性健康的重要手段。本报告将重点关注外阴阴道假丝酵母菌病完带汤的阴道微生态调整机制，以最新研究数据呈现阴道微生态与中医药调节研究进展。

S28-2 见“微”知著—慢性阻塞性肺疾病的气道微生态

付娟娟
四川大学华西医院

呼吸道微生态与呼吸系统正常功能的维持以及呼吸系统疾病的发生发展密切相关，呼吸道微生物生态系统的群落失调进而导致患者免疫功能紊乱可能是慢性呼吸系统疾病发生发展的重要原因。研究初步发现慢阻肺患者呼吸道菌群与健康人存在显著差异，表现为菌群多样性的降低和潜在致病菌的丰度增加。随着慢阻肺呼吸道微生态研究的增加，以多样性指数、差异物种描述慢阻肺气道菌群特征，不同研究间的结论并不一致。微生物间的相互作用对群落结构和功能有重要影响，本报告从呼吸道微生物互作网络角度呈现慢阻肺在疾病不同阶段的菌群特征，并揭示气道微生物互作网络与疾病表型及气道炎症间的密切联系。

S28-3 微生态与代谢性疾病

刘慧鑫
中国医科大学

S28-4 口腔微生态前沿

周学东
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口腔是人体与环境的最重要的交互窗口之一。口腔不同位点的微环境拥有独特的微生物群落，这些微生物群落受复杂的信号系统以及宿主和外部环境因素调节。口腔微生态的动态变化直接影响口腔感染性疾病—龋病和牙周病的疾病进程。口腔微生物与宿主相互作用，可通过沿“口腔-全身”的动态双向通信来反应全身免疫、代谢和神经系统的状态。已经有足够证据证明全身健康状态与口腔微生态的组成有关，口腔微生物微生态的破坏也可诱发或加重全身系统疾病，因此普遍认为口腔微生态可能会影响或反应全身健康。高通量测序技术及生物信息学技术的迅猛发展使得全面而深度研究口腔微生物组成为可能。随着微生物组学研究的深入，口腔微生物与多种重大慢性疾病间的关联逐一被证实，包括肿瘤、心血管疾病、早产、糖尿病、类风湿性关节炎、消化系统疾病等。口腔微生物在全身系统性疾病状态下的改变具有渐进式、可重复性的特点。因此，口腔微生物具备实时反映人体健康与疾病状态的可能，在疾病的风险预警及疗效预测中具有重要价值。

S28-5 全球肠道微生态研究与转化前沿进展

蓝灿辉
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自从 2007 年“人类微生物组计划”启动以来，全球掀起了微生物组尤其是肠道微生物组研究与转化的热潮。近些年来，相关研究频频登上顶尖期刊，从微生物组分析、微生物与疾病相关性、细胞与分子机制到干预与转化等方向，从微生物、免疫、神经到代谢等学科，从基础研究、临床实践到产业转化等场景，肠道微生物组都备受关注。在本次报告中，我们将尝试进行知识梳理和解读，讲述近期有哪些热点领域和研究成果值得关注，研究与转化有什么趋势，中国科学家有哪些突破等内容。

S29：大脑与机体多系统功能交互

S29-1 神经-免疫-内分泌-代谢网络相互调控

王立平
中国科学院深圳先进技术研究院

S29-2 自身免疫性脑炎的神经环路机制

胡霁
上海科技大学

S29-3 神经调控技术的进展和思考

袁逖飞
上海精神卫生中心

S29-4 体温的神经调控

沈伟
上海科技大学

S29-5 脂肪组织的神经支配和调控

曾文文
清华大学

S29-6 骨代谢的神经内分泌调控

杨帆
中国科学院深圳先进技术研究院

S30：肾脏基础研究与疾病机制专场——代谢与高血压

S30-1 血脂与血压交互调节的分子机制

阮雄中
重庆医科大学

S30-2 Dahl 盐敏感大鼠高血压形成的肾脏代谢机制

田中民
西安交通大学

S30-3 肾小管糖脂代谢异常促进 AKI-CKD 的机制

孙世仁
中国人民解放军空军军医大学

S30-4 肾脏细胞命运和功能的基因组精准调控

杨敬平
南京大学

S30-5 肾小管上皮细胞可塑性的表观调控机制

陈宇鹏
天津医科大学

S30-6 Pex11a 激活过氧化物酶体增殖与代谢抑制高血压肾损伤

翁华春
上海健康医学院

S30-7 前列环素及其受体在肾脏纤维化中的作用及机制

李菁
复旦大学附属华山医院

S30-8 朊蛋白激活 TBK1-IRF 通路促进肾脏纤维化

龙潭潭
南方医科大学

S30-9 线粒体内铜过载在肾脏纤维化中的作用及机制研究

朱赛雅
同济大学

S30-10 PRDM16 deficiency triggered by TGF-β signaling aggravated renal fibrosis by promoting tubular mitochondrial dysfunction

袁倩
华中科技大学

CP-1 远曲小管钾通道参与糖尿病盐敏感性高血压的机制研究

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肾脏远曲小管（distal convoluted tubule，DCT）位于髓袢升支粗段和连接小管之间，负责重吸收原尿中大约 5%~10%的 NaCl。作为 DCT 管腔膜侧主要的 Na^+转运体，钠-氯同向转运体（Na^+-Cl^- cotransporter，NCC）广泛参与机体 Na^+、K^+、Ca^{2+}、Mg^{2+}以及血压稳态的维持。2020 年，Puleo 等人报道高盐摄入并未显著抑制 Dahl 盐敏感大鼠 NCC 活性，提示了其在盐敏感性高血压进展中可能扮演重要角色。肾钠处理功能障碍及血压稳态失衡是糖尿病早期的特征性表现，然而其潜在机制尚不清楚。研究发现，无论是 STZ 诱导的 1 型糖尿病还是 leptin 受体缺失所致 2 型糖尿病动物模型均表现出 NCC 蛋白表达的普遍上调。我们近年来的研究表明，NCC 与 DCT 管周膜钾通道的活性变化密切相关。内向整流钾通道 4.1（inwardly rectifying potassium channel 4.1，Kir4.1）主要表达于远端小管管周膜，包括髓袢升支粗段、远曲小管、连接小管以及集合管。然而，其对于肾脏功能的重要性直到最近才被广泛报道。生理条件下，Kir4.1 可与内向整流钾通道 5.1（inwardly rectifying potassium channel 5.1，Kir5.1）相互作用形成一种电导约为 40-pS 的异四聚体钾通道。其中，Kir4.1 构成了绝大部分的功能性钾通道。作为 DCT 管周膜上唯一的钾通道类型，Kir4.1/Kir5.1 不仅在细胞膜电位的产生及 K^+再循环过程中发挥重要作用，而且通过 Cl^-敏感的 WNK-SPAK 途径参与 NCC 的活性调控。通过应用膜片钳、无线遥测血压以及代谢笼等多种功能学手段，我们证实了 Kir4.1 通过影响 NCC 的活性进而参与糖尿病盐敏感性高血压的产生。STZ 诱导的 I 型糖尿病小鼠表现为肾远曲小管 Kir4.1 及 NCC 表达/活性上调，全细胞钾电流增加以及细胞膜电位超极化。高盐摄入显著抑制了非糖尿病对照组小鼠 Kir4.1 活性并去极化细胞膜，然而对于糖尿病小鼠 Kir4.1 和 NCC 的表达及活性并无显著影响。此外，高盐摄入引起糖尿病小鼠尿钠排泄减少、血钠浓度升高以及血压增加，这些现象在肾脏特异性 Kir4.1 缺失小鼠身上完全消失。以上结果表明 Kir4.1-NCC 通路活性的异常改变可能是糖尿病盐敏感性高血压产生的关键因素。本项研究不仅进一步明确了远曲小管 Kir4.1-NCC 通路对于糖尿病状态下肾钠处理及血压稳态维持的重要性，并且为临床上糖尿病高血压的防治提供了新的分子靶点与治疗策略。

关键词：远曲小管，钠-氯同向转运体，内向整流钾通道 4.1，糖尿病，盐敏感性高血压

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CP-2 Series of studies on neurological diseases: Acute ischemic stroke, Alzheimer's disease, and glioma

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Stroke is the second leading cause of death globally and has a high disability rate, with 80% of strokes caused by ischemic injury. It not only diminishes the quality of life of patients, but also brings a heavy burden to society and families. Currently, there is a lack of effective treatment strategies. Our team has been committed to the study of the mechanisms related to acute ischemic stroke (AIS) for a long time, using *in vivo* middle cerebral artery occlusion (MCAO) models and *in vitro* oxygen-glucose deprivation (OGD) models to study the ischemic stress changes in neurons. In our study, we found that transient upregulation of autophagy occurred during acute ischemia, followed closely by dysfunctional lysosomal storage after reperfusion. Moreover, the mechanism of the lysosomal storage is that the basal level of MTOR-dependent lysosomal biogenesis in the reperfusion was not sufficient to clear undegraded cargoes after transient autophagy upregulation. Further investigation revealed that impairment of synaptic ultra-structures, accompanied by dysfunctional lysosomal storage, may result from a failure in dynamic turnover of synaptic proteins at neuronal processes (Autophagy，2021). Our team also found in another study that AIS leads to a decrease in neuronal SNAP29 protein expression levels, and its downregulation can cause synaptic dysfunction and memory cognitive impairment in mice by affecting presynaptic vesicle circulation (*Theranostics*, 2021). In addition, our team also revealed the pathophysiological processes involved in SIRT3 protein during AIS (*Acta Physiologica Sinica*, 2021). Meanwhile, our team's research has extended and expanded to clinical practice in recent years, focusing on risk factors, clinical progress, and prognosis research in patients with AIS. A study explored the endovascular treatment (EVT) of patients with acute large vessel occlusion AIS caused by two different mechanisms, large artery atherosclerosis (LAA) and cardioembolism (CE). It found that patients with LAA who received EVT had better prognosis and lower mortality than those with CE. Age and baseline NIHSS score were independently related to poor prognosis (*Neural Injury and Functional Reconstruction*, 2023). Another study reported the diagnosis and treatment of four AIS patients who had abnormal mental behavior as the initial manifestation,

revealed that the clinical symptoms of AIS patients were diverse and abnormal mental behavior could be the primary or sole clinical symptom, which may be due to the involvement of frontal and temporal infarction areas (*Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease*, 2022).

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder that has become the fourth leading cause of death in the world, occurring mostly in the elderly and pre-elderly. At present, the patient consultation rate is low, the cost of family and social care is high, but there is a lack of effective clinical treatment. Our team is committed to the research of AD related foundations, utilizing *in vivo* injection of Aβ-induced AD model to study the changes in cognitive and synaptic function of AD model after hyperbaric oxygen (HBO) treatment. In our study, we found that AD rats exhibit a phenotype of learning and memory impairment, while HBO therapy can reverse the phenotype to the control level and upregulate the expression levels of BDNF, TrkB, NGF, and SYN proteins closely related to memory. This suggests that HBO therapy can alleviate cognitive impairment in AD model by regulating synaptic and other related proteins (*Chinese Journal of Nautical Medicine and Hyperbaric Medicine*, 2021). In addition, our team also utilized bibliometric software and ClinicalTrials.gov website to comprehensively analyze targets and target-drug-clinical trial-disease associations of mitophagy in AD research over the past 16 years, revealing that mitophagy is an emerging molecular mechanism in AD research and may become a penetrating point for AD candidate drug research (Under Review, 2023).

Low-grade glioma (LGG) belongs to a large class of gliomas in neurological diseases, with IDH mutations being a major subgroup of LGG. However, the clinical diagnosis and treatment of LGG are still controversial. Our team is committed to exploring Runt-related transcription factors (RUNXs) role in immune infiltration and prognosis of LGG. We found that RUNX1 represents the RUNXs as an independent risk factor for LGG, and plays an important role in the differentiation and immune infiltration of IDH mutant subtypes by regulating IFNGR2. Our study revealed that RUNX1 and IFNGR2 may serve as biomarkers for immune infiltration and prognosis in the IDH mutant subtype for LGG (*Biomolecules and Biomedicine*, 2023).

In recent years, our team has focused on neurological diseases, especially AIS, AD, and LGG, focusing on cutting-edge hot scientific issues. We attempt to integrate basic and clinical research to seek new intervention targets and provide theoretical and experimental evidence.

Keywords: Acute ischemic stroke; Alzheimer's disease; Low grade glioma; Cognitive impairment; Autophagy; Prognosis; Biomarkers

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CP-3 The involvement of NLRP3 inflammasome in CUMS-induced depressive-like behaviours and related cognitive decline in mice

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Background: As is reported, the incidence and prevalence of depression are higher in women than in men, but the cause of this sex difference remains elusive. Although recent studies implicated that over-activated microglia played a crucial role in depression, whether hippocampal microglia associates with the sex difference of depressive-like behaviours is intriguing. Recent studies have indicated that sub-anesthetic dose of ketamine exerts rapid antidepressant effects. Upregulation of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors contributes to rapid antidepressant effects of ketamine. A recent study indicated that the increasing expression of AMPARs is related to the inhibition of NLRP3 inflammasome. Thus, we postulated that NLRP3 inflammasome might play an important role in ketamine's antidepressant effects. Numerous studies have found that inhibiting the expression of NLRP3 inflammasome can significantly improve depressive-like behaviors in mice, but the research on its effect on cognitive decline in depression and its mechanism is still lacking. This study aimed to elucidate the role of NLRP3 inflammasome in cognitive decline in depression and explore the common neuroimmunological mechanisms of depression and Alzheimer's disease (AD).

Methods: In the first study, both male and female mice were subjected to chronic unpredictable mild stress (CUMS) for 4 weeks. Behavioural tests were performed to evaluate depressive-like phenotypes, while several microglia-related biomarkers and neurotrophic factor in hippocampi were detected to analyze sex difference. In the second study, male C57BL/6 mice were received an intraperitoneal injection of Lipopolysaccharide (LPS) at a dose of 0.8mg/kg body weight, katamine at a dose of 10mg/kg body weight, the NLRP3 inflammasome inhibitor Ac-YVAD-CMK at 8mg/kg body weight. In the last set of experiments, male C57BL/6 mice were subjected to chronic unpredictable mild stress (CUMS) for 5 weeks, treatment group were administered with the NLRP3 inhibitor MCC950 (10 mg/kg, i.p.), fluoxetine served as positive control. Then, the mice were assessed for cognitive behaviors and depression-like behaviors, and changes of microglia and neurons in hippocampus and levels of Aβ metabolic pathway and tau protein were measured. To explore the mechanism of NLRP3 activation on neurons, we performed

in vitro studies using BV2 microglia and mouse primary neurons. Furthermore, we focused on the role of NLRP3 inflammasome in the function of neurons and the expression of AD pathological indicators.

Results: CUMS interfered with the body weight gain, sucrose preference and spontaneous activity in mice of both sexes. However, this effect tended to be more impressive in females. Generally, hippocampal microglia were activated regardless of sex, but the expressions of pro- and anti-inflammatory factors induced by CUMS were sex-specific. Chronic stress increased hippocampal iNOS and IL-1β mRNA levels only in male mice, while upregulated TNF-α mRNA just in females. Meanwhile, the expressions of hippocampal IL-10, Arg-1 and IL-1ra were all downregulated in CUMS females rather than males. In addition, though the ratios of the pro- vs. anti-inflammatory cytokines elevated after the stress paradigm in both sexes, we noticed more remarkable trends in female mice regarding TNF-α/IL-10 and iNOS/Arg-1. This discovery suggested that females were inclined to be more pro-inflammatory after stress. Afterwards, we observed that the expressions of BDNF and its receptor TrkB in hippocampus decreased greater in female compared to male mice when facing stress stimulations. Furthermore, the depressive-like behaviours were correlated to BDNF mRNA quantities in both sex mice, and there was also a sex-specific relationship between BDNF and hippocampal microglia-related inflammatory biomarkers. We found that sub-anesthesia dose of ketamine (10 ml/kg) ameliorated LPS-induced depressive-like behaviors, including decreased sucrose preference and increased im- mobility times in the tail suspension test. Ketamine also abrogated LPS-induced over expression of IL-1β and NLRP3 and reversed LPS-induced down-regulation of AMPA GluA1 subunits in hippocampi. The selective NLRP3 inflammasome inhibitor Ac-YVAD-CMK exhibited similar anti-inflammatory and antidepressant effects like ke- tamine. Combination of ketamine and Ac-YVAD-CMK showed no enhanced anti-inflammatory and anti-depressant effects than ketamine or Ac-YVAD-CMK administration alone. CUMS induced depressive-like behaviors and cognitive decline in mice, which could be reversed by inhibiting NLRP3 inflammasome. MCC950, a specific NLRP3 inhibitor, alleviated CUMS-induced neuron injury and AD-like pathological changes, including the abnormal expression of Aβ metabolic pathway and the hyperphosphorylation of tau protein. LPS (1μg/mL) +ATP (1mM) treatment activated the expression of NLRP3 inflammasome and IL-1β in vitro. In vitro experiment also proved that inhibiting the expression of NLRP3 inflammasome in microglia can restore the Aβ metabolic pathway to normal, decrease neuronal tau protein phosphorylation and protect neurons.

Conclusions: Our study speculated that the imbalance of microglial pro- and anti-inflammatory states as well as the BDNF-TrkB-dependent pathway in hippocampus is involved in the depressive-like behaviours. The “microglia-neuroinflammation-BDNF”

interconnection may be a fundamental mechanism for sex differences in depression. Besides, NLRP3 inflammasome might be an important mediator, through which ketamine could regulate AMPA receptors to exert rapid antidepressant effects. Inhibition of NLRP3 inflammasome effectively alleviated CUMS-induced depressive-like behaviors and cognitive decline in mice, and inhibited the activation of AD physiological indicators.

Keywords: NLRP3 Inflammasome, Depression, Ketamine, Sex Difference, Alzheimer's Disease, Cognitive Decline, Neuroinflammation

CP-4 转录相关蛋白 BRD4 和 Fli-1 在炎症及肾脏疾病中的作用及机制研究

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肾脏病发病率高，是全球第五位死亡原因，带来沉重经济负担；肾脏局部炎症增加与肾脏疾病的发生发展密切相关，但具体机制不明。转录相关蛋白 BRD4、Fli-1 和 RELA 等参与调控炎症反应，可能与肾脏病的发病机制有关，并有望作为肾脏病的治疗靶点。基于此，本人作为第一作者与所在团队近年来进行了以下探索并发现：

①高血压肾病（HN）是常见的继发性肾病，使用人肾活检和血管紧张素 II（Ang-II）诱导的 HN 小鼠肾脏样本，我们发现 Brd4 在 HN 患者和高血压小鼠模型的肾组织中上调。在 HN 小鼠肾脏和 Ang-II 诱导的 HK2 细胞中，Brd4 抑制剂 JQ1 减轻了 Ang-II 诱导的肾纤维化，并阻断了上皮-间质转化和纤维化基因及蛋白表达，提示 Brd4 参与 HN 的纤维化反应，并可作为 HN 潜在的治疗靶点（Exp Cell Res.2019）。

②狼疮性肾炎（LN）是常见的免疫相关性炎性肾病，Fli-1 是调控炎症的新型转录因子。我们发现，Fli-1 抑制剂 CPT 和 TPT 可显著改善狼疮小鼠的生存率、蛋白尿、肾损伤、脾脏增殖和血清自身抗体水平，同时在体外用 CPT 或 TPT 处理的人肾细胞显著降低干扰素诱导的 MCP1 和 CXCL10 等炎症因子的产生；提示小剂量 Fli-1 抑制剂 CPT 和 TPT 有望应用于治疗 LN（Arthritis Rheumatol.2021）。

③转录因子 Fli-1 调控炎症因子表达的机制不明。我们发现，在 Fli-1 特异性 T 细胞 CKO 的小鼠和体外 T 细胞及内皮细胞中 Fli-1 调节 GM-CSF 的表达。ChIP-qpcr 发现 Fli-1 直接与 GM-CSF 启动子结合。Fli-1 以剂量依赖的方式驱动 GM-CSF 启动子的转录，而 Fli-1 DNA 结合域的突变导致转录激活的显著丧失。Fli-1 蛋白中已知磷酸化位点的突变导致 GM-CSF 启动子激活显著增加。同时，Fli-1 与转录因子 Sp1 以协同方式调节 GM-CSF 的表达。以上结果证明了 Fli-1 调节 GM-CSF 表达的新机制（J Immunol. 2021）。

④CXCL10/CXCR3 轴在包括 LN 在内的多种炎症及肾脏疾病的发病机制中发挥作用，但具体机制不明。我们发现，与野生型狼疮小鼠相比，Fli-1 杂合的狼疮小鼠肾脏 CXCL10

蛋白水平显著降低。在 LPS 或 TNFα 刺激下，Fli-1 的敲低可显著减少小鼠和人内皮细胞及人系膜细胞中 CXCL10 的分泌。Fli-1 抑制剂 CPT 在干扰素刺激下显著降低人单核细胞 CXCL10 的产生。CXCL10 启动子中的 4 个潜在结合位点显示 Fli-1 的显著富集；然而，Fli-1 并不直接驱动人类或小鼠启动子的转录。同时，Fli-1 的 DNA 结合域对于人类 T 细胞中 hCXCR3 启动子活性的调控以及与共激活子的相互作用是必需的。总之，Fli-1 通过直接或间接方式来调节 CXCL10-CXCR3 轴，从而参与和影响 LN 及炎症信号通路。（Front Immunol. 2023）。

⑤气体信号分子硫化氢（H_2S）参与调节炎症信号通路。我们发现 LN 患者肾组织中 H_2S 合成酶 CSE 和 CBS 表达下调，其水平与 LN 的预后相关。LN 中 STAT1、RELA 和 T 细胞相关信号通路富集，且 LN 患者肾组织中 STAT1 和 RELA 表达升高。用 H_2S 供体治疗 MRL/lpr 狼疮小鼠可减轻肾损伤、抑制肾脏的 RELA 水平和 T 细胞浸润。以上结果表明 CSE/CBS/H_2S 参与了 LN 的发病机制，补充 H_2S 可能是 LN 的潜在治疗策略（Biology (Basel). 2023）。

总之，转录相关蛋白 BRD4 和 Fli-1 调控炎症反应参与肾脏疾病的发生发展，有望成为将来肾脏病的治疗靶点。

关键词：狼疮性肾炎，高血压肾病，炎症，BRD4，Fli-1

CP-5 孕期暴露 AT1 受体自身抗体对子代远期健康的影响及机制

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血管紧张素 II-1 型受体（AT1R）是肾素-血管紧张素系统发挥效应的主要介导者，除了内源性配体血管紧张素 II（Ang II）外，20 世纪末，研究者首次在子痫前期患者血清中检测到高滴度的 AT1R 自身抗体（AT1-AA）。AT1-AA 可以特异性识别并激活 AT1R，引起孕鼠出现高血压、蛋白尿等子痫前期样表现，但母体内的 AT1-AA 对子代健康的影响及相关机制尚不清楚。围绕该问题本课题组首先获取人胎盘血管，利用抗体纯化、血管环等技术发现，与 Ang II 引起的一过性血管收缩显著不同，子痫前期患者中分离的 AT1-AA 通过持续激活 AT1R，长时程地收缩人胎盘动静脉，引起血管痉挛，胎盘缺血，影响子代宫内生长发育。为了直接观察母体内 AT1-AA 对子代的具体影响，我们利用尾静脉注射的被动免疫方法建立 AT1-AA 阳性孕鼠模型，原创性发现母体内的 AT1-AA 可通过胎盘和乳汁进入子代体内，在断奶后抗体逐渐消失。这种生命早期暴露于 AT1-AA 环境中的子代鼠在青年期可出现胰岛素抵抗，中年期出现肝脂肪变性、糖原储备下降、对代谢综合征易感性增加等代谢异常，同时伴有心室肥厚和心功能下降。进一步分析 AT1-AA 发挥病理效应的分子机制发现，无论是对胎盘血管还是对子代脏器的损害作用，AT1-AA 的上游作用位点为 AT1R，因此我们利用全

内反射荧光显微镜、荧光共振能量转移等技术，检测 AT1-AA 对 AT1R 的作用特征，结果显示与内源性配体 Ang II 易引起 AT1R 脱敏不同，AT1-AA 使得 AT1R 难以募集 β-arrestin，从而限制 AT1R 内吞，使其 AT1R 下游信号持续存在，引起代谢紊乱及心血管损伤等。我们的上述系列研究在一定程度上解释了现有 AT1R 阻断剂对 AT1-AA 效果不理想的原因，同时丰富了“健康和疾病的发育起源”（DOHaD）学说理论，对于从源头上防治心血管疾病及妊娠期健康指导具有重要的意义。

关键词：血管紧张素 II-1 型受体，自身抗体，子代，代谢综合征，脱敏

CP-6 环境介质中碳纳米材料的细胞毒理学研究

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纳米科技是二十一世纪具有战略性的前沿领域之一，碳纳米材料（如富勒烯、碳纳米管、石墨烯和碳量子点等）作为纳米材料中的一类超大家族，由于其独特的性能和性质，近年来备受关注，人工碳纳米材料的生产和使用逐年递增，可以预测其将不可避免地进入环境系统，带来环境生态风险。碳纳米材料所引起的环境毒理与健康效应成为亟待解决的关键科学问题。本课题组研究了氧化石墨烯(GO)、氧化石墨烯纳米带(GORs)和碳量子点（CQDs）等碳纳米材料的细胞毒性作用及致毒机制。研究表明，氧化石墨烯与 Pb^{2+} 相互作用后，可转变为石墨状、管状和球状结构。经过聚集和/或重组后，氧化石墨烯对细胞的膜穿刺、磷脂提取、氧化应激、营养物质消耗等作用均受到不同程度的抑制，从而降低了氧化石墨烯的细胞毒性。氧化石墨烯纳米带（GORs）呈条带状，可显著抑制大肠杆菌的生长和繁殖，并呈浓度依赖性。GORs 刺激大肠杆菌分泌活性氧，然后氧化并破坏细菌细胞膜。此外，GORs 与大肠杆菌细胞膜相互作用导致 GORs 吸附多糖并释放乳酸脱氢酶，使细菌细胞壁完整性遭到破坏。因此，膜损伤为 GORs 对大肠杆菌的主要致毒机制。对于碳量子点（CQDs）的环境毒理机制，研究结果表明，其在较短的培养时间内与大肠杆菌具有良好的生物相容性。但是，当暴露时间超过 24h 时，CQDs 的毒性开始显现。一方面，CQDs 改变了细胞表面电荷，通过黏附在大肠杆菌表面诱导脂质过氧化，导致细胞壁通透性增加。另一方面，当 CQDs 浓度达到 200μg/mL 时，胞外环境渗透压显著降低。这些都是导致细胞水肿和死亡的主要因素。综上所述，不同碳纳米材料的毒性机制不同，需要进一步评价其毒性，并深入研究其致毒机制，从而为其未来的安全应用提供理论依据。

关键词：碳纳米材料 环境毒理 氧化石墨烯 氧化石墨烯纳米带 碳量子点

CP-7 延髓头端腹外侧区 miR-335 和 LncRNA Inpp5f 以及 CircRNA Galntl6 调控应激性高血压机制研究

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随着社会经济的发展，人们面临着繁重的学业，忙碌的工作节奏，激烈的职位竞争和疲于社交等问题。当这些压力超过人体的承受能力时，会出现心跳加快、血压升高等变化，慢慢发展为应激性高血压（stress-induced hypertension，SIH）。延髓头端腹外侧区（rostral ventrolateral medulla，RVLM）是位于脑干的缩血管区，它可以接收和整合来自外周和其他上游核团信息，随后将这些信息传递给交感神经节前神经元，调节交感缩血管和心交感紧张性活动，使血压升高。当外界不良应激刺激时，传入 RVLM 脑区的信息会导致前交感神经元过度兴奋，进而增强外周交感神经活动，引起血压升高。因此，深入研究 RVLM 脑区前交感神经元异常兴奋的分子机制，并找到有效的干预手段，对 SIH 的预防和治疗意义重大。

以往研究表明，非编码 RNA 广泛参与多种生理和病理过程。但目前未见它们在 RVLM 脑区调控 SIH 发生发展作用的相关研究报道。

miR-335 在 SIH 大鼠 RVLM 脑区的表达显著升高。在 SIH 大鼠 RVLM 脑区沉默 miR-335 表达后，可以显著抑制大鼠 RVLM 脑区神经元兴奋性、阻碍外周交感流出以及降低心率和血压水平。机制上，miR-335 通过抑制 Sphk1 表达，促进 RVLM 脑区神经元凋亡和兴奋性。

LncRNA Inpp5f 在 SIH 大鼠 RVLM 脑区的表达明显减少。在 SIH 大鼠 RVLM 脑区提高 lncRNA INPP5F 的表达后，可以显著抑制大鼠 RVLM 脑区神经元兴奋性和外周交感神经过度激活以及降低心率和血压。机制上，LncRNA Inpp5f 通过吸附 miR-335 促进 Cttn 基因表达，进一步激活 PI3K-AKT 信号通路，抑制 RVLM 神经元凋亡和兴奋性。

CircRNA Galntl6 在 SIH 大鼠 RVLM 脑区的表达显著减少。在 SIH 大鼠 RVLM 脑区过表达 CircRNA Galntl6 后，可以显著降低大鼠 RVLM 脑区神经元兴奋性、外周交感活动亢进、心率和血压。机制上，CircRNA Galntl6 通过吸附 miR-335 促进 Lig3 基因表达，抑制 RVLM 脑区神经元氧化应激和兴奋性。

miR-335、LncRNA Inpp5f 和 CircRNA Galntl6 是 SIH 临床治疗的潜在重要靶点。它们在其他心血管中枢如延髓尾端腹外侧区和延髓孤束核等中的表达变化以及这些变化对 SIH 发生发展的调控作用，值得进一步的研究。

关键词：miR-335；LncRNA Inpp5f；CircRNA Galntl6；延髓头端腹外侧区；应激性高血压

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CP-8 Development of multifunctional and orally active cyclic peptide agonists of opioid/neuropeptide FF receptors that produce potent, long-lasting peripherally restricted antinociception with diminished side effects

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Classical opioid analgesics, including morphine, fentanyl, and oxycodone are widely used in the treatment of clinical pain, and effective to treat moderate-to-severe pain. In general, most opioids used in clinical therapy are mu opioid receptor (MOR) agonists. Although they have potent analgesic effects, they also cause troublesome side effects, such as respiratory depression, tolerance, constipation, and abuse. Especially, in recent years, the phenomenon of overuse and abuse of opioids in the United States, known as the "opioid crisis", has developed into the "most serious public health crisis" and caused an increasing number of deaths per year. Therefore, the developments of novel analgesics with limited side effects have important scientific significance and potential application prospects.

Several recent strategies for designing opioid analgesics with limited adverse effects were explored, such as the biased MOR agonist TRV130, the peripherally acting kappa-opioid receptor (KOR) agonist CR845 (difelikefalin), and the mixed MOR/nociception opioid peptide (NOP) receptor ligands BU08028 and cebranopadol. These strategies may be useful in the development of promising candidates for potent and safe pain therapy.

The neuropeptide FF (NPFF) system, including NPFF and its receptors ($NPFF_1R$ and $NPFF_2R$), exhibits opioid-modulating activities. NPFF exerts complex modulating effects on opioid-induced antinociception, opiate tolerance, dependence and abstinence. Our previous work demonstrated that multifunctional opioid/neuropeptide FF receptor agonist **0** (DN-9) achieved potent analgesia without the development of tolerance at the central level and produced peripherally restricted analgesia with diminished side effects in physiological and pathological pain models after subcutaneous (s.c.) administration. Oral (p.o.) delivery is the most convenient

method for drug administration. However, this peptide drug exhibits poor intestinal permeation and instability in the highly acidic environment of the stomach or in the presence of peptidases expressed in the gastrointestinal tract or systemic blood circulation, limiting its oral delivery in the clinic. The linear parent peptide **0** has poor metabolic stability, duration of analgesia and oral bioavailability.

To obtain orally bioactive peptides as promising candidates for pain therapy, the optimization of peptide structure is highly desirable in drug design. Diverse chemical modifications to improve the oral activity of peptides have been explored, including N-methylation (cyclosporine A analogs), glycosylation (endomorphin-1 analogs), esterification and amidation (dermorphin analogs). A well-studied modification of peptides to produce oral bioactivity is cyclization, which generates peptides with improved affinity, receptor selectivity, stability against enzymatic degradation and intestinal permeability. The macrocyclic tetrapeptide CJ-15208 (cyclo[Phe-*D*-Pro-Phe-Trp]) exhibited dose-dependent antinociceptive activity (ED_{50} = 3.49 mg/kg) for 160 min after p.o. administration. The endomorphin cyclization analog ZH853 was reported as an orally available MOR agonist/delta-opioid receptor (DOR) antagonist with extended metabolic stability in human plasma, and it produced more potent and long-lasting antinociception with improved side effects.

In the present study, to improve the receptor agonistic activity, stability against enzymatic degradation and bioavailability of analog **0**, we synthesized eight lactam-bridged cyclic analogs of **0** with the following modifications: (1) substitution of *D*-Ala^2 and Gly^5 with *D*-Lys and Asp of analog **0**, respectively, with maintenance of chirality (analog **1**); (2) replacement of *D*-Lys^2 and/or Asp^5 with Lys and/or *D*-Asp, respectively (analogs **2**–**4**); (3) exchange of positions of *D*-Lys^2 and Asp^5 of analog **1** with maintenance of chirality (analog **5**); and (4) alteration of the size of the ring of analog **1** via incorporation of *D*-ornithine (*D*-Orn), *D*-diaminobutyric acid (*D*-Dab) and *D*-diaminopropionic acid (*D*-Dap) at position 2 of analog **1** (analogs **6**–**8**). These analogs were evaluated using various assessments, including *in vitro* cAMP functional assays, metabolic stability experiments, acute pain models, and further evaluation of the most promising compound in inflammatory pain, neuropathic pain, antinociceptive tolerance tests, motor disturbance, constipation, addiction, respiratory depression, and pharmacokinetics assays.

In summary, we successfully designed and synthesized eight lactam-bridged cyclic analogs of DN-9. The in vitro cAMP assays indicated that all analogs, except **7**, functioned as full agonists at MOR, DOR, KOR, $NPFF_1R$ and $NPFF_2R$. These analogs exhibited potent peripherally restricted analgesia in the tail-flick test after s.c. administration. Notably, analog **1** exhibited improved potency for KOR and $NPFF_2R$, more potent subcutaneous antinociception and improved plasma stability compared to parent peptide **0** and was selected as the optimized compound. Oral analog **1** produced potent and long-lasting analgesic activity via peripheral MOR and KOR in acute,

inflammatory, and neuropathic pain models, which is consistent with its long half-life and good oral bioavailability in pharmacokinetic experiments. The p.o. administration of analog **1** produced limited motor deficits, constipation, psychological and physical addiction and respiratory depression at the effective analgesic doses. Therefore, our present findings suggest that cyclic analog **1** as a potential drug candidate for clinical and outpatient use for the treatment of moderate-to-severe chronic pain with diminished side effects.

Keywords: Opioid, Neuropeptide FF, Multifunctional agonists, Cyclic peptide, Oral antinociception

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CP-9 帕金森病早期诊断和治疗的靶点探究

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帕金森病（PD）是一种常见的中老年慢性神经退行性疾病，其主要病理特征是中脑多巴胺（DA）神经元的退行性变。临床上治疗PD的代表性药物左旋多巴仅能外源性补充脑内DA，无法阻止运动神经元的退变以及疾病的进展。环状RNA（circRNA）的高稳定性和组织表达特异性使其成为潜在的疾病诊断和预后的生物标志物。目前，circRNA与PD的相关性研究以及其对DA神经元功能的调节作用尚未见报道。研究PD发生发展过程中差异表达的circRNA，揭示其对PD进程的调节机制，有望为PD的早期诊断提供生物标志物，并为基于神经保护的PD治疗策略研发提供潜在靶点。

本课题组收集PD患者的血浆样本进行全基因组的转录组学测序，获得100多个差异表达的circRNA，通过PD患者和健康对照组的差异表达分析，扩大样本验证，筛选出6个差异显著的circRNA。将这6个circRNA进行ROC分析，并结合患者的UPDRS和H-Y分期评估，聚焦于*circEPS15*进行下一步研究。我们发现PD患者血浆中*circEPS15*表达下调与PD运动症状的严重程度之间呈正相关。在此基础上，我们进一步考察离体和在体水平上过表达*circEPS15*对PD发生发展的影响。结果表明过表达*circEPS15*可减轻MPTP所致的小鼠PD样运动功能障碍和病理损伤。同时，过表达*circEPS15*可以抑制MPP^+导致的神经元损伤，发挥神经保护作用。由此，我们深入探讨*circEPS15*发挥神经保护作用的作用机制，发现*circEPS15*通过分子海绵吸附*MIR24-3p*，抑制其对靶基因PINK1的沉默效应进而促进PINK1-PRKN介导的线粒体

自噬，维持线粒体稳态。这项研究揭示了*circEPS15*在PD发生发展中的关键作用，并为深入了解和开发PD潜在生物标志物和治疗靶点的提供了新途径。

抑郁是PD最常见的非运动症状，其发病常早于运动症状，而许多因素导致PD病人抑郁的诊断和治疗不足，高达60%帕金森病伴发抑郁(PDD)的患者得不到治疗，严重影响生活质量。目前，PDD的神经解剖学和神经药理学机制仍不明确，疾病复发率及确切的临床疗效评价也未见报道。因此，进一步明确PDD病理机制，寻找更加迅速有效且安全的抗PDD治疗新策略迫在眉睫。

藏红花主要成分藏红花素（crocin）可作为一种潜在的治疗PD的药物，用于氧化应激介导的神经退行性疾病的辅助治疗。同时我们的研究证实crocin通过增强PACAP信号通路缓解慢性温和不可预知应激模型（CUMS）小鼠的抑郁样行为。据此，我们进一步研究发现crocin可以抑制VTA区DA神经元的自发放电，从而挽救MPTP模型小鼠VTA区DA神经元的结构损伤，促进mPFC区突触可塑性，缓解小鼠的抑郁样行为，发挥抗PDD的作用。因此，我们提出，crocin是一种具有治疗潜能的神经保护剂，可以成为一种新型抗PDD药物。

关键词：帕金森病，*circEPS15*，线粒体自噬，crocin，VTA-mPFC

CP-10 肿瘤分子标记物的筛选及发病机制

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异常的可变剪接（alternative splicing, AS）会严重影响肿瘤的发生和发展。富含丝氨酸/精氨酸的剪接因子 3（SRSF3）调控前体 mRNA 的可变剪接，并在许多肿瘤中充当促癌基因，但其在宫颈癌中的功能和潜在机制仍不清楚。我们通过分析 TCGA 和 GEO 数据库发现，SRSF3 在宫颈癌组织中高表达，并与不良预后显著相关。敲除 SRSF3 可降低 HeLa 细胞的增殖、迁移和侵袭能力，而 SRSF3 的过度表达则具有促进肿瘤发生发展的作用。进一步的研究表明，SRSF3 介导了转录辅因子 DDX5 第 12 号外显子的可变剪接。具体来说，SRSF3 的过表达促进了致癌剪接体 DDX5-L 的产生，抑制了抑癌剪接体 DDX5-S 的产生。SRSF3 和 DDX5-L 都能上调致癌 AKT 的表达，而 DDX5-S 则下调 AKT 的表达水平。总之，我们发现 SRSF3 能够通过调节 DDX5 的可变剪接增加 DDX5-L 的产生，减少 DDX5-S 的产生，进而通过上调 AKT 的表达水平促进宫颈癌的增殖、迁移和侵袭。这些结果揭示了 SRSF3 在宫颈癌中的致癌作用，并强调了 SRSF3-DDX5-AKT 轴在肿瘤发生中的重要性。我们也证明了 SRSF3 和 DDX5 是宫颈癌新的潜在生物标记物和药物治疗靶点。

卵巢肿瘤蛋白酶（OTU）家族成员之一的 OTUD5 在 DNA 修复和免疫中发挥着重要作用。然而，人们对它在肿瘤中的功能知之甚少。我们发现宫颈癌中 OTUD5 的低表达与预后

不良有关。它的表达与肿瘤分期、转移结节和肿瘤亚型有关，如与磷脂酰肌醇-3-激酶（PI3K）-AKT 信号转导、上皮-间质转化（EMT）和激素有关的亚型。此外，我们还分析了 OTUD5 的共表达基因、相关 miRNA、转录因子、激酶、泛素连接酶和相互作用蛋白。结果表明，OTUD5 会影响 WDR45、USP11、GRIPAP1 和 RBM10 的表达水平。此外，hsa-mir-137、hsa-mir-1913、hsa-mir-937、hsa-mir-607、hsa-mir-3149 和 hsa-mir-144 可能会抑制了 OTUD5 的表达。此外，我们还对 22 个共表达基因、33 个相关 miRNA 和 30 个相互作用蛋白进行了富集分析。除了泛素化和免疫学相关过程外，这些基因还参与了 Hippo 信号转导、胰岛素信号转导、EMT、组蛋白甲基化和磷酸化激酶结合等过程。我们的研究首次分析了 OTUD5 在宫颈癌中的表达及其与临床病理学的关系，为进一步研究其在宫颈癌中的调控机制提供了新的见解。

除了乳腺癌，我们在肺腺癌中也进行了新的生物标记物的研究。肺腺癌（LUAD）是人类肺癌的主要亚型。目前，肺腺癌患者的治疗效果和长期生存率都不理想。TRIM56 是 TRIM 蛋白家族的成员，主要在免疫和癌症中发挥作用。TRIM56 在 LUAD 中的表达减少，并与预后不良有关。我们测定了 TRIM56 的基因组拷贝数、负相关 miRNA 和潜在转录因子，并进行了富集分析。其中，hsa-mir-542 和 hsa-mir-627 有可能抑制 TRIM56 的表达。我们还预测了 TRIM56 的相互作用蛋白和潜在泛素化底物。最后，我们证明了过表达 TRIM56 能够抑制 LUAD 细胞的侵袭和迁移。我们的研究首次分析了 TRIM56 的表达及其对 LUAD 细胞侵袭和迁移的抑制作用，为进一步研究 TRIM56 在 LUAD 中低表达的原因及其调控机制提供了新的方向。

关键词：宫颈癌，肺腺癌，SRSF3，OTUD5, TRIM56

Screening and pathogenesis of molecular tumor markers

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Abnormal alternative splicing (AS) can have profound impacts on both tumorigenesis and progression. The precise function and potential mechanisms of serine/arginine-rich splicing factor 3 (SRSF3) in cervical cancer are unclear, although it has been shown to regulate AS of precursor mRNAs and act as an oncogene in many tumors. Through analysis of the TCGA and GEO databases, we discovered that SRSF3 was highly expressed in cervical cancer tissues, and that it exhibited a strong correlation with poor prognosis. Knocking down SRSF3 led to diminished proliferation, migration, and invasion of HeLa cells, whereas the overexpression of SRSF3 played a role in tumor development promotion. Additional investigations illustrated that SRSF3 regulated

alternative splicing of exon 12 in the transcriptional cofactor DDX5. Precisely, SRSF3 overexpression augmented the production of the pro-oncogenic spliceosome DDX5-L and restricted the formation of DDX5-S. Ultimately, both SRSF3 and DDX5-L increased the expression of oncogenic AKT, while DDX5-S decreased AKT expression levels. In conclusion, this study found that SRSF3 upregulated the production of DDX5-L and downregulated the production of DDX5-S by regulating variable splicing of DDX5. This regulation, in turn, promoted cervical cancer proliferation, migration, and invasion by increasing AKT expression levels. These results demonstrate the oncogenic function of SRSF3 in cervical cancer and emphasize the significance of the SRSF3-DDX5-AKT axis in tumorigenesis. Additionally, we have identified SRSF3 and DDX5 as novel biomarkers and therapeutic targets for the treatment of cervical cancer.

OTUD5, a deubiquitinase member of the ovarian tumor protease family, has a significant function in immunity and DNA repair. Although its role in cervical cancer remains unknown, we discovered a correlation between low OTUD5 expression and poor prognosis in cervical cancer patients. Additionally, we observed that its expression was related to tumor stage, metastatic nodes, as well as specific tumor subtypes linked to hormones, epithelial-mesenchymal transition (EMT), and phosphatidylinositol-3-kinase (PI3K)-AKT signaling. Additionally, an analysis was conducted on the co-expressed genes, associated miRNAs, transcription factors, kinases, E3, and interacting proteins of OTUD5. The findings indicate that the expression levels of WDR45, USP11, GRIPAP1, and RBM10 are affected by OTUD5. Furthermore, hsa-mir-137, hsa-mir-1913, hsa-mir-937, hsa-mir-607, hsa-mir-3149, and hsa-mir-144 may have suppressed the expression of OTUD5. Additionally, 22 co-expressed genes, 33 associated miRNAs, and 30 interacting proteins were enriched. In addition to ubiquitination and processes related to immunology, these genes are involved in Hippo signaling, insulin signaling, EMT, histone methylation, and phosphorylated kinase binding. Our study is the first to analyze the expression of OTUD5 in cervical cancer and its relationship with clinicopathology, offering fresh perspectives for further exploration of its regulatory mechanisms in tumors.

In addition to cervical cancer research, we have also conducted studies on new biomarkers for lung adenocarcinoma (LUAD), the primary subtype of lung cancer in humans. Currently, treatment outcomes and long-term survival rates for LUAD patients are discouraging. TRIM56 is a protein member of the TRIM family known to play a role in immunity and cancer. Reduced expression of TRIM56 in LUAD has been associated with dismal prognoses. We analyzed the genomic copy number, negatively related miRNAs, and potential transcription factors of TRIM56 and conducted enrichment analysis. Among them, hsa-mir-542 and hsa-mir-627 showed potential to inhibit TRIM56 expression. We also predicted the interacting proteins and potential

ubiquitination substrates of TRIM56. Lastly, our results demonstrated that the overexpression of TRIM56 impeded the invasion and migration of LUAD cells. In summary, we analyzed the expression of TRIM56 and its inhibitory effect on the invasion and migration of LUAD cells. This provides a new direction for further investigating the cause of low TRIM56 expression in LUAD and its regulatory mechanism.

Keywords: cervical cancer, lung adenocarcinoma, SRSF3, OTUD5, TRIM56

CP-11 HBV 相关肝纤维化及慢加急性肝衰竭的作用机制研究

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全球约有 2.4 亿人感染了慢性乙型肝炎病毒（HBV）。HBV 感染可发展为肝纤维化及慢加急性肝衰竭（ACLF）等，危害巨大。目前临床上缺乏有效逆转肝纤维化及慢加急性肝衰竭的治疗方法，其原因在于其确切靶点及发生发展机制尚未阐明。

我们利用转录组学结合实验验证来确定新的治疗 HBV 相关肝纤维化的靶点。从差异表达基因（DEGs）中筛选出了肿瘤坏死因子（TNF）受体相关因子-2（TRAF2）及溴结构域蛋白 4（BRD4）等重要基因。与健康对照组相比，TRAF2 及 BRD4 在 HBV 相关肝纤维化中异常高表达。TRAF2 及 BRD4 的表达与肝纤维化的严重程度呈正相关，且与血清中天门冬氨酸氨基转移酶（AST）和总胆红素（TBIL）的水平也呈正相关。TRAF2 可能是控制 T 淋巴细胞介导的肝纤维化的关键，而 BRD4 参与肝纤维化与 C-X-C motif 趋化因子配体 6（CXCL6）相关。TRAF2 及 BRD4 在肝纤维化进程中起着关键作用，有望成为干预 HBV 相关肝纤维化的潜在靶点。

此外，我们招募了 747 名慢性 HBV 感染患者。所有患者均填写了匹兹堡睡眠质量指数（PSQI）、患者健康问卷-9（PHQ-9）及健康质量调查（SF-36）等。发现与健康的中国成年人相比，各类型慢性 HBV 感染患者的 PSQI 总分均明显较高。HBV 携带者和轻度 HBV、中度 HBV、重度 HBV、肝衰竭、代偿期肝硬化和失代偿期肝硬化患者的 SD 发病率分别为 25%、26%、32%、47%、56%、31%和 49%。二元逻辑回归分析显示，病程、天冬氨酸氨基转移酶水平、PHQ-9 评分和 VAS 评分是 SDs 的独立危险因素，而 SF-36 总分则是 SDs 的保护因素。临床医生应更加关注慢性乙型肝炎病毒感染患者的 SDs。

其次，我们对随机接受综合药物治疗、血浆置换（PE）或双血浆分子吸附系统（DPMAS）联合半剂量序贯 PE 的 186 名 HBV-ACLF 患者进行了前瞻性评估。根据治疗前凝血酶原活动度（PTA）将患者分为四个亚组： I 组（PTA>40%）、II 组（PTA 30-40%）、III 组（PTA 20-30%）和 IV 组（PTA<20%）。结果发现与综合内科治疗和单纯 PE 相比，DPMAS 联

合半剂量序贯 PE 治疗能更有效地改善 HBV-ACLF 患者的血清总胆红素（TBIL）、谷草转氨酶（AST）和肌酐（Cr）清除率，提高 I 组肝功能衰竭患者的 28 天有效率和 90 天生存率，且更具成本效益。DPMAS 联合半剂量序贯 PE 是一种治疗 HBV-ACLF 的更有效的方法。

最后，我们用脂多糖（LPS）处理人肝细胞（THLE-2）以诱导细胞损伤。通过 MTT 试验、流式细胞术和 Dot 印迹试验检测细胞增殖、凋亡和 m6A 修饰。我们发现，HBV 感染会显著增强 THLE-2 细胞的 m6A 修饰水平，并提高 METTL3 和成熟 miR-146a-5p 的表达，而环亮氨酸（m6A 抑制剂）会抑制它们的表达。METTL3 的过表达促进了 HBV 复制和细胞凋亡，提高了促炎细胞因子、乙肝表面抗原（HBsAg）和乙肝 e 抗原（HBeAg）的水平。且 HBV 感染导致小鼠肝脏严重损伤，肝组织凋亡增加，而 METTL3 敲除可消除这种损伤，并阻碍了 HBV 感染小鼠体内 miR-146a-5p 的成熟。总之，这项研究表明，抑制 METTL3 可改善 HBV- ACLF 小鼠的肝损伤，而 METTL3 有助于抑制 miR-146a-5p 的成熟。这为预防和治疗 HBV-ACLF 提出了一条新的方向。

关键词： HBV 肝纤维化 慢加急性肝衰竭

CP-12 KLF2 通过抑制 BMP/SMAD1/5 信号介导层流对血管钙化的保护作用

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动脉内膜的钙化与动脉硬化的发展紧密相关。组成血管内皮层的内皮细胞感知血流并对不同模式的血流产生的机械信号做出不同的反应。层流区域的内皮细胞呈现出抗动脉粥样硬化的表型，而湍流区域的内皮细胞更倾向介导动脉粥样硬化的发生。然而，血流对动脉粥样硬化血管钙化的作用仍有待探索。我们的研究通过观察钙化的在人体冠状动脉中的位置分布总结出血流对血管钙化的影响，并在动脉粥样硬化血管钙化小鼠模型和体外模拟血流-细胞模型中探索血流对钙化影响的内在信号机制。

我们在病人冠状动脉的计算机断层扫描血管造影分析表明，血流模式为湍流的血管分叉处或者弯曲处的钙化形成远远多于血流为层流的血管直部；这个现象也同样的发生在钙化的主动脉瓣膜和小鼠的血管中。我们利用 Y 型细胞培养板模拟血管，泵驱动的培养基流动模拟血流建立直观的体外血流模型，与体内结果相似，人脐静脉内皮细胞（HUVECs）的钙化在 Y 型细胞培养板的拐角处形成的更多。Krüppel 样因子 2（KLF2）是一种可被层流诱导的转录因子，其表达在钙化的人主动脉瓣膜内皮细胞中和血管钙化小鼠模型的血管内皮中较少，该结果表明 KLF2 下调可能与内膜钙化有关。

我们进一步发现在 HUVECs 和人主动脉内皮细胞（HAECs）中，KLF2 的敲低促进了内皮细胞-间质细胞的转化和骨诱导；并且在 *ApoE*$^{-/-}$小鼠钙化模型中，内皮特异性敲低 KLF2 加重了血管钙化，而 AAV9 介导的内皮特异性 KLF2 过表达改善了血管钙化。

在 HUVECs 中的 RNA 测序显示 KLF2 过表达上调了与血管钙化密切相关的 BMP/SMAD1/5 信号通路。我们发现 KLF2 敲低废除了层流对 BMP/SMAD1/5 的抑制，而 KLF2 过表达抑制了湍流诱导的 BMP/SMAD1/5 信号通路的激活。为了探索 KLF2 对 BMP 表达的调控机制，我们开展了染色质免疫沉淀实验以确定 KLF2 是否直接与 BMP4/BMPER 的启动子结合调控二者的表达。在过表达 KLF2 的 HUVECs 中，KLF2 在 BMP4（转录起始位点上游-1025 - -918 bp，-465 - -355 bp）和 BMPER（转录起始位点上游-636 - -400 bp, -387 - -269 bp）的启动子区域的富集增多，表明 KLF2 可以通过转录机制直接调节 BMP4/BMPER 的表达。此外，KLF2 通过直接与 SMAD1 的启动子结果负向调控 SMAD1 的表达，并且 SMAD1 敲低逆转了 KLF2 敲低对钙化的促进作用。

综上，血管钙化优先形成于血管系统的分叉及分支处。层流通过上调 KLF2 抑制 BMP/SAMD1/5 信号通路降低血管钙化的形成。KLF2 是治疗血管钙化的潜在靶点。

关键词：Krüppel 样因子 2，血管钙化，内皮细胞，层流，湍流

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CP-13 The mechanism of rhubarb promoting ER stress in goblet cell to relieve constipation

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Background: Constipation is a common clinical sign of gastrointestinal dysfunction, accounting for 15% of all cases worldwide. It is defined by difficult or infrequent transit, stool hardness, and/or a sense of incomplete evacuation. With the typical lifestyle of high consumption of sugar and fat, the prevalence of constipation is estimated as 20% or higher, which has serious consequences for the quality of people's lives regardless of age and gender. Rhubarb is an essential traditional Chinese medicinal herb used in therapeutic practice to relieve constipation. A majority of current research on constipation has focused on improving motility. Motility of the gastrointestinal tract is an ambiguous phrase that encompasses various quantifiable phenomena, including enteric contractile activity, gut wall biomechanical functions, and intraluminal flow

responsible for the propulsion of gut contents. To determine whether rhubarb exerted influence on gut motility, we evaluated correlations between the muscle alterations and collagen fiber density to demonstrate the sensitivity enhancements of colonic contraction.

Number of studies provide strong evidence that the microbes and their hosts share a wide range of nutrients needed to sustain physiological requirements. More importantly, the gut microbiota actively creates a great deal of immune regulatory metabolites. Metagenomics has begun to study the composition and genetic potential of the gut microbiota in order to illustrate the breadth of the functional and metabolic potential of microbes. There is no doubt that there exists a link between constipation and microbiota. Accordingly, we performed metagenomics to demonstrate substantial metabolic differences across groups in order to assess the inflfluence of constipation and rhubarb extract on the microbiota.

However, the underlying mechanism by which rhubarb extract is possessed has received little attention. Therefore, this study contributes significantly to the knowlege of constipation by revealing its fundamental process of understanding how rhubarb extract regulates the constitutive constipation response.

Materials and methods: We established a reliable constipation model in C57B/ 6N male mice using intragastric administration diphenoxylate, and the eligible subjects received 600 mg/25 g rhubarb extract to alleviate constipation. The resulting constipation was morphologically and genetically compared to specimens from various ethnicities. To determine the quantity and distribution of collagen, we used hematoxylin and eosin (HE), Masson trichrome, and Sirius Red staining. At the same time, we evaluated the proinflammatary cytokines and anti-inflammatary cytokines by ELISA, such as IL-15, IL-17A, IL-22, IL-23, LPS,NF-κB, ERK,TLR-4 and MyD88. Light microscopy and transmission electron microscopy (TEM) are operated to detect a Muc2-rich inner mucus layer attached to mice colon Under varied settings. Furthermore, 16S rDNA sequencing and Metagenomics Sequencing are performed to examine the gut flora. FITC-Dextran is applied to test the paracellular permeabilityof the colon. LC-MS/MS analysis is performed to unveil the alteration of short-chain fatty acids (SCFAs), medium- and longchain fatty acids (MLCFAs) and polyamine.

Results: Firstly, the weight of mice in the constipation group reduced without significant difference according to daily weight records, although the amount of fecal particles in the rhubarb group did not rise much, the dry weight of feces decreased significantly, as well as the water content in feces. The mice in the constipation group, on the other hand, had considerably lower fecal amount, fecal dry weight, and fecal water content. The rhubarb intervention and control groups did not vary statistically significantly. Secondly, The mucosa and submucosa thicknes increased significantly in the rhubarb group, but the muscle layer thickness fell significantly. In

the constipation group, mucosal thickness decreased, submucosal thickness decreased greatly, and muscle thickness increased significantly. Despite the absence of statistical significance when compared to the control group, rhubarb medication eased the changes in the various layers of constipation. Thirdly, the amount of colon goblet cells increased significantly in the rhubarb group, the inner mucous layer thickened greatly, and the content of mucus in goblet cells decreased significantly. , The number of goblet cells dropped dramatically in the constipation group, while the mucus content in goblet cells increased, mucus particles size increased, and the thickness of the inner mucous layer declined. Fourthly, colon collagenous fiber content and AFM modulus were significantly greater in the constipation group than in the control group. Serum levels of IL-22, NF-B, TLR4, and MyD88 were significantly higher in the rhubarb group, whereas serum levels of IL-17A and IL-23 were significantly higher in the constipation group. When compared to the rhubarb group, the constipation group showed the greatest FITC-Dextran fluorescence intensity in plasma, as well as considerably lower membrane resistance combined with enhanced membrane current, indicating improved intestinal permeability.Last but not least, the number of ER stress-related proteins was significantly greater in the rhubarb intervention group than in the control group, showing that rhubarb elicited an ERS response in the affected cells in the gut. When compared to the control group, the diversity and richness of intestinal flora reduced considerably in the constipation group, however Firmicutes increased greatly, and rhubarb may reverse the change. Putrescine levels rose in the constipation group but decreased in the rhubarb group; cadaverine content increased in the rhubarb group but decreased in the constipation group. Short-chain and medium-long-chain fatty acid content and relationship have been changed. Short-chain fatty acid receptors GPR41 and GPR43 increased significantly with constipation but reduced with rhubarb treatment.

Conclusion: Constipation is caused by a decrease in mucus production, as well as a decrease in inner mucus layer thickness, muscle layer thickening, increased collagen fibers, and an increase in pro-inflammatory factor release. The gut flora's diversity decreases, and the Firmicutes/Bacteroidetes (F/B) ratio alters. The receptor's expression increases considerably when the short-chain fatty acid content decreases. Bioamine's putrescine content increased considerably. When used to treat constipation, rhubarb can increase mucus production, thicken the inner mucus layer, decrease the muscle layer, and restore the intestinal barrier. We show that Rhubarb can stimulate mucin production and discover direct evidence of dendritic structure-linked mucus structures with its assembly into a lamellar network in an isolated colon segment with a pore size distribution. The intestinal flora balance was restored, and biogenic amine and short-chain fatty acid levels were equivalent to those of normal animals.

Keywords: rhubarb, constipation, mucus, ER stress, intestinal flora.

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CP-14 Curcumol's antitumor effect study and its target protein identification in nasopharyngeal carcinoma cell

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Curcuma kwangsiensis S. G. Lee & C. F. Liang (Guangxi ezhu, in Chinese) belongs to the Zingiberaceae family, has been used as a traditionally Chinese medicine nearly 2000 year. Curcumol is one of the guaiane-type sesquiterpenoid hemiketal isolated from medicine plant Curcuma kwangsiensis S. G. Lee & C. F. Liang, which has been reported possesses anti-cancer effects. Our previous study found that the most contribution to inhibit nasopharyngeal carcinoma cell growth was curcumol. Curcumol has been proved to possess antitumor effects *in vivo* and *in vitro* in several cancers. Previously, we have found that curcumol induced apoptosis in CNE-2 cells, but its underlying mechanism has not yet been studied well. In 2015, our team clarified that curcumol inhibited colorectal cancer cells' growth partially through insulin-like growth factor 1 receptor (IGF-1R) pathway. Given the key importance of IGF-1R pathway in tumorigenesis. In 2018, we found that the apoptosis-induction and cell cycle arrest effect of curcumol on NPC cells was related to the inhibition of IGF‐1R and its downstream PI3K/Akt/GSK-3β pathway.

Autophagy is usually considered as a protective mechanism against cell death, and in the meantime, leads to cell injury even apoptosis. Apoptosis and autophagy are very closely connected and may cooperate, coexist or antagonize each other on progressive occurrence of cell death triggered by natural compounds. Therefore, the interplay between the two modes of death is essential for the overall fate of cancer cells. We have revealed that curcumol induced apoptosis in nasopharyngeal carcinoma (NPC) cells. We also found that curcumol can induce autophagy in cancer cells, and different from the pathway of its apoptosis induction, curcumol induced autophagy through AMPK/mTOR pathway in CNE-2 cells. Moreover, induction autophagy by other drugs can enhances the activity of curcumol in NPC cells, and it may be a new therapeutic strategy for NPC.

The above studies showed that curcumol possessed significantly anti-tumor activities. It can inhibit nasopharyngeal carcinoma (NPC) proliferation and induced cell cycle arrest, cell apoptosis and autophagy, but its target protein(s) in NPC cells remains unclear. Identification of the specific

protein target(s) of a drug is a critical step in unraveling its mechanisms of action (MOA) in many natural products. Many natural products showed high bioactivity, while their mechanisms of action (MOA) are very poor or completely missed. Understanding the MOA of natural drugs can thoroughly exploit their therapeutic potential and minimize their adverse side effects. Identification of the specific protein target(s) of a drug is a critical step in unraveling its MOA. Then we employed a mass spectrometry-based chemical proteomics approach revealed NCL is the the possible protein targets of curcumol in NPC cells. Meanwhile, we used cellular thermal shift assay (CETSA), molecular docking and cell function analysis verified that NCL is a target protein of curcumol and revealed that the anti-cancer effects of curcumol in NPC cells are mediated, at least in part, by NCL inhibition.

Excessive autophagy induces cell death and is regarded as the treatment of cancer therapy. We have confirmed that the anti-cancer mechanism of curcumol is related to autophagy induction. As the main target protein of curcumol, RNA binding protein nucleolin (NCL) interacted with many tumor promoters accelerating tumor progression. However, the role of NCL in cancer autophagy and in curcumol's anti-tumor effects haven't elucidated. Then we identified the role of NCL in nasopharyngeal carcinoma autophagy and reveal the immanent mechanisms of NCL played in cell autophagy. We found the expression of NCL play an important role in autophagy induction and further found that it was associated with its effect on NCL RNA-binding domain 2, which affect the level of autophagy induction by curcumol in NPC cells. This study may provide a new perspective on the target protein studies for natural medicines and confirm the effect of curcumol not only regulating the expression of its target protein, but also influencing the function domain of its target protein.

Keywords: Curcumol; anti-tumor; mechanisms of action; target protein; apoptosis; autophagy.

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CP-15 A homotetrameric hemoglobin expressed in alveolar epithelial cells increases blood oxygenation in highaltitude plateau pika (*Ochotona curzoniae*)

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The plateau pika *(Ochotona curzoniae*) is an endemic species in the Qinghai-Tibet Plateau and iinhabits meadows at an altitude of 3000-5000 m. Over long-term evolution, plateau pikas have undergone a series of adaptative physiological and genetic changes in response to the hypoxic environment. The alveolar epithelium of the lungs is primarily composed of alveolar epithelial type I (ATI) and type II (ATII) cells. Pulmonary surfactant (PS) is synthesized by ATII cell pneumocytes and secreted into alveolar cavities through osmiophilic multilamellar bodies (LBs). The PS is composed of ~80% phospholipids, 5%-10% neutral lipids (mainly cholesterol), and 8%-10% proteins. The phospholipids and proteins serve important functions by reducing surface tension, defending against pathogens, maintaining physical surface stabilization, and facilitating respiratory gas exchange by increasing oxygen dissolution capability and oxygen diffusion in the PS. Therefore, gas exchange performance depends on the total alveolar surface area and PS composition and content. In this study, the gene that encodes a heme-binding protein in the PS of the pika is identified. The protein is a homotetrameric hemoglobin (δ_4) encoded by HBD (δ). HBD is expressed in alveolar epithelial type II (ATII) and type I (ATI) cells, upregulated by hypoxia. δ_4 is secreted into alveolar cavities through osmiophilic multilamellar bodies. HBD expression is downregulated by RNAi, which significantly increases hypoxia-inducible factor 1α expression in lung tissue and red blood cells and hemoglobin and blood lactate concentrations but significantly decreases arterial partial pressure of oxygen (PaO_2). Our results indicate that plateau pikas physiologically show hypoxemia when HBD expression is downregulated. Therefore, specific HBD expression in the lungs helps plateau pikas to obtain

oxygen under hypoxia by maintaining higher PaO_2. These findings provide insights into the adaptive mechanisms of plateau pikas to withstand high-altitude environments.

CP-16 电针足三里调控荷瘤小鼠免疫-炎性反应减缓肿瘤进展的效应及机制研究

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炎性反应与免疫应答的动态平衡是维持机体功能状态稳定的关键，而在荷瘤机体，过度的炎性因子会通过多种途径抑制抗肿瘤免疫功能，这种严重失衡状态是促进肿瘤进展的重要危险因素[1]。大量研究证实电针足三里不仅能激活迷走传出神经发挥抗炎效应，还对多种免疫效应细胞和分子具有良好的促进作用，有效增强荷瘤患者的免疫功能[2-3]。本研究以雌性 BALB/c 小鼠为研究对象，注射 4T1-Luc2 细胞制备原位乳腺癌模型，从荷瘤小鼠机体“免疫-炎症”失衡的动态变化入手，观察电针双侧足三里对荷瘤小鼠免疫-炎性反应的调控效应以及相关的作用途径。本研究首先明确了电针足三里抑制荷瘤小鼠瘤体生长的有效时间窗，结果显示，造模同时以及成瘤后电针干预足三里能有效减缓瘤体的生长速度，并提高荷瘤小鼠外周血中 $CD8^+$T 细胞和自然杀伤细胞（NK）的比例，且以成瘤后电针干预的效果最佳[4]。然后，本研究综合观察了成瘤后电针足三里对乳腺癌小鼠肿瘤的生长、瘤体局部和系统性炎性水平、抗肿瘤免疫细胞以及髓系来源免疫抑制细胞（MDSC）的作用。结果显示，电针干预后，小鼠瘤体质量减轻，肿瘤局部成像面积和荧光强度降低；MSD 多因子检测以及流式细胞术结果显示，模型小鼠瘤体局部以及血清内炎性因子的含量升高，循环血及脾脏内 $CD8^+$T 细胞和 NK 细胞的比例降低，并出现大量的 MDSC；电针干预降低了荷瘤小鼠肿瘤局部和血清内促炎性细胞因子的含量，并使小鼠脾脏、循环血以及瘤体局部 $CD8^+$T 细胞和 NK 细胞的比例升高，细胞杀伤功能增强，同时减少荷瘤小鼠脾脏、循环血以及瘤体局部 MDSC 的比例，并降低了 MDSC 的免疫抑制功能；脑干迷走神经背核（DMV）的免疫荧光染色显示，电针干预后荷瘤小鼠 DMV 内胆碱乙酰转移酶（ChAT）阳性神经元的 c-Fos 表达量增多，行膈下迷走神经切断术后，电针足三里调控乳腺癌模型小鼠免疫-炎性反应减缓肿瘤生长的效应被阻断[5]。最后，本研究以雄性 C57BL/6J 小鼠为观察对象，腹腔注射偶氮甲烷（AOM）联合饲喂葡聚糖硫酸钠（DSS）制备结直肠癌模型，并在开始饲喂第 2 个循环 DSS 当天对小鼠双侧足三里行电针干预，结果也显示电针足三里对结肠炎小鼠发挥了良好的抗炎效应，改善了结肠状态，延缓了结肠炎向结肠癌的转化[6]。总之，本研究从多方面验证了电针足三里减缓荷瘤小鼠肿瘤进展的作用，并明确了电针足三里能在迷走神经的参与下对荷瘤机体“免疫-炎症”失衡状态进行调节，减轻炎性水平并增强免疫功能，从而减缓肿瘤的生长。

关键词：电针，肿瘤，炎性因子，抗肿瘤免疫，迷走神经

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CP-17 Association analysis of gut microbiota-metabolites-neuroendocrine changes in male rats acute exposure to simulated altitude of 5500m

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Hyperactivation of hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-thyroid (HPT) axis were found in acute high altitude challenge, but the role of gut microbiota and metabolites is unknown. We utilized adult male SD rats at a simulated altitude of 5500m for 3 days in a hypobaric-hypoxic chamber. ELISA and metabolomic analyses of serum and 16s rRNA analysis and metabolomic analyses of fecal samples were then performed. Compared with the normoxic group, serum corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), corticosterone (CORT), and thyroxine (tT_4) were increased in the hypoxia group, whereas thyrotropin-releasing hormone (TRH) was decreased. *Bacteroides, Lactobacillus, Parabacteroides, Butyricimonas, SMB53, Akkermansia, Phascolarctobacterium,*

and *Aerococcus* were enriched in hypoxic group, whereas *[Prevotella], Prevotella, Kaistobacter, Salinibacterium,* and *Vogesella* were enriched in normoxic group. Metabolomic analysis indicated that acute hypoxia significantly affected fecal and serum lipid metabolism. In addition, we found 5 fecal metabolites may mediate the cross-talk between TRH, tT_4, and CORT with *[Prevotella], Kaistobacter, Parabacteroides,* and *Aerococcus,* and 6 serum metabolites may mediate the effect of TRH and tT_4 on *[Prevotella]* and *Kaistobacter* by causal mediation analysis. In conclusion, this study provides new evidence that key metabolites mediate the cross-talk between gut microbiota with HPA and HPT axis under acute hypobaric hypoxia challenge.

Keywords: Hypobaric hypoxia; HPA axis, hypothalamic-pituitary-adrenal axis; HPT axis, hypothalamic-pituitary-thyroid axis; Gut microbiota; Metabolomics

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CP-18 针刺调节皮质-臂旁核-孤束核环路对中风后吞咽障碍模型动物干预作用的研究

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流行病学资料显示急性卒中后吞咽障碍的发病率可高达 50%。伴有吞咽障碍的中风患者的死亡率明显高于其他脑卒中患者，而且现代医学缺乏有效治疗吞咽障碍的方法。古代医籍记载“下食难，取廉泉”。廉泉穴位于舌骨上方凹陷处，深层分布有舌下神经及舌咽神经的分支，既往的研究表明针灸廉泉穴治疗中风后吞咽障碍有着较好的临床效果。然而，这种外周刺激方法治疗吞咽困难的神经环路机制尚不明确。因此，我们首先采用嗜神经病毒标记和在体电生理结合光遗传技术确定小鼠与吞咽相关的初级运动皮质-臂旁核-孤束核环路的具体位置坐标及功能特性。然后将小鼠随机分为空白对照组，模型组，针刺组以及假针刺组。使用光化学法损伤单侧的运动皮质建立中风后吞咽障碍小鼠模型。与造模前相比，造模后小鼠皮质吞咽区的血流明显下降（$P<0.01$），提示了造模成功。随后，我们观察了各组小鼠的下颌舌骨肌肌电和饮水量，结果显示模型组和假针刺组小鼠的肌电曲线下面积明显低于空白对照组和针刺组（$P<0.01$），饮水量的统计结果也显示相同的下降趋势（$P<0.01$）。这些实验结果初步表明针刺廉泉穴可以改善模型小鼠吞咽障碍的症状。免疫荧光的结果显示与模型组相比，针刺组小鼠损伤对侧运动皮质的 c-Fos 蛋白表达明显增多（$P<0.05$）。双光子钙成像的结果显示，与假针刺相比，电针廉泉穴可以明显促进运动皮层兴奋性神经元的活

动（$P<0.01$）。使用化学遗传学抑制皮质活动后，针刺的效应明显减弱（$P<0.01$）。这些结果提示针刺效应的发挥可能与其激活损伤对侧运动皮质神经元的活动相关。为了进一步探究下游通路，我们检测了臂旁核的 c-Fos 蛋白表达量，结果显示，与模型组相比，电针组小鼠臂旁核的 c-Fos 蛋白表达量明显上升（$P<0.05$）。光遗传学与化学遗传学的结果显示：生理状态下，激活运动皮质而抑制臂旁核与孤束核会使小鼠吞咽功能受损，而在病理状态下，同时激活运动皮质，臂旁核和孤束核比只激活运动皮质更能放大电针廉泉穴的效应。综上所述，本研究阐述了电针廉泉穴可以使单侧皮质中风小鼠损伤对侧皮质吞咽区的锥体神经元激活从而代偿受损脑区的功能，并且通过运动皮质-臂旁核-孤束核环路调节吞咽肌群的活动，促进吞咽功能的恢复。这些研究成果为临床上使用针灸治疗吞咽障碍提供科学依据的同时，也为其它方法治疗吞咽障碍提供了潜在策略。

关键词：针刺，廉泉，中风，吞咽障碍，神经环路

Effect of Acupuncture on primary motor cortex-parabrachial nuclei-nucleus tractus solitarii Loop in Animal Model of Post-stroke Dysphagia

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It has been reported that the prevalence of dysphagia after acute stroke can be as high as 50%. Patients with post-stroke dysphagia have a significantly higher mortality rate than other stroke patients without swallowing problem. However, the therapeutic effect of modern medicine in the treatment of dysphagia is limited. Ancient Chinese medicine has recorded: “Hard to swallow, Lianquan (CV23) selected”. CV23 is located at the depression superior to the hyoid bone, with branches of the hypoglossal and glossopharyngeal nerves distributed in the deep layer. It has been showed that Electroacupuncture (EA) at CV23 acupoint has a good clinical effect in the treatment of post-stroke dysphagia. However, little is known about the neurological mechanism by which this peripheral stimulation approach treats for dysphagia. Therefore, we firstly used neurotropic virus labeling strategy and in vivo electrophysiology combined with optogenetic techniques to determine the specific positional coordinates and functional properties of the primary motor cortex-parabrachial nuclei-nucleus tractus solitarii (M1-PBN-NTS) loop associated with swallowing in mice. The mice were then randomly divided into control (Con), PSD model mice

(PSD), EA-treated PSD model mice (PSD + EA) and sham EA-treated PSD model mice (PSD+ ShamEA) groups. A mouse model of post-stroke dysphagia was established by using photochemical method to make cortical infarction in unilateral motor cortex. Blood flow was significantly decreased after modeling (p<0.01). Subsequently, we observed the electromyogram (EMG) of the mandibular hyoid muscle and water consumption form the mice. The results showed that area under curve (AUC) of EMG responses from PSD and PSD+ ShamEA mice were significantly lower than the Con and PSD + EA mice (p<0.01), and the statistics of water consumption showed the same decreasing trend (p<0.01). Overall, these results preliminarily supported that EA-CV23 improved swallowing function in a mouse model of dysphagia. The results of immunofluorescence showed that the excitatory neurons in M1 were activated by EA-CV23 in PSD model mice (p < 0.05). Two-photon laser microscopy imaging showed that individual somatic Ca2+ transients in M1 were increased upon EA-CV23 in PSD model mice (p < 0.01). The effects of EA were significantly attenuated after inhibiting cortical activity using chemogenetic strategy (p<0.01). These results supported the essential contribution of contralateral M1 excitatory neurons to the improvement of swallowing function elicited by EACV23 in PSD model mice. Next, we recorded the M1 activation-induced EMG responses during simultaneous activation or inhibition of both PBN and NTS neurons. It was observed that the EMG responses induced by optogenetic activation of the M1 were decreased after simultaneous inhibition of both PBN and NTS neurons, and the EA-CV23-mediated improvement of EMG responses was also prevented (p <0.01, p < 0.05). Nevertheless, simultaneous activation of both PBN and NTS neurons increased the mylohyoid activity induced by optogenetic activation of the M1 in both control mice and PSD mice, while simultaneous activation of these neurons could not increase the EMG responses in PSD mice subjected to EA-CV23 (p <0.01, p < 0.05). In conclusion, our study demonstrated that electrical stimulation at the CV23 acupoint, as a peripheral stimulation strategy, could improve the swallowing function in PSD model mice through the activation of motor cortex inputs to the NTS through the PBN. Our study not only provides an experimental basis for the application of EACV23 for the treatment of PSD, but also suggest a potential valuable treatment strategy for swallowing related disorders.

Keywords: Acupuncture, Lianquan(CV23), Stroke, dysphagia, Neural circuit

YP 第 15 届全国青年生理学工作者学术会议

YP-1 Differential regulation of autophagy on urine-concentrating capability through modulating the renal AQP2 expression and renin-angiotensin system in mice

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Autophagy, a cellular process of "self-eating", plays an essential role in renal pathophysiology. However, the effect of autophagy on urine-concentrating ability in physiological conditions is still unknown. This study aimed to determine the relevance and mechanisms of autophagy for maintaining urine-concentrating capability during antidiuresis. The extent of the autophagic response to water deprivation (WD) was different between the renal cortex and medulla in mice. Autophagy activity levels in the renal cortex were initially suppressed and then stimulated by WD in a time‐dependent manner. During 48h WD, the urine-concentrating capability of mice was impaired by rapamycin but not 3-Methyladenine, accompanied by the suppressed renal aquaporin 2 (AQP2), V2 receptor (V2R), renin, and angiotensin-converting enzyme (ACE) expression, and the levels of prorenin/renin, angiotensin II (AngII), and aldosterone in the plasma and urine. In contrast, 3-Methyladenine and chloroquine suppressed the urine-concentrating capability in WD72 mice, accompanied by downregulation of AQP2 and V2R expression in the renal cortex. 3-Methyladenine and chloroquine further increased AQP2 and V2R expression in the renal medulla of WD72 mice. Compared to 3-MA and CQ, Rapa administration yielded completely opposite results on the above parameters in WD72 mice. In addition, 3-Methyladenine and chloroquine abolished the upregulation of prorenin/renin, AngII, and aldosterone levels in the plasma and urine in WD72 mice. Taken together, our study demonstrated that autophagy regulated urine-concentrating capability through differential regulation of the renal AQP2/V2R and ACE/AngII signaling during WD.

Keywords: Autophagy, water dehydration, urinary concentration, aquaporin-2, renin-angiotensin system

YP-2 miR-22-3p in the rostral ventrolateral medulla promotes hypertension through inhibiting β-arrestin1

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Abstract: It has been documented that increased sympathetic activity contributes to the development of cardiovascular diseases, such as hypertension. We previously reported that β-arrestin1, a multifunctional cytoskeletal protein, was downregulated in the rostral ventrolateral medulla (RVLM) of spontaneous hypertensive rat (SHR), and its overexpression elicited an inhibitory effect on sympathetic activity in hypertension. The micro ribonucleic acid (miR)-22-3p has been reported to be associated with the pathological progress of hypertension. The purpose of this study was to determine the role of miR-22-3p in β-arrestin1-mediated central cardiovascular regulation in hypertension. It was observed that miR-22-3p was upregulated in the RVLM of SHR compared with normotensive Wistar-Kyoto (WKY) rats, and it was subsequently confirmed to target β-arrestin1 gene via dual-luciferase reporter assay. miR-22-3p was downregulated in the RVLM using adeno associated virus (AAV9) with "Tough Decoys (TuD)" (anti-miR-22-3p TuD), which caused a significant increase of β-arrestin1 expression while decrease of norepinephrine (NE) and blood pressure (BP) in SHR. However, upregulation of miR-22-3p using lentivirus (Lv-miR-22-3p) in the RVLM of WKY rats significantly increased BP. In vitro PC12 cells, enhanced oxidative stress activity induced by angiotensin II (Ang II) was counteracted by pretreatment with miR-22-3p inhibitor, while this effect could be abolished by β-arrestin1 knockdown. Furthermore, microglia exhaustion significantly diminished miR-22-3p expression, and enhanced β-arrestin1 expression in the RVLM of SHR. Activation of BV2 cells in vitro evoked a significant increase of miR-22-3p expression, and this BV2 cells culture medium was also able to facilitate miR-22-3p expression in PC12 cells. Collectively, our findings supported a critical role for microglia-derived miR-22-3p in inhibiting β-arrestin1 in the RVLM, which is involved in central cardiovascular regulation in hypertension.

Keywords: miR-22-3p, β-arrestin1, RVLM, sympathetic activity, hypertension

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YP-3 心脏肌小节 Z 线的体内邻近蛋白组学研究

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背景：Z 线是肌原纤维中肌小节之间的富含多种蛋白质的横纹状结构。心脏的各种病理生理过程均与 Z 线密切相关。 Z 线上的细胞骨架蛋白 ACTN2 将细肌丝、肌联蛋白等纤维交联在一起，直接调节心肌细胞的收缩舒张功能。Z 线同时在心肌细胞粘附、细胞器组织功能、以及分子信号转导等过程中发挥重要作用。虽然 Z 线上的多种蛋白已知调节心肌损伤与重构，但是由于 Z 线的蛋白组学数据十分缺乏，Z 线蛋白调节心肌病理生理过程的机制尚不清楚。

方法：我们以 ACTN2 为标记物，基于腺相关病毒（AAV）基因递送载体和 BioID2 生物素转移酶，开发了小鼠体内的心肌细胞特异的 Z 线邻近蛋白质组学研究方法， 发现新的 Z 线蛋白。我们制备基因敲除小鼠模型，利用心肌原位成像等技术对新发现的 Z 线蛋白进行验证，并以异丙肾上腺素（ISO）诱发的心肌损伤为模型，研究其在心肌损伤与重构中的功能。

结果：我们建立了体内心肌细胞特异性的 Z 线邻近蛋白质组研究平台，确定了 237 个富集在 Z 线附近的蛋白质。其中，我们发现 PALMD 为心脏肌原纤维 Z 线的新组分。*Palmd* 全身敲除小鼠在基线水平心脏功能正常。在异丙肾上腺素处理的小鼠中，Palmd 敲除导致心肌肥厚缺陷，心肌损伤加重，心功能下降。相反，AAV 介导的 Palmd 过表达能够增强心肌肥厚过程，降低心肌损伤。在分子水平，Palmd 敲除导致 CAV3 等横管的关键分子标记物空间定位异常。免疫共沉淀发现 PALMD 与横管蛋白 CAV3、JPH2、NEXN 等均存在相互作用。

结论和创新点：基于 AAV 和 BioID2 的体内临近蛋白质组学技术是探究心肌细胞亚细胞组分的强大工具。PALMD 是心脏肌原纤维 Z 线的新成分，对异丙肾上腺素诱导的心肌损伤与重构有保护作用。在分子机制层面， PALMD 可能通过与 CAV3、JPH2、NEXN 相互作用调节横管组织与重构，从而影响心肌损伤与重构。

关键词：Z 线，邻近蛋白质组，PALMD

YP-4 心肌再生的时空调控

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背景：缺血性心脏病会造成大量不可逆的心肌细胞死亡，最终导致心力衰竭和心源性猝

死。刺激心肌细胞原位增殖，是补充缺失的心肌细胞，逆转缺血性心脏病的有效策略。YAP 转录调节因子是已知促进心肌增殖和再生的核心分子。然而，YAP 信号的长时间过度激活会导致心肌病理性肥厚、线粒体功能障碍、心率失常等严重后果。如何对 YAP 进行精细的时空调控，是避免 YAP 激活的副作用，实现安全有效的心肌再生的关键科学问题。

方法：基于一种已进入临床试验的小分子可变剪接调节剂，我们开发了下一代基因表达调控技术，称作 DreAM 系统。基于此技术，我们实现了腺相关病毒（AAV）心肌基因递送在时间、空间、表达量三个层次的口服小分子调控。利用 AAV-DreAM 体系，我们在小鼠心肌细胞中灵活地调节 YAP1 的表达时间和表达量，在急性心梗（MI）模型中实现了心脏修复再生的时空调控。

结果：我们证明了口服小分子可以对 AAV 递送的转基因进行心肌细胞特异性的、小分子剂量依赖性的、反复可逆的基因表达调控。基于此技术，我们利用 AAV 载体向小鼠心肌细胞中特异性地递送 YAP1，并通过口服小分子，实现了对 YAP1 表达量和表达时间的灵活调控，并且在 MI 小鼠模型中，证明了 AAV-DreAM-YAP1 的心肌修复能力。

结论和创新点：DreAM 技术可以实现 AAV 递送基因在时间、空间、表达量的灵活调控。基于 DreAM 技术，AAV 递送 YAP1 到心肌可以实现心肌修复再生的时空调控。DreAM 技术可广泛应用于所有需要基因表达调控的 AAV 基因治疗场景，有潜力催生下一代 AAV 基因治疗药物。

关键词：缺血性心脏病、心肌再生、YAP1、DreAM

YP-5 Transcutaneous Auricular Vagus stimulation reduces depressive symptoms by regulating centralα7nAChR/JAK2 signaling

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Depression is a serious disabling and fatal disease worldwide. Accumulating evidence supports that there is a close relationship between depression and inflammation, then inhibition of neuroinflammation may be another mechanism for the treatment of depression. Transcutaneous Auricular Vagus Stimulation(taVNS), as a non-invasive transcutaneous electrical stimulation, could effectively treat depression, but its mechanism is unclear. In this study, rats with

depression-like behavior were induced by intraperitoneal injection of lipopolysaccharide (LPS). The rats were randomly divided to Control group, LPS group, taVNS+LPS group and the same as the α7nAChR (-/-) gene knockout rats. The expressions of tumor necrosis factor-alpha (TNF-α) and phosphorylated-Janus kinase2(p-JAK2), phosphorylated-signal transducer and activator of transcription3(p-STAT3) in the hypothalamus, amygdala and hippocampus were detected by Western Blot. We observed that LPS significantly decreased the sucrose preference, the time of into the open arms in the elevated plus maze, and the number of corssing and reaing in the open field test. TaVNS treatment improves these depression-like behaviors, but taVNS is not effective in α7nAChR (-/-) gene knockout rats. The expression of TNF-α signifciantly increased, and the expression of p-Jak2 and p-STAT3 markedly decreased in the hypothalamus and amygdala induced by LPS. TaVNS could significantly reverse the above-mentioned phenomena but had rare improvement effect for α7nAChR(-/-) rats. We conclude that the antidepressant effect of taVNS for LPS-induced depressive rats is related to α7nAchR/JAK2 signal pathway in the hypothalamus and amygdala.

Keywords: Depression, Transcutaneous auricular vagus nerve stimulation, αlpha 7 nicotinic acetylcholine receptor,JAK2 signaling pathway

YP-6 利用单碱基编辑技术在体内纠正 *Lmna* c.1621C>T 致病突变

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背景：*LMNA* 基因的单核苷酸变异（SNV）是导致扩张型心肌病的主要原因之一。然而，目前 *LMNA* 心肌病的发生机制尚不清楚，治疗效果欠佳。腺嘌呤单碱基编辑器（ABE）是一种可以精确高效地将腺嘌呤转化为鸟嘌呤的基因编辑工具，有潜力用于治疗 SNV 造成的遗传疾病。然而，ABE 是否可用于治疗 *LMNA* 相关心肌病尚不清楚。

方法：我们对临床样本进行全外显子测序，发现 *LMNA* 心肌病相关的 SNV。我们制备携带 *Lmna* 致病 SNV 的小鼠模型，用超声心动图、免疫荧光成像、全转录测序等技术分析心肌病表型和机制。基于 DeepABE 深度学习模型，我们设计靶向 *Lmna* 致病 SNV 的 ABE 元件，使用腺相关病毒（AAV）载体递送至小鼠体内，利用扩增子测序研究体内基因编辑结果。通过对 ABE 元件和 AAV 载体进行改造，我们尝试提高 ABE 在小鼠心脏中的编辑效率。

结果：我们报告了两例患有扩张型心肌病的男性儿童病例，均携带 *LMNA* c.1621C>T/p.R541C 突变。我们新建了含有相同突变的 $Lmna^{RC/RC}$ 小鼠模型，发现小鼠在 6 月龄时表现出心脏收缩功能下降、左心室扩张等表型。$Lmna^{RC/RC}$ 小鼠心肌细胞体积增大，

线粒体形态被破坏，线粒体功能受损，线粒体氧化呼吸链基因表达水平降低。针对 *Lmna* c.1621C>T 突变，我们筛选出编辑效率最高、旁观者效应最低的一条 sgRNA，利用双 AAV 载体递送 ABE 到 $Lmna^{RC/RC}$ 小鼠体内，在心脏和肝脏组织中均检测到 *Lmna* c.1621C>T 突变的成功纠正。通过优化 TadA、Cas9 等 ABE 的核心元件，我们将心脏中的碱基编辑效率提高到约 10%。利用微型 Cas9 同源物 SauriCas9，我们实现了单个 AAV 介导的体内碱基编辑。

结论和创新点：我们结合临床病例成功新建了一种可以模拟 *LMNA* c.1621C>T/p.R541C 突变造成的扩张型心肌病的小鼠模型，发现该突变引起心肌病的机制与线粒体缺陷密切相关。我们成功设计并构建了能够在体内纠正 *LMNA* c.1621C>T/p.R541C 突变的 ABE 元件，并通过优化 AAV 和 ABE 元件，提高了其体内基因编辑效率，为 ABE 治疗 *LMNA* 心肌病的策略提供了概念和技术验证。

关键词： LMNA 心肌病，腺嘌呤单碱基编辑器（ABE），腺相关病毒载体（AAV）

YP-7 蒽环类药物心肌病运动训练中的 TRPC6 的作用及对线粒体动态的影响

Effects of TRPC6 on mitochondrial dynamic in Doxorubicin-induced cardiomyopathy exercise training

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目的：评估蒽环类药物心肌病运动训练中 TRPC6 的变化及对心脏结构功能、心肌线粒体动态的影响，初步探索运动训练改善蒽环类药物心肌病的潜在机制。

方法：利用阿霉素小鼠心肌损伤模型，采用化疗前+化疗中运动训练方案，以 Hyperforin（HY）或 Larixyl Acetate（LA）特异性激动或抑制 TRPC6。①心脏超声、HE、WGA、Masson 染色、Elisa 及透射电镜分析心脏结构功能改变。②Western blot 分析各组 TRPC6、线粒体动态蛋白（LONP1、MFN2、Drp1、PINK、Parkin）含量的变化。③Real-time PCR 分析线粒体拷贝数变化。④共聚焦技术检测线粒体分裂融合、线粒体 ROS 水平。

结果：①DOX 组小鼠心脏 LVFS 及 LVEF 明显低于正常对照组；心肌 TRPC6 蛋白含量增加 56.3%。运动训练明显改善 DOX 损伤小鼠心脏 LVFS 及 LVEF,心肌 TRPC6 含量降低 23.1%。②DOX 组心肌线粒体肿胀溶解，线粒体拷贝数降低 63.74 %，线粒体过度分裂，形态因子由 1.327 降至 1.049，长宽比由 1.856 降至 1.496，线粒体调控蛋白 DRP1、PINK、Parkin 水平升高，LONP1、MFN2 蛋白水平下降，线粒体 ROS 水平较正常组上升 8 倍。与 DOX 比较，运动+DOX 组小鼠心肌线粒体结构较完整，轻微肿胀。线粒体动态明显改善，线粒体拷贝数增加 1.67 倍，线粒体形态因子趋于正常水平，DRP1、PINK、Parkin 蛋白水平下降，LONP1、MFN2 蛋白水平升高，线粒体 ROS 降低。③运动训练对心功能及线粒体动

态的作用，被 TRPC6 激动剂 HY 削弱。与运动+DOX 组相比，运动+DOX+HY 组 LVEF、LVFS 降低，线粒体拷贝数减少，线粒体形态因子降低，DRP1、PINK、Parkin 水平升高，LONP1、MFN2 蛋白水平下降，ROS 产生增加。④TRPC6 抑制剂 LA 对 DOX 损伤小鼠心功能和心肌线粒体动态的作用与运动相似，DOX+LA 组 LVEF、LVFS 显著改善，线粒体结构形态、拷贝数及形态因子趋于正常， DRP1、PINK、Parkin 蛋白水平下降，LONP1、MFN2 蛋白水平升高，ROS 水平下降。

结论：运动训练可能通过 TRPC6 改善 DOX 损伤小鼠心功能和线粒体动态。

YP-8 Macrophage FOXK2 promotes cardiac repair in nondiabetic myocardial infarction with stress hyperglycemia

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Rationale: Acute myocardial infarction (MI) is one of the most frequent causes of myocardial injury. Macrophage-associated immune responses are critical for the repair of injured tissues. It has been found that stress hyperglycemia (SHG) was strongly associated with poorer outcomes in patients with MI. FOXK2, a member of the Forkhead transcription factors, is emerging as a key regulator of the glucose metabolic response. However, the role of FOXK2 in regulating macrophage phenotype and function in MI remains unclear.

Objective: To identify the function and underlying mechanisms of macrophage FOXK2 in cardiac repair post-MI with SHG.

Methods and Results: FOXK2 levels were found to be significantly decreased in macrophages obtained from cardiac tissue in mice with MI accompanied by SHG. Using Cx3Cr1-Cre mediated FOXK2-deficient mice, we found that FOXK2 deficiency exacerbated cardiac dysfunction post-MI by increasing the production of pro-inflammatory factors. Mechanistically, short-term exposure of macrophages to high glucose levels resulted in a decrease in the FOXK2 protein level.

Conclusions: Together, our work reveals that macrophage FOXK2 is involved in cardiac repair post-MI. Inhibiting the degradation of FOXK2 may exert effective clinical protection.

Keywords: FOXK2; Myocardial Infarction; Macrophage; Stress Hyperglycemia; Cardiac Repair

YP-9 Transcriptomics and molecular docking reveal the potential mechanism of lycorine against pancreatic cancer

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Background: Pancreatic cancer is an extremely malignant digestive tumor, but due to the high drug resistance of pancreatic cancer, the search for more effective anti-pancreatic cancer drugs is extremely urgent. Lycorine, an alkaloid of natural plant origin, has anti-tumor effects against a variety of tumors.

Purpose: This study aimed to investigate the therapeutic effect of Lycorine on pancreatic cancer and to further elucidate its potential molecular mechanism.

Methods: Two pancreatic cancer cell lines, PANC-1 and BxPC-3, were used to investigate the therapeutic effects of Lycorine on pancreatic cancer at the in *vitro* level by CCK8, colony formation and EdU incorporation assay, flow cytometry, and Western blot. Transcriptome sequencing and GSEA were used to analyze differential genes and pathways after Lycorine treatment. Molecular docking, qRT-PCR, oil red O staining, siRNA transfection and other experiments were performed to further validate the differential genes and pathways. In *vivo* experiments were conducted to investigate the inhibitory effect and drug toxicity of Lycorine on pancreatic cancer by constructing a tumor-bearing mouse model.

Results: Lycorine inhibited the proliferation of pancreatic cancer cells, caused G2/M phase cycle arrest and induced apoptosis. Transcriptome sequencing and GSEA results showed that the inhibition of pancreatic cancer by Lycorine was associated with fatty acid metabolism, and Aldehyde dehydrogenase 3A1 (ALDH3A1) was a significantly enriched target in the fatty acid metabolism process. ALDH3A1 expression was significantly upregulated in pancreatic cancer, which was closely associated with prognosis. The results of molecular docking showed that Lycorine has strong binding activity to ALDH3A1. Further studies revealed that Lycorine inhibited the fatty acid oxidation (FAO) process in pancreatic cancer cells, and induced cell growth and apoptosis through ALDH3A1.

Conclusion: In conclusion, Lycorine was found to inhibit pancreatic cancer cell proliferation, block the cell cycle and induce apoptosis by targeting ALDH3A1, and FAO inhibition was identified for the first time as a possible mechanism for the anticancer effects of Lycorine. These findings enrich the theory of targeted therapy for pancreatic cancer, expand the understanding of the pharmacological targets of Lycorine, and provide a certain reference for the exploration of

natural components.

Keywords: Pancreatic cancer; Lycorine; Transcriptomics; ALDH3A1; Fatty acid oxidation; Molecular Docking

YP-10 A new miniMOS tool kit capable of visualizing single copy insertions in *C. elegans*

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The miniMOS technique has been widely used in the *C. elegans* community for generating single copy insertion. The insertion candidate is preliminarily defined if the worm is resistant to G418 antibiotics and does not express a fluorescent co-injection marker. A worm can be falsely recognized as a miniMOS candidate if the expression of the extrachromosomal array is extremely low, which is sufficient to conduct G418 resistance without a recognizable fluorescence from the co-injection marker. This may lead to a waste of effort in the following steps for identifying the insertion locus. In the present study, we modified the plasmid platform for miniMOS by incorporating a *myo-2* promotor-driven TagRFP or a ubiquitous H2B::GFP expression cassette into the targeting vector and introducing two LoxP sites flanking the selection cassettes. Based on this new miniMOS tool kit, the removable fluorescence reporters can visualize the single copy insertions, greatly reducing insertion locus identification efforts. Based on our experience, this new platform greatly facilitates the isolation of the miniMOS strains.

Keywords: *Mos1*, *C. elegans*, miniMOS, single copy insertion

YP-11 Glutaminolysis boosts cardiac performance under high workload via elevating mitochondrial glutathione

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Background: Recent studies have unveiled the unique role of amino acids in cardiac

pathophysiology. Glutamine, the most abundant non-essential amino acid in circulation, serves as an important energy source in proliferating cells. Current clinical studies reveal that impaired glutaminolysis is associated with an increased risk of cardiovascular events but the underlying mechanism remains largely unknown.

Aims: This study aims to investigate the role of glutaminolysis in regulating cardiac function at rest and under high workload and the underlying mechanism.

Methods: We analyzed cardiac structure and function in a mouse model with cardiac-specific knockdown of glutaminase (GLS), a key enzyme of glutaminolysis. Cardiac reserve was assessed by isoproterenol stress echocardiography. We performed transcriptomic, ^{13}C isotopic labeling, and reactive oxygen species emission analyses to investigate the underlying mechanism.

Results: GLS deficiency impaired cardiac reserve and exercise capacity in mice, but had no discernible effects on cardiac structure or function under baseline condition. Inhibition of glutaminolysis in pressure-overloaded hearts further exacerbated cardiac dysfunction, indicating the critical role of glutaminolysis in cardiomyocytes under high workload. Comprehensive analyses of targeted metabolome and metabolic flux demonstrated that cardiac glutaminolysis was upregulated to enhance glutathione (GSH) production, particularly within the mitochondria, under high workload. Inhibition of glutaminolysis decreased both cytosolic and mitochondrial GSH levels, resulting in compromised cell contraction in isolated cardiomyocytes under high workload. Additionally, heterologous expression of an engineered mitochondrial GSH biosynthetic enzyme increased mitochondrial GSH levels and enhanced cardiac reserve in GLS knockout mice.

Conclusions: Our findings establish the previously unrecognized role of glutaminolysis in cardiomyocytes, maintaining cardiac reserve via upregulating mitochondrial GSH levels. This suggests that targeting glutaminolysis is a potential strategy for improving cardiac reserve and managing cardiac diseases.

Keywords: glutaminolysis; cardiac reserve; mitochondria glutathione; cardiomyocyte

YP-12 耳穴电刺激对糖尿病模型大鼠实时血糖的影响

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目的：观察耳穴电刺激 (Transcutaneous auricular vagus nerve stimulation, taVNS)对糖尿病模型大鼠实时血糖的影响；**方法：**将 12 只 Sprague-Dawley（SD）大鼠随机分为空白组（Control，C 组），模型组（Model, M 组），耳穴电刺激组（taVNS，T 组）。高脂饲料喂

养 4w 后，M 组、T 组大鼠采用高脂饲料联合腹腔注射 35mg/kg 1% STZ（0.1mol/L, pH=4.4 柠檬酸缓冲液溶解）使大鼠处于持续高血糖状态，以空腹血糖值（Fasting blood-glucose，FBG）≥16.7mmol/L 作为评,定造模是否成功的标准。其余两组大鼠,给予正常饮食，保证,饮食充足和正,常昼,夜交替。C 组、T 组：造模成功后开始在吸入异氟烷条件下给予 taVNS 干预，在 2%异氟烷吸入麻醉下，采用韩氏电针仪，连接两个正负极，自吸附，导电磁铁，无创固定，于大鼠的耳甲内外两侧，选用的电刺激部位为耳迷走神经的分布区域，刺激参数选用疏密波 2/15 Hz， 2mA，每次 30min，每天 1 次，持续 7 天；M 组：大鼠自由摄入食水，不给予干预。应用美国 DSI 植入式生理信号遥测系统，在大鼠清醒自由活动的状态下，持续连续实时监测各组大鼠在不同时间点的血糖和体温的变化情况。**结果：**(1)血糖昼夜变化：与 C 组比较，M 组大鼠血糖昼夜波动较大；经过 taVNS 干预后，与 M 组比较，T 组大鼠昼夜血糖波动趋近于 C 组。(2)温度昼夜变化：与 C 组相比，M 组大鼠温度变化波动显著增大（P<0.05）；经 taVNS 干预后，与 M 组相比，T 组大鼠温度变化波动显著减小（P<0.05）。(3) taVNS 对大鼠实时血糖的影响：taVNS 使各组大鼠随机血糖呈上升趋势，C 组大鼠在干预停止后，随机血糖在 60min 内下降至平稳，与干预前无统计学差异（P>0.05）。M 组大鼠第 1 天、第 4 天干预结束后 25min 随机血糖下降到最低值，在第 7 天干预结束后 40min 随机血糖下降到最低值，随后血糖呈上升趋势，在干预结束后 60min 随机血糖趋于平稳，与干预前相比随机血糖显著降低（P<0.05）。与第 1 天的初始血糖相比，第 7 天的随机血糖值显著降低（P<0.05）。持续 7 天刺激后，与随机血糖的基线比较，C 组大鼠随机血糖无统计学差异（P>0.05），M 组大鼠随机血糖显著降低（P<0.01）。

关键词：耳穴电刺激，糖尿病，实时血糖

YP-13 从系统动力学的视角理解运动损伤的风险因素：因果循环图的使用

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当前，运动损伤已经成为运动员、研究人员和卫生专业人员日益关注的流行病问题，运动损伤不仅影响运动员的正常训练，造成竞技能力下降，而且在一定程度上可对健康产生一系列的不良后果。探索运动损伤的风险因素可有效预防运动损伤。现有研究多从运动损伤直接或间接原因入手分析风险因素，发现运动员预防损伤知识缺乏、运动负荷过大、疲劳过度、场地器材不完善等是运动损伤的主要风险因素，但是仅从风险因素视角解读运动损伤会忽略各个因素的动态关系，没有考虑损伤问题的复杂性。因此，需要考虑因素关系之间的动态属性，深入了解运动行为的潜在机制，并通过反馈机制实现干预，对解决运动员损伤问题具有指导意义。

目的：通过系统动力学了解运动员运动损伤背后的复杂因果关系。方法：应用基于文献的定性方法来绘制运动损伤的因果循环图（CLD）,再通过专家访谈反复审查，结合实证文献来增强 CLD 模型。结果：根据文献和专家意见绘制运动损伤 CLD 模型，CLD 由身体状态、心理状态、物理环境和社会文化环境组成；出现了三种类型的动力学：（1）反馈循环，（2）反馈回路和子系统因素之间的联系，（3）机制；最终因果循环图定义显示由 11 个强化反馈循环和 9 个平衡反馈循环回路组成，解释了 35 个变量，其中涉及干预措施。结论：CLD 提供了系统视角对运动损伤研究的见解，确定了一系列机制包含多个层次的连接，而导致运动损伤因素有可能为多因素；了解运动损伤如何受到多方面干预因素的互相影响；了解预期后果的全面看法。这种构建问题的方式将有助于扩展运动损伤领域，为公共卫生提供干预措施，以应对复杂的现实世界。

关键词：运动损伤；风险因素；反馈回路

YP-14 多巴胺对鸣禽前脑鸣唱相关通路 HVC-RA 和 LMAN-RA 突触传递的差异性调控

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摘要：鸣禽是研究发声学习与感觉运动的重要模式动物，其发声受相关神经通路控制。弓状皮质栎核（RA）是鸣禽前脑鸣唱前运动核团，RA 中的投射神经元（PNs）直接调控鸣曲的声学特征。RA PNs 不仅同时接受发声运动通路最高级核团 HVC 和鸣唱学习相关核团巢皮质前部巨细胞核外侧部（LMAN）的兴奋性突触传入，还接受 RA 内 GABA 能中间神经元的抑制性突触传入。多巴胺（DA）是脑内主要的神经递质系统之一，广泛参与了脑的重要功能。我们前期研究显示，DA 信号可通过 D1 样 DA 受体（D1R）参与调控成年雄性鸣禽斑胸草雀 RA PNs 的膜特性和兴奋性突触传递。然而，DA 对 RA PNs 接受的两条主要兴奋性突触传入 HVC-RA 和 LMAN-RA 以及来自中间神经元网络的抑制性突触传入是否存在差异性调控需深入研究，同时 RA 接受的 DA 信号可否影响鸣唱行为仍有待证明。我们依然以成年雄性斑胸草雀为研究对象，运用离体脑片全细胞膜片钳技术研究的结果显示，DA 可降低 HVC-RA PNs 和 LMAN-RA PNs 诱发兴奋性突触后电流（eEPSCs）以及 RA 中间神经元网络-RA PNs 诱发抑制性突触后电流（eIPSCs）的幅值。该结果表明，DA 信号可同步降低 RA PNs 两条主要的兴奋性突触传入以及抑制性突触传入。在体微量渗透靶向给药的实验结果显示，DA 可有效降低鸣唱音节的熵值，并提高鸣曲的相似度，表明 DA 可提高鸣曲的稳定性。以上研究结果提示，DA 信号可通过调控 RA PNs 兴奋性和抑制性突触传递的平衡，稳定鸣唱行为。

关键词：鸣禽，RA 投射神经元，多巴胺，突触传递，鸣唱行为

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YP-15 雌二醇调控鸣禽 RA 投射神经元兴奋性突触传递及鸣唱行为

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鸣禽鸣唱是一种复杂的发声学习行为，并受脑中一组相互联系的神经核团调控。鸣禽已成为研究发声学习神经机理的重要模式动物。鸣禽前脑鸣唱前运动核团 RA 投射神经元（PNs）同时接受发声运动通路最高级核团 HVC 和发声学习通路皮层核团 LMAN 的谷氨酸能兴奋性突触传入，并接受 RA 内 GABA 能中间神经元的抑制性突触传入，且下行投射至舌下神经气管鸣管亚核，通过支配鸣肌最终产生鸣唱行为。两条兴奋性传入通路的功能不同，其中 HVC-RA 控制着鸣唱稳定性，而 LMAN-RA 控制鸣曲的可塑性。研究证实，雌激素对鸣禽鸣唱学习行为有重要调控作用。鸣禽脑内的雌激素主要为雌二醇（E2），由睾酮经芳香化酶作用转化而来。我们前期研究表明，E2 可经 G 蛋白偶联膜结合雌激素受体（GPER）快速降低成年雄性斑胸草雀 RA PNs 的兴奋性。然而，E2 调控 RA PNs 突触传递的机制及对鸣唱行为的影响仍不清楚。本研究仍然以成年雄性斑胸草雀为研究对象，在体实验的结果表明，双侧 RA 内微量渗透 E2 可快速降低鸣曲稳定性。与此同时，离体脑片膜片钳全细胞记录的实验结果显示，E2 可降低 HVC-RA PNs 诱发 EPSCs 的幅值，而升高 LMAN-RA PNs 诱发 EPSCs 的幅值，此外还降低 RA PNs 接受的中间神经元网络抑制性突触传递诱发 IPSCs 的幅值，且 GPER 激动剂可模拟这种作用，而 GPER 阻断剂则阻断该作用。上述研究结果表明，E2 可通过 GPER 调控 RA PNs 兴奋性和抑制性突触传递，并可能通过此过程调控鸣曲稳定性。我们这些发现有助于理解 E2 信号对鸣禽鸣唱前运动核团 RA 投射神经元突触传递及鸣唱行为的调控及受体机制。

关键词：雌二醇；鸣禽；鸣唱行为；RA 投射神经元；突触传递

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YP-16 Near-infrared photothermal manipulates cellular excitability and animal behavior in Caenorhabditis elegans

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Near-infrared (NIR) photothermal manipulation is emerged as a promising and noninvasive technology for neuroscience research and disease therapy due to its deep tissue penetration. Especially, NIR-stimulated techniques have been used to modulate neural activity. However, due to the lack of suitable in vivo control systems, most studies are limited to the cellular level. Indocyanine green (ICG) is an FDA-approved photothermal agent, which can transfer optical energy to thermal energy in responding to NIR stimuli. We describe here a NIR photothermal system to modulate cellular excitability and animal behaviors in Caenorhabditis elegans via the thermosensitive TRPV1 channels with ICG in vivo. Upon NIR stimuli, exogenous expression of TRPV1 in AFD sensory neurons causes Ca^{2+} influx, leading to increased neural excitability and reversal behaviors, in the presence of ICG. And the GABAergic D-class motor neurons can also be activated by NIR irradiation, resulting in slower thrashing behaviors. Moreover, we successfully apply the photothermal manipulation in different types of muscle cells, enhancing muscular excitability, leading to muscle contractions and physiological behavior changes in C. elegans. Meanwhile, ICG shows no biotoxicity to the survival, reproduction and lifespan of the nematodes. Altogether, this study demonstrates a noninvasive and effective method to precisely regulate the excitability of different types of cells and related behaviors in vivo by NIR photothermal manipulation, which may be applied in mammals and clinical therapy.

Keywords: near-infrared (NIR) light, photothermal manipulation, TRPV1, ICG, Caenorhabditis elegans, cellular excitability, animal behavior.

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YP-17 三氯乙烯对大鼠心肌细胞发育毒性的影响

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背景和目的：三氯乙烯（Trichloroethylene，TCE）在环境中广泛存在，已被确定为人类致癌物，与一系列健康问题有关，我国卫生部和国家标准化管理委员会颁布的《生活饮用水卫生标准》中规定，饮用水中三氯乙烯含量限定为 70μg/L(70ppb)。流行病学研究，动物实验和体外实验都表明 TCE 暴露与先天性心脏病密切相关。本实验室曾报道暴露于 TCE 下的斑马鱼心脏发育畸形；并发现调控心脏发育的 Wnt 信号通路表达异常；但 TCE 主要的心脏发育毒性作用机制尚不明确。本研究采用分化的大鼠心肌细胞（H9C2）作为细胞模型，探究 TCE 暴露对分化心肌细胞的影响。

方法：本实验采用分化的大鼠心肌细胞作为细胞模型，cck8 测定细胞细胞活力，发现 10ppb-100ppb 之间不会导致细胞毒性，最终采用 60ppb 作为后续实验处理，该浓度低于饮用水三氯乙烯含量。采用 Confocal 技术检测氧化应激以及衰老相关基因 $P16^{INK4a}$、P21，Confocal 技术检测 γH2Ax 以及核纤层蛋白 LaminB，Confocal 以及 Western Blot 技术检测 β-catenin 表达。

结果：研究发现：①60ppbTCE 浓度处理下，DCFH-DA，MitoSox 显著上调，提示该浓度下导致分化的大鼠心肌细胞发生氧化应激；②TCE 导致 β-半乳糖苷酶的活性升高，衰老相关基因 $P16^{INK4a}$、P21 表达增强，DNA 双链损伤增加，核纤层蛋白 LaminB 缺失，这表明 TCE 暴露导致心肌细胞衰老；③TCE 抑制 Wnt 信号通路，β-catenin 表达下降，加入激活剂 CHIR 后逆转衰老相关表型；④转录组测序分析结果显示，TCE 处理的心肌细胞白介素等细胞因子也出现显著变化，GO 分析差异性表达基因富集于炎症反应生物学过程。⑤加入氧化应激的清除剂，显著缓解 TCE 对 Wnt 信号通路的抑制效应以及细胞衰老表型的出现。

结论：综上，TCE 可能通过激活氧化应激，抑制 Wnt 信号通路，促进细胞衰老，导致心肌细胞发育毒性，相关机制的探讨将有利于全面评估及科学预防 TCE 所致心脏发育缺陷等健康风险。

关键字：三氯乙烯；大鼠心肌细胞；Wnt 信号通路；氧化应激；衰老

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YP-18 Microglial TRPM2 deficiency accelerates seizure development via increasing neuronal excitability

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Epilepsy is a common neurological disorder, occurred as a result of an enhancement of neural excitability with complex mechanisms. Emerging evidence indicate microglia play a critical role in epilepsy, but the underlying mechanism is unknown. In this study, our results show that the transient receptor potential melastatin type 2 (TRPM2) channel as a calcium permeable non-selective cation channel, its deficiency accelerates seizure development in various mouse seizure models including PTZ-, KA- and kindling-induced models, but do not affect seizure susceptibility in initial acute seizure. Interesting, we further found that deficiency of TRPM2 in microglia, but not CaMKⅡα$^+$ or PV$^+$ neurons, is mainly responsible for seizure development. Moreover, microglial *Trpm2* deficiency increases the excitability of hippocampal pyramidal neurons via enhancing the AMPAR-mediated excitatory synaptic transmission but does not influence the expression of inflammation cytokines. These findings not only show new light on microglia contributed to epilepsy independent of inflammation, also uncover the microglia instead of neuron TRPM2 channel play a key role in seizure development, providing a novel therapeutic strategy for epilepsy by targeting microglia TRPM2 channel.

Keywords: TRPM2 channel, seizure, microglia, AMPAR, neuron

YP-19 Identification of CD38^{high} monocyte as a novel signature driving innate immune dysfunction through metabolic reprogramming during sepsis

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Sepsis, a systemic response to infection characterized by acute organ dysfunction and a high mortality risk, necessitates detailed understanding of its cellular characteristics to pinpoint effective immunotherapeutic targets for diagnosis and treatment. In this study, we performed mass cytometry and single-cell transcriptome sequencing to assess immune cell alterations in peripheral blood from septic patients (n = 45, sepsis individuals), relating findings to clinical parameters. We identified novel CD38high monocyte features in circulation were specifically accumulated, correlating with Sequential Organ Failure Assessment (SOFA) scores and C-reactive protein (CRP) levels. Additionally, single-cell metabolic protein map sequencing (scMPP) revealed that $CD38^{high}$ monocytes showed hyperactivated glycolysis, suggesting involvement in dysregulated innate immune responses. Knockdown or inhibition of CD38 significantly mitigated immune dysfunction and maladaptive response, potentially linking to NAD+ consumption triggered by CD38 induced mitochondrial dysfunction and hypoxia-inducible factor-2α (HIF-2α) stability. These results demonstrated that $CD38^{high}$ monocyte characteristic with a unique disease metabolic phenotype may be a specific early warning and immunotherapy target against sepsis, which helps to better illustrate the heterogeneous processes of sepsis.

Keywords：CD38; Sepsis; ScRNA-seq; Glycolysis; Metabolic reprogramming

YP-20 Erythroid-intrinsic activation of TLR8 impairs erythropoiesis in Diamond-Blackfan anemia-like syndrome

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Diamond-Blackfan anemia (DBA) is a rare congenital bone marrow disorder characterized by impaired erythropoiesis. Mutations in ribosomal proteins (RPs) as well as some non-RPs account for approximately 70% of DBA cases, but the pathogenic basis of the remainder is unknown. It is crucial for deciphering the pathogenesis of DBA to uncover novel pathogenic gene(s) involved. Here, we identified in a diseased pedigree that a gain-of-function mutation in toll-like receptor 8 (TLR8) was implicated in DBA. Further studies showed that TLR8 was expressed in erythroid lineage from as early as the BFU-E stage. Besides, erythroid survival, proliferation and early differentiation were impaired by TLR8 activation and enhanced by TLR8 inhibition from CFU-E stage. Mechanistically, TLR8 activation disrupted EPO signaling through inhibiting STAT5 phosphorylation. Furthermore, TLR8 inhibitor improved erythropoiesis of $CD34^+$ HSPCs from DBA patients. Collectively, we report a novel causative gene for DBA and previously undescribed role for TLR8 under both physiological and pathological erythropoiesis. It could be one of the potential therapeutic target for erythropoiesis-disturbing conditions including DBA.

Keywords: Erythropoiesis; Diamond-blackfan anemia; TLR8; STAT5.

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YP-21 二妙散调节 PGC-1α 蛋白乙酰化抑制肝脏糖异生的作用研究

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目的：糖尿病等代谢性疾病的发病率全球性增加，严重威胁人类健康，而采用中药经方二妙散健脾助运、清热燥湿在改善机体糖代谢稳态方面有积极作用。肝脏糖异生紊乱是导致糖尿病等代谢性疾病空腹血糖升高的重要因素。过氧化物酶体增殖物激活受体 γ 辅激活因子 1α (Peroxisome proliferator activated receptor-γ coactivator-1α, PGC-1α)是一转录辅助因子，能够通过其蛋白赖氨酸乙酰化修饰参与肝脏糖异生关键酶的转录调节。本研究以 PGC-1α 蛋白乙酰化活性调节为切入点，探明二妙散干预肝脏糖异生的功效表现和作用机制。**方法：**建立空腹(Fasted)小鼠、高脂饲喂(High-fat diet, HFD)小鼠动物模型和饱和脂肪酸棕榈酸(Palmitate, PA)刺激肝细胞模型，考察二妙散调节 PGC-1α 蛋白乙酰化抑制肝脏糖异生的作用及分子机制。**结果：**二妙散能够抑制 Fasted 和 HFD 模型小鼠肝脏糖异生，降低 HFD 小鼠空腹血糖水平。分子机制上，二妙散能够降低肝组织中 NAD^+/NADH 比值，从而抑制去乙酰化酶 Sirtuin 1 (SIRT1)活性；此外，二妙散促进 AMPK 及其下游靶标乙酰辅酶 A 羧化酶(Acetyl-CoA carboxylase, ACC)蛋白水平磷酸化，通过阻断脂质合成而减少乙酰辅酶 A 的消耗，促进 GCN5 介导的 PGC-1α 蛋白乙酰化，抑制其蛋白活性，减少肝脏糖异生。**结论：**二妙散通过 AMPK/ACC 信号调节促进 PGC-1α 蛋白乙酰化，抑制 PGC-1α 蛋白活性，减少肝糖输出。本研究为二妙散治疗代谢性疾病提供了实验数据，并为糖尿病等代谢性疾病提供了新的治疗思路和策略。

YP-22 交感-肾上腺轴介导电针天枢穴治疗脓毒症模型大鼠的机制研究

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背景：肾上腺参与电针抗炎效应，但其调控规律及效应机制尚不明确。我们前期观察到针刺对靶器官的调控效应具有节段性差异，表现为刺激同节段穴位以兴奋交感神经为主，刺激远节段穴位以兴奋迷走神经为主。因此，是否电针肾上腺同节段穴位天枢穴是调控交感-肾上腺轴的最优穴，并发挥系统性抗炎效应？研究内容及方法：本研究以大鼠为实验对象，采用在体电生理、质谱检测、ELISA 等多种实验手段，研究：①电针驱动交感-肾上腺轴的穴位分布及刺激参数规律；②在脓毒症模型中，探讨电针驱动交感-肾上腺抗炎途径的神经生物学机制。结果：3 mA 单脉冲刺激天枢穴是诱发肾上腺交感神经放电的最佳强度（$P<0.001$），并能显著增加外周血中去甲肾上腺素（$P<0.001$）水平，但对其代谢产物 3-甲基

去甲肾上腺素无显著影响。与模型组相比，电针天枢穴能够显著提高大鼠生存率（P＜0.05），改善模型评分（P＜0.05）。同时，电针组外周血中促炎因子 IL-6，IL-1β 较模型组显著下降（P＜0.01），抗炎因子 IL-10 较模型组显著增加（P＜0.01）。结论： 3 mA 是电针天枢穴激活肾上腺交感神经兴奋的最佳强度，增加去甲肾上腺素水平，发挥治疗脓毒症的抗炎效应。本结果为指导电针治疗炎症相关疾病的选穴及刺激参数、完善针灸自主神经抗炎的神经生物学机制提供了重要的实验依据。

关键词：脓毒症；神经-免疫；去甲肾上腺素；外周神经刺激

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YP-23 电针调控自主神经干预心肌缺血大鼠心功能动态变化

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目的：观察心肌缺血大鼠心功能及自主神经功能连续和动态变化；明确电针干预对心肌缺血的自主神经-靶器官结构功能的影响。**方法：**雄性 SD 大鼠分为对照组（CON）、模型组（MI）、针刺内关穴组（EA-PC6）和针刺足三里穴组（EA-ST36）。采用冠状动脉左前降支结扎法制备心肌缺血模型。选取心脏同节段 PC6 及异节段 ST36 进行电针干预（15 Hz，1.5 mA）隔天 1 次，连续 4 周。采用 II 导联心电图检测各组大鼠 ST 段高度及心率变异性（HRV）；双钩电极记录各组大鼠心交感/颈迷走神经放电频率变化；超声心动图检测各组大鼠射血分数（EF）及短轴收缩率（FS）； Millar 管监测左室压力-容积环导出心功能指标，包括每搏输出量（SV）、每搏功（SW）、心输出量（CO）、dp/dt max、Tau、ESPVR 斜率 Ees、EDPVR 斜率 Eed。**结果：**与 MI 组比，EA-ST36 在 Day 7 时 ST 段低于 MI 组，EA-PC6 组 ST 段 Day 21、28 较 MI 组明显升高（P < 0.05，P < 0.01）。与 CON 组比，MI 后大鼠心交感神经放电频率在 Day 7 和 Day 14 时明显高于 CON（P < 0.05）；Day 28 时，EA-PC6 组心交感神经放电频率较 CON 组和 MI 组显著升高（P＜0.01）。MI 后各组 EF 和 FS 水平均较基线降低；Day 28 时，EA-PC6 组与 EA-ST36 组 EF 和 FS 水平较 MI 后均有显著升高；Day 28 时，EA-PC6 组的 EF 和 FS 较 MI 组明显升高（P＜0.05，P＜0.01）。与 CON 组比，MI 组和 EA-ST36 组大鼠的 SV、SW、CO、dp/dt max 和 Ees 显著降低，MI 组的 dp/dt min 显著降低（P＜0.05，P＜0.01）；各组的 Tau 均显著高于 CON 组（P＜0.0001）。与 MI 组比，EA-PC6 组的 SV、SW、CO、dp/dt max 和 Ees 显著升高，dp/dt min 显著升高（P＜0.05，P＜0.01）。**结论：**MI 后大鼠心交感/颈迷走神经放电频率呈现先增强后减弱的动态变化。电针 PC6 能使心交感活动在模型后 28 天仍维持较高的水平；电针心同节段 PC6 较异节段 ST36 能明显改善 MI 模型大鼠心功能，特别是心肌收缩功能。

关键词：针刺，心肌缺血，自主神经功能，心功能

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YP-24 电针调节 DRG 神经元兴奋性改善溃疡性结肠炎小鼠痛觉超敏

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溃疡性结肠炎（Ulcerative colitis，UC）是炎症性肠病的一种，好发于结肠粘膜，是由免疫、遗传、环境等因素引起的，以腹痛、腹泻以及血便为主要临床症状的慢性炎症性肠道疾病。电针是治疗溃疡性结肠炎使用最多的非药物疗法，可以有效缓解患者的疼痛症状。背根神经节（Dorsal Root Ganglia，DRG）在伤害性信息和本体感觉传入通路中发挥着重要的作用，溃疡性结肠炎患者常伴有腰背部疼痛的症状，这可能与 DRG 神经元的兴奋性增强有关。为探究电针调节 UC 疼痛的神经生物学机制，我们基于 UC 小鼠模型，综合使用了形态学和电生理学的方法开展了研究。

在 C57B/L6 小鼠上使用葡聚糖硫酸钠（DSS）诱导急性溃疡性结肠炎模型，对比造模前与造模第七天疾病活动指数评分判断模型有效性，天枢组及上巨虚组分别在模型基础上给予电针（2 Hz，1 mA）30 分钟。通过给予对照组、模型组、天枢组和上巨虚组小鼠直结肠扩张刺激以诱发小鼠内脏运动反射并记录腹直肌电。结果显示，DSS 组腹直肌放电数量多于其他三组。在各组小鼠远端结肠肌层注射示踪剂，标记 DRG 中的结肠感觉神经元，并急性分离 T12-L2 节段双侧 DRG，全细胞膜片钳记录 DRG 中、小直径神经元的兴奋性。电流钳结果显示：DSS 组静息膜电位高于对照组、天枢组和上巨虚组;基强度低于其他三组；动作电位数量高于其他三组；去极化速率大于其他三组。对各组小鼠 T12-L2 DRG 进行免疫荧光染色观察 $Na_v1.8$ 与 CGRP 共标情况，结果显示 DSS 组共标细胞数量大于其他三组。这些结果表明，电针能有效缓解结肠炎小鼠的疼痛，其有效机制可能是通过调节 DRG 神经元上 $Na_v1.8$ 的表达量从而影响动作电位的发放频率降低神经元兴奋性，改善模型小鼠痛觉超敏症状。本研究从亚细胞和细胞水平揭示了电针治疗小鼠结肠炎痛觉超敏的机制，为临床上电针治疗溃疡性结肠炎提供了可靠证据。

关键词：电针，背根神经节，痛觉超敏，钠离子通道

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YP-25 vlPAG 中 GABA 能神经元参与电针缓解 IBS 小鼠内脏痛的机制研究

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目的：采用光遗传技术调控腹外侧中脑导水管周围灰质(Ventrolateral Periaqueductal Gray，vlPAG)中的 GABA 能神经元，探讨 vlPAG 中 GABA 能神经元参与电针缓解 IBS 小鼠内脏痛的机制。方法：将 Vgat-Cre 小鼠随机分为（1）正常组：给予与电针组相同的固定；（2）模型组：给予与电针组相同的固定；（3）模型＋eNpHR 组：注射 rAAV2/9-EF1α-DIO-eNpHR3.0-EGFP 病毒，给予黄光刺激（20Hz，5ms，4mW）；（4）模型＋ChR2 组：注射 rAAV2/9-EF1α-DIO-hChR2-EGFP 病毒，给予蓝光刺激（20Hz，5ms，4mW）；（5）电针组：取穴：双侧“足三里”，疏密波，频率 2/100Hz，电流 1mA，30min/次，每日一次，连续治疗 7 天。采用 TNBS 溶液灌肠制备 IBS 慢性内脏痛模型；通过一般情况观察、腹壁撤回反射评分确认模型制备成功后，利用光遗传技术对 vlPAG 的 GABA 能神经元进行激活和抑制调控，分析各组小鼠的 AWR 评分变化。结果：1）与正常组比较（干预前），模型组小鼠 AWR 评分上升（P<0.01）；2）与给光前相比，模型＋eNpHR 组小鼠在给予黄光抑制 GABA 能神经元时，AWR 评分上升（P＜0.05）；模型＋ChR2 组小鼠在给予蓝光激活 GABA 能神经元时，AWR 评分下降（P<0.05）；3）与正常组相比（干预后），模型组小鼠 AWR 评分上升（P＜0.01）；与模型组相比，模型＋eNpHR 组 AWR 评分上升（P<0.05）；模型＋ChR2 组 AWR 评分下降（P<0.05）；电针组 AWR 评分　下降（P<0.05）。结论：光遗传技术能够有效的调控 vlPAG 脑区中的 GABA 能神经元，而电针对 IBS 小鼠的疼痛行为学影响与光遗传激活 GABA 能　神经元产生的效应趋势一致，说明电针可能通过激活 vlPAG 中的 GABA 能神经元发挥缓解 IBS 小鼠内脏痛的作用。

关键词：电针；光遗传；vlPAG；GABA；IBS；内脏痛。

GABAergic neurons in vlPAG downregulates visceral hypersensitivity by electroacupuncture in IBS mice

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Objective: Optogenetic technology was used to regulate GABAergic neurons in ventrolateral periaqueductal gray (vlPAG), and the mechanism of GABAergic neurons in vlPAG participating in electroacupuncture to relieve visceral pain in IBS mice was discussed. **Methods:** Vgat-Cre mice were randomly divided into (1) Normal Group: no treatment was given, only the same fixation as the electroacupuncture group was given; (2) Model group: do not do any treatment, only give the same fixation as the electroacupuncture group; (3) Model + eNpHR group: injection of rAAV2/9-EF1α-DIO-eNpHR3.0-EGFP virus, yellow light stimulation (20Hz, 5ms, 4mW) ;(4) Model + ChR2 group: injection of rAAV2/9-EF1α-DIO-hChR2-EGFP virus, blue light stimulation (20 Hz, 5ms, 4mW); (5) Electroacupuncture group: acupuncture: Zusanli (double), dense wave, frequency 2/100Hz, current 1mA, 30min/time, once a day, continuous treatment for 7 days. A model of chronic visceral pain of IBS was prepared by enema with TNBS solution. After the model was successfully prepared by general observation and abdominal wall withdrawal reflex score, the GABAergic neurons of vlPAG were activated or inhibited by optogenetic technology, and the changes of AWR scores in each group of mice were analyzed. **Results:** 1) Compared with the normal group, the AWR score of mice in the model group increased ($P<0.01$); 2) Compared with before giving light, the AWR score of mice in the model + eNpHR group increased ($P<0.05$) when given yellow light to inhibit GABAergic neurons; the model+ChR2 group decreased when blue light activated GABAergic neurons ($P<0.05$); 3) Compared with the normal group, the AWR score of mice in the model group increased ($P<0.01$), and compared with the model group, the AWR score of the model + eNpHR group increased ($P<0.05$); The AWR score of the model + ChR2 group decreased ($P<0.05$); The AWR score decreased in the electroacupuncture group ($P<0.05$). **Conclusion:** Optogenetic technology can effectively regulate GABAergic neurons in vlPAG brain regions, and the pain behavior effect of electricity on IBS mice is consistent with the effect trend of optogenetic activation of GABAergic neurons, indicating that electroacupuncture may play a role in alleviating visceral pain in IBS mice by activating GABAergic neurons in vlPAG.

Key words： Electroacupuncture; Optogenetics; vlPAG; GABA; IBS; Visceral pain.

YP-26 不同呼吸方法下的中国古典舞动作表现及影响因素探析

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目的：对舞者而言，呼吸不仅是日常重要的生命活动，同时也是舞蹈中必不可少的技术

手段，而中国古典舞者则尤为如此。本文以中国古典舞躯干后伸动作为例，分析不同呼吸方法下动作的表现效果及其影响因素，并探讨其解剖生理基础，以期为中国古典舞的呼吸训练提供一定的科学理论依据与实践方法借鉴。

方法：首先，通过文献资料法和专家访谈法，对中国古典舞中常见的呼吸方法进行梳理和分析总结。其次，运用跨学科研究法及对比分析法，基于生理学、解剖学和运动力学等理论，同时结合中国古典舞审美及动作技术特点，针对不同呼吸方法下舞者躯干后伸动作的效果进行对比，分析探讨其影响因素等理论基础。

结果：合理的呼吸在帮助舞蹈进行动作呈现、情感表达、风格表现等多个方面，具有不可忽视的作用。不同呼吸方法下躯干后伸动作的表现效果不同，同时运动关节、工作肌群、及腹内压也不同。采用吸气方法完成“下腰”时，躯干后伸曲线不平滑，颈椎、胸椎后伸活动受限，整体后伸幅度减小，躯干稳定性降低，脊柱压迫性负荷增大，增加损伤的风险；采用呼气方法时，躯干后伸整体呈平滑曲线，颈椎、胸椎伸展幅度增大，躯干动作幅度较大、稳定性增强，脊柱压迫性负荷减小，动作安全性提高；采用屏气方法时，虽整体呈较为平滑曲线，胸腹稳定性提高，脊柱压迫性负荷减小，但颈椎因部分喉部及颈部肌肉的牵拉而后伸幅度变小，长时间保持易引发缺氧等问题。

结论：不同呼吸方法对中国古典舞躯干后伸动作表现有不同的影响，不同动作应采取不同的呼吸方式。“胸腰”动作应采用吸气方式，“下大腰”动作应采用呼气方法，而“屏气”方式应谨慎采用，一般仅在“控腰”等需加强稳定性动作中采用。研究提示在舞蹈训练、表演中要更多关注呼吸的使用与配合，有必要进一步深化相关理论与实践方法科学研究。

关键词：中国古典舞；呼吸方法；躯干后伸；下腰

YP-27 联合本体感觉的“倒踢紫金冠”核心力量训练方法研究

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目的：“倒踢紫金冠”是中国古典舞剧目中常被选用的跳跃技巧，以空中“紫金冠”舞姿展现强烈风格。本文将探讨针对该技巧进行联合本体感觉的核心力量辅助训练方法的设计，以期为提高该技巧及舞蹈中同类跳跃技巧的训练提供参考。

方法：通过对“倒踢紫金冠”技巧的解剖生理学分析，探讨核心力量和本体感觉对该动作的影响，结合舞蹈动作风格特点，研究设计联合本体感觉的核心力量辅助训练方法。

结果：良好的起跳、滞空时间长且优美的空中舞姿、轻盈稳定的落地是决定一个优秀“倒踢紫金冠”技巧的重要因素。若在现有传统训练方法，如蹬伸、踢摆等单一技术练习基础上，将单一技术有序组织与整体配合进行练习，将有益于该技巧的形成效果，而这需舞者擅于通过本体感觉准确感知身体状态，同时拥有即时调整身体状态的核心力量。分析认为，在起跳

前，需集中意识收缩“腰椎—骨盆—髋关节”为主体的深层小肌肉群，以稳定脊柱与骨盆；起跳蹬伸阶段，需感知肌肉张力长度、关节位置，在每次练习中获得反馈，逐步优化蹉步步幅及垂直高度、起跳关节角度等关键技术；提高核心肌群力量，为前踢腿、后摆腿等提供有力支撑，助力爆发起跳；加强竖脊肌、腹直肌等肌肉力量，提升空中“紫金冠”舞姿的“滞空”效果；最后在姿势还原中控制重心而获得平稳落地。据此分析结果进行辅助训练方法的设计，训练包括热身、基础训练、收整放松三大部分，训练中结合呼吸及意象等身心引导的同时，利用小器械进行辅助提高相应能力。

结论：核心力量和本体感觉是影响“倒踢紫金冠”技巧的重要因素，结合该技巧的特点进行核心力量联合本体感觉的针对性练习方法设计，将促进各动作阶段单一技术的优化，更有助于各技术配合发挥，提示该方法作为该技巧及同类舞蹈跳跃技巧课后补充与延伸练习的必要。

关键词：倒踢紫金冠；舞蹈技术技巧；核心力量训练；本体感觉

YP-28 牵张反射原理在舞者下肢爆发力训练中的应用研究

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目的：下肢爆发力是影响舞者动作技术质量与动作表现的重要因素。本文应用牵张反射原理，探讨符合中国古典舞动作审美特征的下肢爆发力训练动作方法，以期为舞者身体能力训练提供方法借鉴。

方法：首先，运用文献资料法，以“牵张反射”“中国古典舞”“下肢爆发力”为检索词，在中国知网数据库上检索相关文献，分析总结目前相关训练的理论与方法。其次，通过跨学科研究法，运用运动生理学、运动解剖学和运动训练学等学科理论和方法，针对基于牵张反射原理的舞者下肢爆发力训练方法设计展开研究。

结果：基于牵张反射原理的舞者下肢爆发力训练应重点遵循以牵张反射原理为动作设计基础，以 FITT 原则为训练负荷和量的制定依据，以符合中国古典舞审美特点为前提的基本原则与思路。基于此，该训练可分为基础训练、提高训练、强化训练三个阶段。第一阶段以原地连续跳跃为主，其中包含双脚、单脚以及交换起跳的方式。第二阶段侧重连续跳跃方向的变化，有侧向、对角线等四类方向的跳跃。第三阶段侧重移动、原地相结合的连续跳跃动作。在各训练阶段，连续跳跃动作过程中的速度性冲击负荷作用，使下肢肌群先发生被迫迅速的离心收缩后即刻转为向心收缩，进而产生较大的爆发力；同时，需结合舞姿跳等舞蹈动作元素进行。因此，该训练方法既达到牵张反射作用，也满足了舞蹈的需求。

结论：牵张反射原理的应用将有助于古典舞者下肢爆发力的提高，肌肉离心收缩后在极短的时间内向心收缩，提高了肌肉在短时间内快速收缩的能力，满足了古典舞中对于下肢爆

发力的训练要求。本研究提出的基于牵张反射原理的舞者下肢爆发力训练方法设计思路与具体内容，可应用于舞蹈教学实践中进一步完善与验证，以丰富舞蹈基本功训练方法，拓宽牵张反射原理的应用范围，为舞蹈教学训练提供有益的借鉴。

关键词：牵张反射原理；下肢爆发力；中国古典舞

YP-29 Cordycepin exerts anti-exercise fatigue effects and improves learning and memory impairment in mice with exercise fatigue

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Excessive exercise leads to physical fatigue and disrupts the balance of the antioxidant system in the body, thus damaging the central nervous system and reducing the ability to learn and remember. Cordycepin is the main active ingredient of Cordyceps militaris, which has a variety of pharmacological effects such as antidiabetic, anti-inflammatory, immunomodulatory, and antioxidant effects. However, the anti-fatigue effect of cordycepin and its specific mechanism are still unclear. The aim of this study was to investigate the anti-fatigue effect of cordycepin and its ability to improve learning and memory capacity. In in vivo experiments, the results showed that cordycepin significantly increased superoxide dismutase (SOD) activity in hydrogen peroxide-stimulated myogenic C2C12 cells, while cordycepin reduced malondialdehyde (MDA) levels. Compared with H_2O_2-stimulated C2C12 cells, cordycepin significantly decreased the levels of fatigue-inducing factors such as lactate dehydrogenase (LDH), creatine kinase (CK), and urea nitrogen (BUN), whereas cordycepin significantly increased the levels of the anti-fatigue-related factor glycogen. In treadmill incremental loading training, cordycepin prolongs exercise endurance in mice and improves liver glycogen (LG) and myoglycogen (MG) levels during treadmill exercise in mice, in addition to increasing superoxide dismutase (SOD) activity while decreasing the levels of lactic acid (LA), blood urea nitrogen (BUN), malondialdehyde (MDA) in peripheral serum, creatine kinase (CK) activity, and lactate dehydrogenase (LDH) activity. It was also found that cordycepin increased glutamate (Glu) and acetylcholine (Ach) levels in peripheral

serum while decreasing aminobutyric acid (GABA) and 5-hydroxytryptamine (5-HT) levels. Behavioural studies further showed that cordycepin significantly improved the correct rate of spontaneous alternation in exercise-fatigued mice compared with the model control group and significantly reduced the fatigue metabolism level in the hippocampus, as well as significantly increasing the neurotransmitter level and the number of neurons in hippocampal CA1 and CA3 regions and the level of c-fos in the hippocampus, which indicated that cordycepin could significantly improve the learning memory impairment in exercise-fatigued mice. In summary, cordycepin has significant anti-fatigue effects and significant potential to improve the learning and memory abilities of exercise-fatigued mice, and our systematic study provides strong supporting evidence for the future use of cordycepin in nutraceuticals to improve anti-fatigue abilities.

Keywords: Cordycepin; Anti-fatigue; Learning and memory; Neurotransmitter; Central fatigue

YP-30 90dB 纯音暴露对食蟹猴听觉及心脑功能的影响

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目的意义：过度接触噪声可能会对人类的健康造成严重损害。除了造成听觉系统的直接损伤外，噪声暴露还与心血管系统、中枢神经系统等的病变或损伤有关。揭示噪声暴露对机体的生理影响，有助于理解噪声暴露对健康带来的潜在风险，建立和更新职业噪声暴露的安全标准和限值。

材料和方法：食蟹猴 3 只，雄性，体重 6-8Kg，采用低强度纯音暴露（强度为 90dB，频率为 500Hz，重复频率 40Hz，每天 10min，连续暴露 5 天），通过听觉脑干诱发电位（ABR）技术测量噪声暴露前、暴露后即刻、7d、14d 和 28d 食蟹猴双耳的 V 波阈值及潜伏期，通过心电图（ECG）测量噪声暴露各时间点食蟹猴的心电指标，通过脑电图（EEG）记录噪声暴露各时间点的脑电相关指标，以评价噪声对食蟹猴听觉及心脑系统的影响。

结果：（1）听力指标变化：相比于噪声暴露前，暴露后即刻食蟹猴双耳的 V 波平均阈值上升了约 30dB（$p < 0.01$），这种升高效应持续 7 天（$p < 0.05$）。（2）心电指标变化：暴露后一只食蟹猴 QRS 波呈 RS 型，T 波自暴露后即刻至 14d 波形倒置，28d 恢复正常；另外两只食蟹猴心电指标无明显改变。（3）脑电指标变化：噪声暴露时，各脑区在 40Hz 处显著激活，40Hz 重复频率的噪声刺激可诱发以颞叶为起点的全脑 δ（1-3Hz）、θ（4-8Hz）、α（8-12Hz）、β1（12-20Hz）、β2（20-30Hz）和 γ（30-48Hz）频段静息态脑电功率谱密度（PSD）异常；噪声暴露后，以颞叶为代表的各脑区各频段静息态脑电 PSD 呈下降趋势，

并随时间增加无明显恢复。

结论：90dB 噪声暴露可致食蟹猴听觉系统受损、脑功能异常、心电指标异常存在个体差异，表现为短暂的听阈偏移；T 波倒置；各脑区 40Hz 脑电信号显著激活，全脑各频段静息态脑电 PSD 紊乱。以后可进一步结合病理学和行为学指标，深入探究低强度噪声暴露对食蟹猴听觉和听觉外系统的影响及机制。

关键词：噪声暴露，食蟹猴，听觉，ECG，EEG

YP-31 肠道菌群对脊髓损伤后焦虑情绪的调控作用及分子机制研究

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背景：脊髓损伤（spinal cord injury，SCI）是一种具有严重后果的中枢神经系统创伤性疾病，会对患者身体功能、情感和社会交往等多方面造成损害。大量相关研究表明脊髓损伤后焦虑情绪的发生已经高达 15%-32%，严重高出正常人焦虑患病率。研究发现，焦虑情绪的发生不仅会对脊髓损伤患者的生活质量和身心健康造成极大的影响，而且会影响疾病的后续治疗效果，因此加强对脊髓损伤并发焦虑的诊断与治疗尤为重要。最近，肠道菌群被认为是情绪和心理调节的重要靶点，研究发现焦虑患者的肠道菌群发生改变，同时患有焦虑症的人也可以通过调节肠道菌群，缓解焦虑症状，说明肠道菌群的稳态至关重要。我们的预实验结果也提示，脊髓损伤后肠道菌群分布的多样性及丰度也发生改变。因此，本研究通过分析脊髓损伤后焦虑情绪的发生与肠道菌群之间的内在联系，为临床预防、治疗此病提供新途径，具有重要的临床意义与价值。

目的：观察脊髓损伤后焦虑情绪的发生，明确肠道菌群在 SCI 后焦虑情绪中的作用；阐明肠道菌群对脊髓损伤后焦虑情绪发生的调节作用及其分子机制。

方法：

1、构建 SD 大鼠脊髓损伤模型，使用高架十字迷宫实验、旷场实验评估脊髓损伤后焦虑情绪的发生。

2、16Sr DNA 高通量测序分析脊髓损伤后肠道菌群在门、科、属分布的多样性及丰度的改变。

3、采用免疫荧光、Western Blot、ELISA 检测大脑中缝背核、基底外侧杏仁核脑区中 5-羟色胺能神经元表达水平、5-HT 含量、5-HT_{1A} 受体表达变化，明确 5-HT 系统在脊髓损伤后焦虑情绪中的变化。

4、粪菌移植验证正常菌群对脊髓损伤后焦虑情绪的调节作用，16Sr DNA 高通量测序分析肠道菌群的改变及对 5-羟色胺系统的调节作用。

5、采用 GraphPad Prism 软件进行统计学分析。

预期结果：

1、脊髓损伤后大鼠肠道菌群改变的同时伴有焦虑情绪的发生。

2、粪菌移植可以通过提升脑内 5-羟色胺系统的表达水平，缓解脊髓损伤后的焦虑样情绪。

关键词：脊髓损伤；肠道菌群；焦虑；5-HT；

YP-32 Frataxin inhibits ferroptosis to improve myocardial ischemia/reperfusion injury

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Rationale: Myocardial ischemia/reperfusion (I/R) injury is characterized by cell death via various cellular mechanisms upon reperfusion. As a new type of cell death, ferroptosis provides new opportunities to reduce myocardial cell death. Ferroptosis is known to be more active during reperfusion than ischemia. However, the mechanisms regulating ferroptosis during ischemia and reperfusion remain largely unknown.

Methods: The contribution of ferroptosis in ischemic and reperfused myocardium were detected by administered of Fer-1, a ferroptosis inhibitor to C57BL/6 mice, followed by left anterior descending (LAD) ligation surgery. Ferroptosis was evaluated by measurement of cell viability, *ptgs2* mRNA level, iron production, malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) levels. H9C2 cells were exposed to hypoxia/reoxygenation to mimic in vivo I/R. We used LC-MS/MS to identify potential E3 ligases that interacted with frataxin in heart tissue. Cardiac-specific overexpression of frataxin in whole heart was achieved by intracardiac injection of frataxin, carried by adeno-associated virus serotype 9 (AAV9) containing cardiac troponin T (cTnT) promoter, then cardiac function as well as ferroptosis were measured.

Results: We showed that regulators of iron metabolism, especially iron regulatory protein, were increased in the ischemic myocardium or hypoxia cardiomyocytes. In addition, we found that frataxin, which is involved in iron metabolism, is differentially expressed in the ischemic and reperfused myocardium and involved in the regulation of cardiomyocyte ferroptosis. Furthermore, we identified an E3 ligase, NHL repeat-containing 1 (NHLRC1), that mediates frataxin ubiquitination degradation. Cardiac-specific overexpression of frataxin ameliorated myocardial I/R injury through ferroptosis inhibition.

Conclusions: Through a multi-level study from molecule to animal model, these findings uncover the key role of frataxin in inhibiting cardiomyocyte ferroptosis and provide new strategies and perspectives for the treatment of myocardial I/R injury.

Keywords: myocardial ischemia/reperfusion injury, ischemia, ferroptosis, iron regulatory protein, NHLRC1

YP-33 Cognitive effect of a single underwater operation is time-dependent and CCR3-mediated neuroinflammation contributes to cognitive decline induced by prolonged underwater operations

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Background Underwater operations are widely used in various domains such as marine exploration, underwater construction and infrastructure maintenance, and military missions. Previous studies have emphsized the importance of maintaining cognition in these tasks. However, the impact of underwater operations on cognitive functions and the underlying mechanisms remain unclear. Therefore, this study aimed to examine the effects of underwater operations on cognitive functions and to explore the potential molecular mechanisms involved.

Methods For the individual study, a total of 33 underwater special operation divers were recruited. The study assessed their stress response, anxiety, and cognitive performance before and after underwater operations of two different durations. As for the animal studies, firstly, 75 male Sprague-Dawley rats, aged 8 weeks, were selected and exposed to swimming in a hyperbaric environment at 2.0ATA (atmospheres absolute) for varying durations to simulate underwater operations. Anxiety-like and cognitive behaviors were evaluated using the open field test (OFT) and Morris water maze test (MWM). Hippocampal tissues were collected for analysis, including histological examinations such as HE (hematoxylin-eosin) and Nissl staining, as well as several biochemical assays including enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, immunofluorescence, quantitative real-time polymerase chain reaction (qRT-PCR), and western blotting (WB). Furthermore, RNA-sequencing was conducted, leading to the identification of C-C chemokine receptor type 3(CCR3) as a potential target for further investigation. Knockdown experiments were performed using an adeno-associated virus (AAV) vector containing shRNA (CCR3)-EGFP injected to the hippocampus to explore the involvement

of CCR3 in cognitive impairment induced by prolonged underwater operations.

Results Underwater operations affect cognitive function and prolonged operations induces significant cognitive decline. In animal models, the effect of exercise in hyperbaric environment is closely related to the durations. Prolonged exercise in hyperbaric environment induced significant acute stress response, anxiety and cognitive impairment in rats. Prolonged exercise in hyperbaric environment causes notable damage to hippocampal neurons, neuroinflammation, and a reduction in the expression of BDNF/TRKB, which are vital factors for brain health and cognitive function. The group exhibiting the most severe cognitive impairment was chosen to further explore the molecular mechanism underlying cognitive impairment induced by prolonged underwater exercise. RNA sequencing analysis revealed that neuroinflammation is the primary biological process involved, in which CCR3 may play a crucial role. CCR3 knockdown significantly alleviated neuroinflammation, pathological alterations in hippocampus and cognitive impairment induced by prolonged underwater exercise. Moreover, prolonged underwater exercise activated microglia and promotes their polarization towards the pro-inflammatory phenotype. Conversely, CCR3 knockdown switched the activated microglia to the anti-inflammatory phenotype.

Conclusions The cognitive effect of underwater operations is time-dependent and prolonged operation induces significant cognitive decline. The underlying molecular mechanism may involve CCR3-mediated neuroinflammation. Knocking down CCR3 can alleviate neuroinflammation and cognitive impairment by regulating microglial activation. Our study suggests that targeting CCR3 or neuroinflammation may be a potential intervention for protecting the brain in prolonged underwater operations.

Key words: Underwater operations; Cognitive function; CCR3; Neuroinflammation；microglia activation

YP-34 Andrographolide exhibits antinociceptive effects in neuropathic rats via inhibiting class Ⅱ MHC associated response and regulating synaptic plasticity

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Background: Andrographolide is a traditional bioactive compound, derived from Andrographis paniculate, exhibiting anti-inflammatory and neuroprotective effects in psychiatric disorders. However, the underlying analgesic mechanism of andrographolide is unclear.

Methods: Dorsal horn neurons in laminae Ⅱ were recorded by whole-cell recording

following spinal nerve ligation (SNL) in rodents. we further explored the molecular and gene alterations by R packages of weighted gene co-expression network analysis (WGCNA) and differential gene expression analysis (DEGs) in spinal dorsal horn after andrographolide treatments in neuropathic pain.

Results: We found that intrathecal andrographolide dose and time-dependently alleviated mechanical allodynia in neuropathic rats, with Emax values 100% and ED50 values of 37.21μg. Plastic mechanism study showed that bath application of andrographolide remarkable ameliorated the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs) compared with sham group in a dose-dependently manner (10~100 μmol) in laminae Ⅱ neurons of L3-L5. Furthermore, andrographolide showed significantly transcriptional adaption through signaling, such as molecular, cellular, and biological process following andrographolide exposure. Of identified modules, immune system, immune response, and innate immune system were the most related to clinical traits in module salmon.

Conclusions: Our results ultimately provided a critical understanding of the underlying mechanism of andrographolide in the perspective of pharmacological activity.

Keywords: Andrographolide, Neuropathic pain, MHCII, microglia neuronal plasticity

YP-35 人体共生普氏粪杆菌通过调节肠道微生物-丁酸-肾脏 GPR43 轴改善肾脏炎症和损伤

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目的：近年研究表明，菌群失调在导致肾脏炎症反应中扮演着重要角色，尤其是补充益生菌可显著抑制肾脏炎症反应。探索既能改善肾脏炎症又对肾脏损伤有防治作用的新型益生菌，对慢性肾脏病（CKD）患者的治疗尤为重要。

方法：本研究首先通过美国肠道计划（n=283）和中国 CKD 病人（n=75）菌群测序分析发现，普氏粪杆菌在美国和中国 CKD 病人中丰富度均降低，且普氏粪杆的丰富度与肌酐、肾小球滤过率等临床指标相关性最高。随后本项目以 5/6 肾切除小鼠、肾足细胞和肾小管上皮细胞为研究对象，结合宏基因组测序等技术：① 通过粪菌移植实验，结合 CKD 动物模型给予普氏粪杆菌，观察该菌对肠道微生物、肾脏炎症和损伤的影响。② 构建性 G 蛋白偶联受体（GPR）43 基因敲除稳定表达的肾足细胞和肾小管上皮细胞，给予普氏粪杆菌培养上清液和丁酸钠，明确炎症状态下普氏粪杆菌是否通过丁酸-GPR43 信号路径发挥作用。③ 应用肾脏特异 GPR43 基因敲除小鼠给予普氏粪杆菌，验证丁酸-GPR43 信号是否介导普氏粪

杆菌产生的有益效应。

结果：普氏粪杆菌能够改善 5/6 肾切除诱导肾功能损伤和炎症，减少各种尿毒症毒素。同时重塑 CKD 小鼠肠道菌群，促进丁酸的产生，激活肾脏丁酸结合受体 GPR43。发现丁酸-GPR43 信号介导普氏粪杆菌产生的有益效应。

结论：人类共生普氏粪杆菌能够通过调节肠道微生物-丁酸-肾脏 GPR43 轴改善肾脏炎症和损伤，减缓 CKD 的进展。补充普氏粪杆菌有望成为治疗慢性肾病的新策略。

YP-36 经皮颅-耳穴位电刺激抗抑郁的脑电微状态特征研究

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背景：抑郁症（MDD）与大脑功能网络活动异常有关。脑电微状态是研究脑功能网络、探索精神障碍疾病脑机制的有效指标之一。前期多中心随机对照试验（N = 470）已表明经皮颅-耳穴位电刺激（TECAS）治疗 MDD 有效，但其机制尚不清楚。**目的：**观察 TECAS 对 MDD 患者脑电微状态的影响，筛选适宜人群。方法：纳入 50 例轻中度 MDD 患者，给予 8 周 TECAS 治疗，分别于治疗前后评估汉密尔顿抑郁量表、汉密尔顿焦虑量表，采集闭眼静息态脑电信号。通过 MATLAB、EEGLAB 等工具对脑电数据进行预处理和微状态分析，包括持续时间、发生频率、覆盖率，比较治疗前后各个指标的差异。**结果：**1. MDD 患者经过 8 周 TECAS 治疗后，微状态 A 的持续时间、覆盖率及发生频率与微状态 C 的覆盖率及发生频率显著升高（$P < 0.001$）；2. 对 TECAS 治疗有应答的患者在治疗前表现出更高的微状态 D。**结论：**1. TECAS 抗抑郁疗效与 MDD 患者脑电微状态 A 和 C 有关；2. 微状态 D 可能是 MDD 患者 TECAS 疗效预测的神经电生理特征指标；3. 调节“默认网络-突显网络-注意网络”可能是 TECAS 抗抑郁潜在效应机制之一。

关键词：经皮颅-耳穴位电刺激；抑郁症；脑电微状态；抗抑郁效应机制

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YP-37 ALDH2 protects blood-brain barrier against cerebral ischemia/ reperfusion injury via alleviating ROS-related NLRP3 inflammasome axis by AKT/ mTOR pathway

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Background: Impairment of the blood-brain barrier (BBB) has an essential effect on the prognosis of ischemic stroke. BBB disruption is closely related to inflammation, reactive oxygen species (ROS), but the underlying mechanisms involved have not been elucidated. Previous studies have shown that Aldehyde dehydrogenase 2 (ALDH2) plays a protective by inhibiting ROS and inflammatory responses. However, whether ALDH2 protects the BBB during cerebral ischemia/ reperfusion (I/R) is unclear. Therefore, the aim of this study was to investigate the effect of ALDH2 on the BBB after cerebral I/R and its underlying mechanisms.

Methods: This research utilized the middle cerebral artery occlusion (MCAO) mouse model and oxygen-glucose deprivation and reperfusion (OGD/R) as in vitro model to study cerebral I/R injury. Neurological deficit scores, 2, 3, 5-triphenyl tetrazolium chloride (TTC) staining, and Hematoxylin and Eosin (HE) staining were used to detect the protective effects of ALDH2 in cerebral I/R mice. Also, Evans blue dye leakage and brain water content measurements, as well as transmission electron microscopy (TEM) were used to observe the effects of ALDH2 on the BBB and intercellular tight junctions. In vitro, the protective effect of ALDH2 on bEnd.3 cells was evaluated using cell viability via CCK-8 assay, transendothelial electrical resistance (TEER) measurement, and fluorescein isothiocyanate (FITC)-dextran permeability assay. In addition, changes in ROS and inflammatory factors were observed, and western blotting was performed to explore changes in the expression of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, inflammation-related factors, tight junction proteins, as well as p-AKT and p-mTOR. Finally, ALDH2 overexpressing cells were obtained by lentiviral transfection of bEnd.3 cells, and rotenone was used as an intervention to validate the exact mechanism underlying the protective effect of ALDH2 and the ROS-related NLRP3 inflammasome axis.

Results: We observed that activation of ALDH2 reduced the area of cerebral infarcts as well

as neurological deficits and attenuated cerebral histopathological damage after cerebral I/R. Evans blue dye leakage and brain water content results demonstrated that ALDH2 attenuated endothelial barrier permeability and brain tissue edema. In addition, we observed by TEM that ALDH2 alleviated disruption of intercellular tight junction structures. ALDH2 also inhibited I/R-induced oxidative stress, suppressed Malondialdehyde (MDA) and 4-Hydroxynonenal (4-HNE) levels and increased the levels of antioxidant factor Superoxide Dismutase (SOD). In vitro, we observed that ALDH2 significantly increased cell viability and attenuated OGD/R-induced bEnd.3 cell injury. ALDH2 improved TEER values and reduced FITC-dextran permeability. ALDH2 also significantly inhibited the OGD/R-induced increase in ROS levels, as observed by dihydroethidium acetate (DHE-DA). In vivo and in vitro, ALDH2 inhibited the expression of NLRP3 inflammasome and inflammation-related factors IL-1β and IL-18, and increased the expression of the tight junction proteins zonula occludens-1 (ZO-1) and Occludin, which was associated with the upregulation of p-AKT and p-mTOR, as detected by western blotting. To further validate our findings, we successfully constructed ALDH2 overexpressing bEnd.3 cells using lentiviral transfection. It could alleviate the oxidative stress and inflammatory response caused by OGD/R and increased the expression of tight junction proteins. However, when we intervened with rotenone, it was found that rotenone induced the production of excessive ROS and reversed the protective effect of ALDH2.

Conclusions: In conclusion, ALDH2 protects the BBB from cerebral I/R injury by inhibiting the NLRP3 inflammasome axis associated with ROS, and the Akt/ mTOR pathway is involved in the regulation. Our findings provide novel insights into cerebral I/R therapy.

Keywords: ALDH2, Cerebral ischemia/ reperfusion, Anti-inflammatory, Anti-oxidative stress, Blood-brain barrier, AKT/ mTOR

YP-38 Voluntary exercise ameliorates post-stroke cognitive impairment by modulating the microbiota-gut-brain axis to protect the brain-gut barriers

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Objective Post-stroke cognitive impairment (PSCI) is one of the most common complications of ischemic stroke, but current prevention and treatment methods are limited, and the pathogenesis is unclear. Exercise is currently receiving significant attention as a non-pharmacological approach to maintaining brain health. Nevertheless, the impact of exercise preconditioning on PSCI has not been sufficiently studied. This study aims to explore the potential neuroprotective effects and mechanisms of voluntary exercise preconditioning on PSCI from the perspective of the "microbiota-gut-brain" (MGB) axis.

Methods In this study, we investigated the effects of exercise preconditioning on cognitive function, brain-gut barrier integrity, gut microbiota, and targeted short-chain fatty acids (SCFAs) in mice by establishing a mouse model of right middle cerebral artery occlusion. To verify the role of gut microbes in exercise-nerve benefits and whether the beneficial effects can be transmitted through microbiota, we used antibiotic cocktail intervention and FMT to transfer the gut microbiota of exercise donor mice to mice with depleted microbiota. The severity of cognitive impairment was evaluated based on Longa's score, Morris water maze, and TTC staining. HE staining was used to assess the pathological damage in the hippocampal region and colonic tissues. Evans blue staining and FITC-dextran concentration assay were used to observe brain-gut barrier permeability. The protein and mRNA expression levels of Occludin, Claudin-5, and ZO-1, were detected with western blot and real-time polymerase chain reaction, separately. The microbial composition was analyzed by 16S rRNA sequencing and the SCFAs in the cecal contents of mice were quantitatively detected by gas chromatography and mass spectrometry.

Results Both voluntary exercise preconditioning and FMT exerted excellent improvement effects on PSCI, as evidenced by the reduction in Longa's score and cerebral infarction volume, as well as the increase in learning and memory capacity. Exercise preconditioning and FMT showed similar effects: (1) reduced inflammatory infiltrates of hippocampal and colonic tissue in HE staining; (2) decreased brain water content, Evans blue content, and the concentration of FD4, along with enhanced expression of ZO-1, Occludin, and Claudin-5; (3) enhanced production of total SCFA in the fecal contents, increased abundance of gut microbial diversity and flora composition; (4) decreased abundance of two phyla (Helicobacter and Proteus) strongly associated with ischemic stroke, and increased levels of SCFAs positively related genera in the gut microbiota (Lactobacillus, Akkermansia, Alistipes, and Oscillospira).

Conclusions This study deeply demonstrated the protective effect of voluntary exercise on PSCI from the perspective of the MGB axis and brain-gut barriers. The finding indicates that exercise may regulate the MGB axis through SCFAs derived from the gut microbiota, repair the barrier damage and play a neuroprotective role. Furthermore, FMT from exercise donors may be a novel approach for both the prevention and treatment of PSCI.

Keywords: Voluntary exercise, Microbiota-gut-brain axis, Fecal microbiota transplantation, Post-stroke cognitive impairment

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YP-39 The mechanism investigation of lipocalin-2 in different pathways of ferroptosis in septic myocardial injury

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Objective: To observe the changes of different pathways of ferroptosis in myocardial injury in septic mice and HL-1 cardiomyocyte model, and investigate whether lipocalin-2 (Lcn2) plays a key role in septic myocardial injury through regulating DHODH-mediated mitochondrial ferroptosis pathway.

Methods: The experiments were divided into two parts:

1. In *vivo* part:

Sixty 8-week-old male C57BL/6J mice were randomly divided into sham operation group (Sham) group, CLP group, CLP + ferroptosis inhibitor ferrostain-1 (CLP + Fer-1, mice were injected intraperitoneally with 5 mg/kg Fer-1 2h before CLP) group, CLP + Dexrazoxane (CLP + DXZ, mice were injected intraperitoneally with 50 mg/kg DXZ 2 h before CLP) group, CLP + low expression Lcn2 recombinant adeno-associated virus (CLP + shRNA-Lcn2) group, CLP + low expression Lcn2 recombinant adeno-associated virus empty vector (CLP + NCRNA) group and CLP + low expression Lcn2 recombinant adeno-associated virus + DHODH inhibitor Brequinar (CLP + shRNA-Lcn2 + Brequinar, mice were injected intraperitoneally with 20 mg/kg Brequinar 4h before CLP) group. Blood and heart tissue were taken from anaesthetized mice at 24 h postoperatively. The changes of cardiac function were detected by echocardiography; the changes of myocardial tissue and mitochondrial structure were observed by H&E staining and transmission

electron microscopy; the changes of myocardial ROS were detected by DHE fluorescent probe; the levels of CK-MB, LDH, MDA were detected by the related kits; the mRNA expressions level of Lcn2 was detected by qPCR; and the protein expressions levels of myocardial Lcn2, GPX4, xCT, FSP1, mitochondrial DHODH, GPX4, and xCT were all detected by Western blot. Molecular docking was used to predict the interaction of Lcn2 with key proteins in different pathways of ferroptosis.

2. In *vitro* part

Lentiviral transfection of HL-1 cardiomyocytes was used to construct a stable overexpression cell line of DHODH gene; septic cardiomyocyte model was established by intervening with 100 μg/ml LPS, and the cardiomyocytes were randomly divided into 8 groups: normal control group (NG), LPS group, ferroptosis inducer RSL3 group, LPS + Fer-1 group, LPS + DXZ group, LPS + GFP group, LPS + overexpression group of DHODH gene (LPS + DHODH-GFP), LPS + DHODH-GFP+Lcn2 group. The cell activity was detected by CCK8 kit, LDH and CK-MB levels were measured by spectrophotometer; the positive rate of cells was detected by PI staining; the changes of mitochondrial membrane potential were detected by JC-1 probe; the mRNA expression levels of Lcn2, IL-6 and DHODH were detected by qPCR; and the protein levels of Lcn2, DHODH and GPX4 were determined by western blotting.

Results:

1. In *vivo* experiments:

Compared with the Sham group, the cardiac systolic and diastolic function were significantly decreased in the CLP group; myocardial fibers were not well aligned; mitochondria became smaller, ridge disappeared, and the outer membrane was broken; myocardial ROS, MDA levels and serum CK-MB, LDH levels were increased ($P<0.01$); myocardial SOD levels was decreased ($P<0.01$); the protein expression levels of GPX4, xCT, cytoplasmic FSP1 and mitochondrial DHODH were decreased ($P<0.01$); the levels of Lcn2 at mRNA and protein expression were increased ($P<0.01$). Compared with the CLP and CLP + NCRNA groups, in CLP + Fer-1, CLP + DXZ and CLP + shRNA-Lcn2 groups, myocardial morphology and mitochondrial damage were improved; serum CK-MB, LDH, myocardial ROS and MDA levels were decreased ($P<0.01$); myocardial SOD level was increased ($P<0.01$); the protein expression levels of GPX4, xCT, FSP1 and mitochondrial DHODH were increased ($P<0.01$); the levels of Lcn2 at mRNA and protein expressions were decreased ($P<0.01$). Molecular docking suggested that Lcn2 was bounden to the DHODH catalytic site. Compared with CLP + shRNA-Lcn2 group, more cardiac function damage, inflammatory cells infiltration, mitochondrial damage, and higher ROS level were showed in the CLP + shRNA-Lcn2 + Brequinar group.

2. In *vitro* part

Compared with NG group, cell viability was significantly decreased (P<0.01) in LPS group and RSL3 group; LDH, CK-MB levels and mitochondrial membrane potential were decreased (P<0.01); the mRNA expression levels of Lcn2 and IL-6 were increased, while DHODH mRNA expression level was decreased (P<0.05). Lcn2 protein expression level was increased, while the protein expression levels of GPX4 and DHODH were decreased (P<0.05). Compared with LPS group, cell viability was significantly increased in LPS + DHODH-GFP group (P<0.01), as well as the levels of LDH, CK-MB levels and mitochondrial membrane potential (P<0.05). Lcn2 protein expression was decreased, while DHODH protein expression of was increased (P<0.05). Compared with LPS + DHODH-GFP group, the cell viability level and mitochondrial membrane potential were significantly decreased (P<0.05) in LPS + DHODH-GFP + Lcn2 group. Lcn2 protein expression of was increased, while DHODH protein expression was decreased (P<0.05).

Conclusion: Our findings revealed that different pathways of ferroptosis were happened in myocardial injury in septic mice. Low expression of Lcn2 reduced myocardial injury in sepsis, it may play a protective role mainly by regulating DHODH-mediated mitochondrial ferroptosis pathway.

Key words: Lipocalin-2; DHODH, Septic myocardial injury; Ferroptosis

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YP-40 Mechanism investigation of Beclin 1 in mitochondrial ferroptosis in doxorubicin induced mice myocardial injury

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Objective: To observe the changes of mitochondrial ferroptosis in Doxorubicin (DOX) induced myocardial injury in mice model, and explore the changes and likely mechanisms of Beclin 1. **Methods:** The mice were injected with DOX (15mg/kg) to induce myocardial injury model, and were randomly divided into 7 groups (10 mice/group): Normal control group (CON), DOX group (DOX), DOX + ferroptosis inhibitor Ferrostain-1 group (DOX + Fer-1), DOX + viral no-loading group (DOX+NCRNA), DOX + Beclin 1 knock-down group (DOX+ shRNA-Beclin 1),

DOX + Beclin 1 knock-down + DHODH inhibitor Brequinar group (DOX + shRNA-Beclin 1 + Brequinar), DOX + Beclin 1 knock-down + glutathione peroxidase 4 (GPX4) inhibitor FIN56 group (DOX + shRNA-Beclin 1 + FIN56). The changes of cardiac function were detected by echocardiography, the changes of myocardial tissue and mitochondrial structure were observed by H&E staining and transmission electron microscopy. Serum creatine isoenzyme (CK-MB), lactate dehydrogenase (LDH) levels, myocardial superoxide dismutase (SOD) and peroxidase malondialdehyde (MDA) levels were detected by the related kits. The changes of ROS levels in myocardial tissue were detected by DHE fluorescent probe, and changes of myocardial mitochondrial membrane potential (MMP) were detected by JC-1 test kit. The mitochondrial energy production in myocardial tissue was detected by ATP test kit. The protein expressions levels of Beclin 1, DHODH, mitochondrial iron storage protein (FTMT), mitochondrial iron export protein (ABCB8), cystine-glutamate reverse transport system (xCT), and GPX4 in myocardial tissues were detected by Western blot. **Results:** Compared with CON group, in DOX group, the myocardial systolic and diastolic functions were significantly impaired, and a large number of speckled necrosis and inflammatory cell infiltration were appeared in myocardial tissue, and serum CK-MB and LDH levels, myocardial MDA and Beclin 1 levels were increased ($P < 0.05$), SOD level, MMP, ATP level and xCT, DHODH, GPX4, FTMT, ABCB8 protein expression levels were decreased ($P < 0.01$); Compared with DOX group, in DOX+Fer-1 group, myocardial morphology was improved, cardiac systolic and diastolic functions were significantly improved, serum CK-MB and LDH levels, myocardial MDA and ROS levels and Beclin 1 protein expression levels were decreased ($P < 0.05$), SOD level, MMP, ATP level and the protein expression levels of xCT, DHODH, GPX4, FTMT and ABCB8 were increased ($P < 0.01$); Compared with DOX + NCRNA group, in DOX + shRNA-Beclin 1 group, serum CK-MB and LDH levels, myocardial MDA and ROS levels and Beclin 1 protein expression level were decreased ($P < 0.05$), SOD level, MMP, ATP level and xCT, DHODH, GPX4, FTMT, ABCB8 protein expression levels were increased ($P < 0.01$); Compared with DOX + shRNA-Beclin 1 group, in DOX + shRNA-Beclin 1 + Brequinar and DOX + shRNA-Beclin 1 + FIN56 groups, the cardiac systolic and diastolic functions were significantly impaired, and myocardial tissue had a large number of speckled necrosis and inflammatory cell infiltration, and serum CK-MB and LDH levels, myocardial MDA and Beclin 1 levels were increased ($P < 0.05$), SOD level, MMP, ATP level and xCT, DHODH, GPX4, FTMT, ABCB8 protein expression levels were decreased ($P < 0.01$). **Conclusion:** In DOX-induced myocardial injury in mice model, there are two pathways of mitochondrial ferroptosis mediated by DHODH and GPX4 respectively. Inhibition of mitochondrial ferroptosis and Beclin 1 knockdown can both protect mice from mitochondrial dysfunction and myocardial cell ferroptosis caused by DOX induced myocardial injury, Beclin 1 may play a protective role by

indirectly inhibiting GPX4 protein activity by blocking the activity of xCT system and inhibiting DHODH activity.

Key words: Doxorubicin myocardial injury; Mitochondria; Ferroptosis; Beclin 1

Fund Projects: Major Scientific Research Project of Anhui Provincial Department of Education (No. 2022AH040213), Graduate Research Innovation Program of Bengbu Medical College (No. Byycx22001).

YP-41 肠道微生物通过调节能量代谢水平参与老化心脏功能的恢复

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目的：肠道菌群及代谢物与心血管疾病的发生发展密切相关，调节肠道菌群已成为防治心血管疾病的潜在靶标，但肠道菌群对正常衰老心脏的作用尚不完全清楚。因此，本研究旨在探究衰老状态下，肠道菌群组成改变对心脏老化的调节作用，并进一步探索其可能的作用机制。

方法：建立老年与年轻大鼠交叉粪菌移植的动物模型，通过超声心动图及 PET-CT 检测大鼠心脏结构和功能的变化，基因测序检测肠道菌群的变化，LC/MS 检测大鼠心肌代谢物的改变，PET-CT 观察各组大鼠心肌葡萄糖代谢的改变，电镜观察大鼠心肌细胞线粒体的形态， TBA 法检测大鼠心肌组织中 MDA 含量，WST-1 法检测心肌组织 SOD 活性，化学发光法检测 ATP 含量，β-gel 染色测定 β-gel 阳性细胞率。

结果：（1）老年鼠移植了年轻鼠的粪便后（Y-A 组），其反映左心室舒张功能的指标峰充盈率-1/3 充盈速率（44.08±6.10 cmm/s）明显优于以老年鼠为供体的老年鼠（A-A 组）（66.23±5.56 cmm/s，P<0.05）。同时，Y-A 组大鼠心脏 IVSd（1.53±0.11mm）明显低于 A-A 组（1.92±0.12mm，P<0.05）；Y-A 组大鼠心脏 IVSs（3.01±0.08 mm）明显低于 A-A 组（3.43±0.12 mm，P<0.01）；Y-A 组大鼠心脏 LVPWd（1.87±0.04mm）明显低于 A-A 组（2.26±0.14mm，P<0.05）。（2）α 多样性 Chao1 指数显示：Y-A 组大鼠肠道菌群的丰富度显著高于 A-A 组；β 多样性的 NMDS 分析显示：Y-A 组肠道菌群结构分布与其对照 A-A 组有明显不同（P<0.05）。（3）OPLS-DA 分析显示：Y-A 组与 A-A 组大鼠的心肌代谢物存在显著差异。和 Y-A 组相比，A-A 组大鼠心肌组织中磷酸胆碱等物质显著上调；棕榈酰-L-左旋肉碱等物质显著下调（P<0.05）。（4）Y-A 组大鼠心肌组织中 β-gel 水平（39.49±2.90%）显著低于 A-A 对照组（55.10±3.45%，P<0.05）。（5）Y-A 组大鼠 FDG SUVmax 值（6.83±0.31）显著高于 A-A 组（5.27±0.36，P<0.05），表明心肌葡萄糖代谢水平明显升高。（6）Y-A 组大鼠心肌细胞中线粒体嵴排列较为整齐，其心肌细胞线粒体平均面积（1.323±0.137μm²）和平均直径

（1.278±0.087μm）均小于 A-A 组（2.009±0.164μm²，1.827±0.133μm，P<0.05）。（7）Y-A 组大鼠心肌细胞中 ATP 水平（0.67±0.02μmol/g）显著高于 A-A 对照组（0.55±0.02μmol/g，P<0.05）（8）Y-A 组心肌中 MDA 含量显著降低（1.531±0.172 nmol/mg，P<0.01 vs. A-A 组），SOD 活性显著升高（56.04±2.811 U/mg，P<0.05 vs. A-A 组），心肌氧化应激水平得以改善。

结论：在大鼠心脏老化过程中，肠道菌群组成及心肌代谢物发生显著改变；年轻大鼠的肠道菌群移植可通过调节老年大鼠心脏的能量代谢参与老化心脏结构和功能的恢复。

关键词：肠道微生态；代谢物；心肌；衰老；能量代谢；

YP-42 Molecular mechanism of natural grass feed improving muscle quality of grass carp through IFN-γ2 regulation

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Grass carp (*Ctenopharyngodon idella*) is an important source of protein for human food worldwide, and improving muscle quality in the grass carp farming industry is a key purpose of commercial production and breeding systems. Previous studies have shown that natural grass feed can improve muscle quality of grass carp to a certain extent, but the mechanism of influence of natural grass feed on muscle quality is still unclear. In the present study, grass carp were fed with natural grass feed (GF) and artificial feed (AF) to investigate the mechanism of influence of different diets on muscle quality of grass carp. The muscle quality after eight weeks of feeding was identified, and it was found that the muscle tissue structure of GF grass carp was denser, the amino acid types were more abundant, and the muscle fat content was lower. Therefore, we combined transcriptome and metabolism to analyze the molecular mechanism by which grass diet improves muscle quality of grass carp. Through multivariate and pathway enrichment analysis of differential genes and differential metabolites, we found that glycolysis/gluconeogenesis, arginine and proline metabolism, glycerophospholipid metabolism and glycerophospholipid metabolism are key regulatory networks involved in improving muscle quality in grass diets. Meanwhile, we enriched IFN-γ2, a gene that plays a key role in improving muscle quality. Thereupon, we obtained IFN-γ2 protein through prokaryotic expression and purification, and explored the signaling mechanism of its regulation on grass carp muscle cells (GCMC). We found that IFN-γ2 can promote the proliferation, differentiation, and migration of GCMC, which is essential for the improvement of muscle quality. Further, by transcriptome sequencing, we found that IFN-γ2 can facilitate the expression of proliferation (elmo2, capn2, angpt1, etc.), differentiation (pax3, mybpc,

myh11, etc.), and migration related gene (ddr1, gstp1, dock4, etc.) to regulate GCMC. Furthermore, by blocking IFN-γ2 receptor (CRFBs) and inhibiting downstream signaling pathway JAK/STAT1, we determined that IFN-γ2 promotes proliferation and differentiation of GCMC by signaling through CRFBS-JAK /STAT1. Finally, through the interference of IFN-γ2 *in vivo*, we verified the key role of IFN-γ2 in improving the muscle quality of grass carp. This study revealed the mechanism of natural grass feed regulating muscle quality and provided implications for the development of high-quality feed in aquaculture.

Keywords: *Ctenopharyngodon idella*, muscle quality, transcriptome and metabolism, IFN-γ2, JAK/STAT

P1 神经生理

P1-1 dCA1 星形胶质细胞 β2-AR 下调致乳酸分泌减少引起疼痛和记忆障碍

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研究目的：神经病理性疼痛患者常伴随记忆障碍。但是，其共病机制仍不清楚。在本研究中，我们探索了背侧海马 CA1（dCA1）星形胶质细胞激活减弱导致乳酸分泌和合成减少在其中的作用以及蓝斑去甲肾上腺素能纤维投射的调控作用。

实验方法：C57BL/6J 小鼠行坐骨神经分支选择损伤（spared nerve injury, SNI）建立病理性疼痛/记忆障碍共病模型。在体光纤钙成像方法观察星形胶质细胞钙信号的变化。膜片钳记录锥体神经元兴奋性，Up-down 方法测定 50%机械刺激撤足阈值，条件性位置偏爱或厌恶测定情绪反应，新物体识别实验测定记忆能力，免疫荧光和 Western-blot 检测相关蛋白定位和表达情况，ELISA 测定乳酸水平。

实验结果：

1. SNI 十天后小鼠出现机械痛阈下降、新奇事物认知系数下降。同时，背侧海马 dCA1 星形胶质细胞钙信号对机械痛刺激的反应明显减弱、乳酸含量明显降低，锥体神经元动作电位发放频率明显下降。而在 SNI 鼠 dCA1 补充乳酸能够提高机械痛阈、认知系数，引起位置性偏爱反应并增强锥体神经元的兴奋性。相反，在正常动物用糖原磷酸化酶抑制剂抑制 dCA1 乳酸合成或通过抑制单羧酸转运体阻断乳酸转运到神经元，可导致疼痛和记忆障碍共病。

2. 与假手术组鼠相比，在 SNI 鼠 dCA1 星形胶质细胞 β_2 去甲肾上腺素能受体（β_2-AR）明显减少，而神经元内 β_2-AR 不变。SNI 鼠 dCA1 给予 β_2-AR 激动剂 Zinterol 能提高机械痛阈、引起位置性偏爱反应、并引起认知能力增加，同时星形胶质细胞激活、乳酸含量升高。

而在正常动物 dCA1 给予 β_2-AR 拮抗剂导致相反的结果。

3. 化学遗传学特异性激活蓝斑到dCA1去甲肾上腺素能投射可提高SNI鼠机械痛阈并提高认知系数，同时提高 dCA1 星形胶质细胞对机械刺激的钙信号反应，以及乳酸含量。

结论：外周神经损伤后蓝斑去甲肾上腺素能神经元未能充分驱动 dCA1 星形胶质细胞的乳酸释放功能来支持锥体神经元的兴奋性，导致共病。

关键词：病理性疼痛，记忆障碍，乳酸，海马

P1-2 GLP-1 modulates the spontaneous firing activity of globus pallidus neurons

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Abstract: The glucagon-like peptide-1 (GLP-1) is mainly synthesized and secreted by intestinal L cells, and synthesized by preproglucagon (PPG) neurons in the central nervous system. GLP-1 receptors (GLP-1Rs) are widely distributed in the human brain, especially in the globus pallidus and other brain regions with a high density. The globus pallidus is the central hub of the basal ganglia circuit and is closely related to motor regulation. Noticeably, GLP-1 has many physiological functions, for instance, GLP-1 and its receptor agonists can modulate the spontaneous firing activity of neurons in some brain regions. GLP-1 is also closely linked to Parkinson's disease, for example, it can alleviate motor dysfunctions of Parkinson's disease patients. However, the electrophysiological effects of GLP-1 on the globus pallidus neurons and its possible mechanisms are still not known. Thus, the aim of the present study was to observe the effects of GLP-1 on the spontaneous firing activity of globus pallidus neurons and its mechanisms. **Methods** *In vivo* extracellular single unit recordings and immunohistochemical staining were performed in the present study. **Results** (1) Immunohistochemical staining showed that GLP-1Rs were expressed in the globus pallidus neurons. (2) In 28 out of the 42 globus pallidus neurons of normal rats recorded, micro-pressure administration of 10 μM GLP-1 analogue, exendin-4, significantly increased the spontaneous firing rate from 12.78 ± 2.32 Hz to 20.13 ± 3.24 Hz ($P<0.001$). The average reaction percentage was 159.60 ± 36.50 %. (3) In 16 out of the 22 globus pallidus neurons of normal rats recorded, micro-pressure administration of 10 μM GLP-1 receptor antagonist, exendin-9-39, alone decreased the spontaneous firing rate from 22.98 ± 4.53 Hz to

16.71 ± 3.19 Hz (P<0.01). The average reaction percentage was 29.29 ± 5.08 %, suggesting that endogenous GLP-1 may modulate the firing activity of globus pallidus neurons. (4) Co-application of exendin-9-39 and exendin-4 completely blocked GLP-1-induced excitation of 5 globus pallidus neurons recorded in normal rats (P<0.05 compared with exendin-4 alone), suggesting that GLP-1 modulates the firing activity of globus pallidus neurons via GLP-1Rs. **Conclusion** The present electrophysiological results suggest that endogenous GLP-1 is involved in the modulation of spontaneous firing activity of globus pallidus neurons. Exogenous GLP-1 increases the spontaneous firing rate of globus pallidus neurons via GLP-1Rs. The present studies may provide a rational for further investigation of the modulation of GLP-1 on movement as well as its possible involvement in Parkinson's disease.

Keywords: globus pallidus neurons; GLP-1; single unit recording

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P1-3 Effect of cannabidiol on learning and memory function and neural network oscillation in rats with sporadic Alzheimer's disease

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Objective To observe the alteration of neural network oscillations in the hippocampal CA1 field and the ventral part of the dorsal raphe nucleus (DRV) in rats with sporadic Alzheimer's disease model and the effect of cannabidiol on them. **Methods** Fifty adult male SD rats were randomly divided into 5 groups: control + carrier solution group (n=10), control + drug group (n=10), sham operation group (n=10), model + carrier solution group (n=10) and model + drug group (n=10). Rats in the model group were injected with streptozotocin (STZ, 3mg/kg) bilaterally in the lateral ventricles to establish the sporadic Alzheimer's disease (sAD) model, while those in the sham operation group were injected with an equal amount of saline. After two weeks of postoperative recovery, rats in the administered group were injected intraperitoneally with cannabidiol (CBD, 20 mg/kg) once a day for a week, and then three times weekly for the next 2

weeks, and the remaining groups were injected with an equal amount of carrier solution. Next, we used the novel object recognition test and Y-maze test to assess the learning and memory function of rats in each group, and the extracellular electrical activities of hippocampal CA1 field and DRV were simultaneously recorded to analyze the alteration of neural network oscillations in them. **Results** (1) Compared with the control + carrier solution group and the sham operation group, the index of new object preference and spontaneous alternative rate in the model + carrier solution group decreased obviously (P<0.05 or P<0.001 or P<0.0001), while the latency of novel arm increased significantly (P<0.05). (2) The discharge frequency of hippocampal CA1 field and DRV in the model + carrier solution group was significantly lower than that in the control + carrier solution group (P<0.001). (3) Compared with the control + carrier solution group, in the model + carrier solution group, the power of theta rhythm in hippocampal CA1 field decreased obviously (P<0.05), while that of beta rhythm increased significantly (P<0.05); the power of beta rhythm in DRV increased (P<0.01), while that of gamma rhythm decreased (P<0.01). (4) Compared with the model + carrier solution group, the index of new object preference and spontaneous alternative rate in the model + drug group increased significantly (P<0.05 or P<0.0001), while the latency of novel arm decreased obviously (P<0.001). (5) The discharge frequency of hippocampal CA1 field and DRV in the model + drug administration group was significantly higher than that in the model + carrier solution group (P<0.05). (6) Compared with the model + carrier solution group, in the model + administration group, the power of gamma rhythm in hippocampal CA1 field increased (P<0.05); the power of beta rhythm in DRV decreased (P<0.01), while that of gamma rhythm increased (P<0.05). **Conclusion** Cannabidiol can effectively alleviate STZ-induced impairment of learning and memory function and abnormalities of neural network oscillations in the hippocampal CA1 field and DRV. *This study was supported by NSFC 31200828, NSFAH 2108085MC91 and the Academic funding project for top-notch talents in colleges and universities (gxbjZD2021061).*

Keywords: Cannabidiol; Alzheimer's disease; Hippocampal CA1 field; Dorsal raphe nucleus; Neural network oscillation

P1-4 Psychological stress-induced masseter pain sensitization in rats may involve the central amygdala-caudal subnuclear mechanism of the trigeminal spinal tract nucleus

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Objective: To observe the bioelectric activities of central amygdala (CeA) and caudal subnucleus of the trigeminal spinal tract nucleus (SPVC) of rats with masseter pain sensitization in rats caused by chronic psychological stress, and to explore the possible CeA-SPVC pathway mechanism. **Methods:** Twenty-two male healthy SD rats weighing 220~240g were randomly divided into control group and model group (n=11). Rats in model group were intervened by continued chronic unpredictable mild stress (CUMS) for 5 weeks, during which each group was tested for masseter pain sensitivity score using von Frey hairs every two weeks. Then, under the urethane anesthesia, the bioelectric activity of CeA, SPVC, ECG and other physiological indicators were recorded synchronously. **Results:** (1) Compared with the control group, the preference for sucrose solution in the model group was reduced after the CUMS intervention (P<0.01). (2) In the open field test, rats in the model group showed lower total distance (P<0.01), crossing score (P<0.01) and the distance in central zone (P<0.05), while fecal particle number increased (P<0.01). (3) The masseter pain sensitivity score began to increase (P<0.01) in rats in the model group 3w after modeling, and reached a peak (P<0.01) after 5w. (4) The discharge freqency of CeA and SPVC in the model group increased (P<0.05). (5) The phase lock value of delta and theta oscillations between two nuclei was increased (P<0.05). **Conclusion:** The CUMS-induced masseter pain sensitization in rats may involve the mechanism of the CeA-SPVC pathway.

Keywords: Psychological stress; Pain; Central amygdala; Caudal subnucleus of the trigeminal spinal tract nucleus

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P1-5 Effects of dexmedetomidine combined with etomidate on BLA-LC activities of D-galactose-induced aging rats

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Objective: To explore the effects of dexmedetomidine (DEX) combined with etomidate (ETO) on the learning and memory functions of D-galactose (D-gal)-induced aging rats as well as its possible brain mechanisms between basolateral amygdala (BLA) and locus coeruleus (LC). **Methods:** Fifty adult male SD rats weighing 130~150g were randomly divided into control group (*n*=10) and modelling group (*n*=40). The aging rats with cognitive dysfunction were induced by D-gal (300mg/kg) with intraperitoneal injection for 6 weeks. The novel object recognition test (NORT) was used to assess the learning and memory functions of rats. Qualified aging rats were divided into model group (*n*=9), DEX group (*n*=7), ETO group (*n*=7) and DEX+ETO group (*n*=6). Rats in DEX group, ETO group and DEX+ETO group received 20μg/kg DEX, 10mg/kg ETO, and 20μg/kg DEX+10mg/kg ETO, respectively, for one week, while those in control group and model group were treated with the same volume of saline. Novel object recognition test was used to observe the impact of drugs on learning and memory function of rats. The extracellular recordings were simultaneously performed from BLA and LC in urethane-anesthetized rats, and the alteration was observed after drug intervention during recording in each group. **Results:** (1) Compared with control group, the discrimination index of model group decreased ($P<0.01$). (2) After drug treatment, the discrimination index of ETO group and DEX+ETO group increased ($P<0.01$, $P<0.05$), while those in control group, model group and DEX group showed no significant difference. Compared with control group, the discrimination index of model group and DEX group both decreased ($P<0.05$), while ETO group and DEX+ETO group both showed an increasing tendency compared with model group. (3) After drug intervention during electrical recording of BLA and LC, the discharge frequency of BLA in DEX+ETO group decreased ($P<0.05$) and showed a decrease compared with model group ($P<0.05$), while the discharge frequency of LC in DEX group, ETO group and DEX+ETO group also decreased ($P<0.05$). (4) After drug intervention, the power at gamma rhythm of BLA in DEX+ETO group increased ($P<0.05$) and showed an increase compared with model group ($P<0.05$); but the power at delta,

theta and beta rhythm in LC all decreased (P<0.05, P<0.01, and P<0.05), while the power at gamma rhythm also increased (P<0.01). (5) After drug intervention, the phase locking value at gamma rhythm between BLA and LC increased in DEX+ETO group (P<0.05). **Conclusion:** Dexmedetomidine combined with etomidate can partially restore the learning and memory functions of D-galactose-induced aging rats, which may involve the mechanism of enhancing information exchange between BLA and LC at gamma rhythm.

Keywords: dexmetomidine; etomidate; cognitive dysfunction; basolateral amygdala; locus coeruleus; neural network oscillation

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P1-6 Effects of Emodin on cognitive function and brain energy metabolism in MCAO model rats

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Abstract Objective To study the effects of Emodin on cognitive function and brain energy metabolism in middle cerebral artery occlusion (MCAO) rats. **Methods** Thirty six SPF grade healthy male SD rats aged 3 to 5 months were randomly divided into five groups: control group (n=8), sham-operated group (n=8), MCAO model group (n=8), low dose Emodin group (n=8, 20mg·kg^{-1}), high dose Emodin group (n=4, 40mg·kg^{-1}), to observe the effect of intragastric administration of Emodin 20 and 40 mg·kg^{-1} on cognitive function of MCAO rats, and to determine the brain index and hippocampal Na+, K+- ATPase activity of rats in each group. **Results** (1) Compared with the model group, the Longa 5 neurological function scores of the low and high dose Emodin groups both decreased (P<0.05). (2) In the Y-maze experiment, compared with the control group and sham-operated group, the dwell time of new arm in the model group both decreased (P<0.01), and the rate of autonomous alternation showed a decreasing trend. Compared with the model group, the dwell time of new arm and the rate of autonomous alternation of the low dose Emodin group both increased (P<0.05, P<0.01). (3) In Morris water

maze experiment, compared with the control group, the escape latency of the sham-operated group had no significant difference (P>0.05), compared with the control group and sham-operated group, the escape latency of the model group both increased (P<0.01), and compared with the model group, the escape latency of the low and high dose Emodin group both decreased (P<0.01). (4) Compared with the sham-operated group, the target quadrant activity time of the model group decreased (P<0.05), and compared with the model group, the low and high dose Emodin groups showed an increasing trend. Compared with the control group, the time of first arrival at the virtual platform of model group increased (P<0.05), and compared with the model group, the low and high dose Emodin groups showed a decreasing trend. Compared with the control group, the times of crossing the virtual platform of the model group decreased (P<0.01), and compared with the model group, the high dose Emodin group showed an increasing trend. (5) Compared with the sham-operated group, the brain index of the model group decreased (P<0.01). Compared with the model group, the Na^+, K^+- ATPase activity in the hippocampus of the high dose Emodin group increased (P<0.05). **Conclusion** Emodin can improve the cognitive function of MCAO rats and may be related to the improvement of Na^+, K^+- ATPase activity.

Key words: Emodin; MCAO; Na^+, K^+- ATPase; cognitive function

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P1-7 LncRNA MSTRG.81401 对 2 型糖尿病神经病理痛合并抑郁大鼠海马细胞焦亡的影响

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研究目的：通过建立糖尿病神经病理性疼痛（DNP）合并抑郁症（MDD）模型，观察 lncRNA MSTRG.81401 的 shRNA 处理对 DNP 合并 MDD 大鼠的海马细胞焦亡的影响。

研究方法：建立 DNP 合并 MDD 大鼠模型，通过热缩足反射潜伏期(TWL）、机械缩足反射阈（MWT）、旷场实验（OFT）、糖水偏好实验（SPT）、强迫游泳实验（FST）检测和筛选出有疼痛和抑郁行为的大鼠。采用实时荧光定量 PCR（qPCR）方法检测各组大鼠海马 MSTRG.81401 和 P2X7R mRNA 的表达情况。原位杂交技术检测大鼠海马 lncRNA MSTRG.81401 的表达。蛋白印迹检测各组大鼠海马 P2X7 受体以及细胞焦亡通路蛋白 NLRP3、ASC、Pro-caspase-1、Cleaved-caspase-1、IL-1β 的表达变化。免疫荧光双标检测各组大鼠海马 P2X7 受体与 GFAP 共表达的情况。酶联免疫吸附法检测大鼠血清炎性细胞因子白介素 18(IL-18)、肿瘤坏死因子-α（TNF-α）等变化。

研究结果：DNP 合并 MDD 大鼠模型建立成功后，与正常组大鼠相比，模型组大鼠的 TWL、MWT、SPT 和 OFT 明显降低（$p<0.01$），FST 不动时间明显延长（$p<0.01$），当 MSTRG.81401 shRNA 处理后，模型大鼠的上述行为均得到好转（$p<0.01$）。原位杂交和 qPCR 结果表明与正常组相比，模型组大鼠 MSTRG.81401 表达明显升高（$p<0.01$），在 MSTRG.81401 shRNA 干扰后，模型大鼠 MSTRG.81401 表达明显下降（$p<0.01$）。免疫荧光双标结果显示 P2X7R 和 GFAP 在大鼠海马存在共表达，模型组大鼠的共表达明显高于对照组（$p<0.01$），而 MSTRG.81401 的 shRNA 可降低这种表达（$p<0.01$）。蛋白印迹结果表明与正常组大鼠相比，模型组大鼠 P2X7R、NLRP3、ASC、Pro-caspase-1、Cleaved-caspase-1、IL-1β 蛋白表达量均明显升高（$p<0.01$），在注射 MSTRG.81401 的 shRNA 后，模型大鼠以上升高的蛋白表达量明显下降（$p<0.01$）。与正常组大鼠相比，模型组大鼠血清中 IL-18、TNF-α 的含量明显升高（$p<0.01$），但 MSTRG.81401 shRNA 处理后模型大鼠血清中 IL-18、TNF-α 的含量明显降低（$p<0.01$）。

结论：lncRNA MSTRG.81401 的 shRNA 可以改善大鼠糖尿病神经病理痛和抑郁样行为，其机制可能是通过抑制海马 P2X7R 的表达进而下调细胞焦亡相关。

关键词：糖尿病神经病理痛；抑郁症；长非编码 RNA；P2X7 受体；细胞焦亡；海马

P1-8 The deficiency of FRMD5 results in neurodevelopment dysfunction and autistic-like behavior in mice

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The postsynaptic scaffolding proteins are causally associated with the pathophysiology of autism spectrum disorders (ASD), which is supported by several large-scale genomic studies, as well as of *in vitro* and *in vivo* neurobiological studies of mutations in animal model. However,

Since ASD patients illustrate distinct phenotypic heterogeneity and genetic heterogeneity, each individual mutation gene accounts for only a small proportion (<2%) of cases. Recently, a human genetic study indicates that *de novo* variants in FERM domain-containing-5 (*FRMD5*) are related to neurodevelopment abnormalities. Here we reveal that the deficiency of scaffolding protein FRMD5 results in neurodevelopment dysfunction and ASD-like behavior in mice.

FRMD5 is highly expressed in the nervous system, especially at the early stage of brain development in mice. According to recent researches, autism spectrum disorder leads to deficits in social-emotional reciprocity and restricted, repetitive patterns of behavior. To reveal the potential function of *Frmd5* in ASD, we applied a three-chambered social approach task and compulsive behavior tests, finding that knockout of *Frmd5* led to complex ASD-like behavioral abnormalities in mice, including social deficiency, increased compulsive behaviors and memory abnormalities.

To further investigate the innate function of FRMD5 in the nervous system, we identified its distribution in various brain regions. The Western blot results showed that FRMD5 is highly expressed in the hippocampus, especially in the CA1 and DG. Knockout of *Frmd5* led to a decrease in the length and complexity of basal dendrites on CA1 pyramidal neurons but did not affect the length or complexity of apical dendrites on CA1 pyramidal neurons visualized by Golgi-Cox staining. Notably, by sparse neuron labeling in the DG, we found that *Frmd5*-KO did not affect the length or complexity of dendrites, although it led to an increase in stubby dendrite spines. Moreover, knockout of *Frmd5* led to longer heads and lengths of mushroom and long/thin spines, which showed more immature spines in *Frmd5*-KO mice. Taken together, the deficiency of *Frmd5* leads to morphological abnormalities of neurons and synaptic dysfunction.

To examine the potential impact of previously identified morphological alterations in neurons on synaptic transmission function, we applied the whole-cell patch-clamp technique to DG granule cells of *Frmd5*-KO mice. The results showed that FRMD5 deficiency led to increased input resistance, which revealed increased intrinsic excitability in granule cells of the DG. After current injection from a baseline potential, a lower injected current led to an increased number of spines in *Frmd5*$^{-/-}$ DG granule cells; however, a higher injected current led to decreased responsivity. Moreover, the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) decreased in *Frmd5*$^{-/-}$ DG granule cells, which led to a decrease in neuronal transmission to DG neurons. Taken together, Knockout of *Frmd5* leads to increased intrinsic excitability and decreased neuronal transmission in granule cells of the DG.

To investigate the molecular mechanism underlying the abnormal function and behavior of mouse neurons caused by the deletion of *Frmd5*, we examined the subcellular localization of the FRMD5 protein in neurons using live cell imaging and synaptic component isolation. With live cell imaging of primary hippocampal neurons, we found that FRMD5 is located at the cell

membrane and cell-matrix adhesion, especially at the dendritic shaft, branch point and basilar region of the dendritic spine. Mechanistically, Tandem Mass Tag (TMT) labeled quantitative proteomics showed that FRMD5 deletion affected the distribution of synaptic proteins involved in the pathological process of ASD.

This study represents the pioneering work that comprehensively explores the involvement of the FRMD5 protein in the molecular, morphological, synaptic, and behavioral aspects of neural development and ASD pathology, shedding new light on the role of FERM domain-containing proteins in the nervous system. Above all, our findings provide new insights into the personalized and precise treatment of ASD patients, and more research on its innate mechanism and potential value for clinical practice is still needed.

Keywords: Scaffolding protein, ASD, FRMD5

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P1-9 Effect of photoperiodic intervention on behavior in Parkinson's disease model rats and its mechanism

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Abstract: Objective: Light therapy is a novel and effective physiotherapy method that can affect the progression of Parkinson's disease (PD) by interfering with the circadian rhythm. Some studies have shown that it has therapeutic effects on sleep disorders and mental disorders in PD, but there are few studies on the influence of behavior and cognitive impairment. Therefore, this study aimed to explore whether photoperiodic intervention can improve the behavior of PD model rats. **Methods:** In this study, sixty adult male SD rats were randomly divided into control group (*n*=12), PD model group (*n*=12), 8/16 photoperiodic intervention group (*n*=12), 12/12 photoperiodic intervention group (*n*=12), and 16/8 photoperiodic intervention group (*n*=12). The control group was injected with sunflower oil subcutaneously on the neck and back, and the other four groups were injected with rotenone-sunflower oil mixture (1.5mg/kg, qd) for 28 days. After

modeling, the suspension test and climbing pole test were used to identify the model. The three photoperiod intervention groups were placed in the environment controlled by white LED, which the light intensity on each rat cage was 300lux for 28 days. The control group and PD model group were placed in the natural light environment. Then the changes of rats were detected by inclined plate test and Y-maze experiment. The content of dopamine(DA) in striatum, alpha-synuclein(α-syn) in substantia nigra and BMAL1 in suprachiasmatic nucleus (SCN) were measured by ELISA. **Results:** (1)The score of pole climbing test in control group was significantly lower than that in PD model group and the photoperiodic intervention groups (P<0.01). The suspension time of control group was significantly higher than that of PD model group (P<0.01), 8/16 photoperiod intervention group (P<0.01), 12/12 photoperiod intervention group (P<0.01) and 16/8 photoperiod intervention group (P<0.05). (2)In the inclined plate test, the maximum residence angle of the control group was significantly higher than that of the PD model group (P<0.01). There was no significant difference between the photoperiod intervention groups and the PD model group. (3) In the Y-maze experiment, the latency of the novel arm in the control group was significantly lower than that in the PD model group (P<0.05). Compared with the PD model group, the control group and the 16/8 photoperiod intervention group had significantly higher residence time of the novel arm and autonomic alternation rate (P<0.05). The 8/16 photoperiod intervention group and the 12/12 photoperiod intervention group also had an increasing trend.(4)Compared with the PD model group, the control group (P<0.05), 8/16 photoperiod intervention group (P<0.05), 12/12 photoperiod intervention group (P<0.05) and 16/8 photoperiod intervention group (P<0.01) had significantly increased DA content in striatum. **Conclusion:** Photoperiod intervention can significantly improve the cognitive impairment of PD rats, especially the 16/8 photoperiod intervention group. The mechanism may be related to the effect of photoperiod intervention on circadian rhythm, which can regulate the secretion of DA to improve the cognitive impairment of PD rats. This study preliminarily verifies the theory that photoperiod intervention exerts its improving cognition effect, which can provide new ideas for the research of light therapy in PD.

Keywords： Photoperiod, Circadian rhythms, Light therapy, Cognitive impairment

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P1-10 Effects of chronic psychological stress on rat salivary secretion may involve central amygdala-inferior salivatory nucleus pathway mechanisms

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Objective: To observe the effects of chronic unpredictable mild stress (CUMS) on rat salivary flow rate, and to analyze the neural network oscillations and functional relationships of the central amygdala nucleus (CeA) and inferior salivatory nucleus (IS), which are key nuclei to regulating emotion and salivary secretion activity. **Methods:** Twenty-four male SD rats weighing 180-200 g were even and randomly divided into control group and model group (n=12). At the end of 9-week CUMS, open field test and sucrose preference test were employed to evaluate depression-like activities, citric acid filter paper was used to induce the stimulated saliva, cotton ball weight method was applied to detect both unstimulated and stimulated salivary flow rate, PowerLab 8-channel polygraph was used to record CeA and IS electrical activities, and electrocardiogram (ECG) simultaneously under anesthesia. **Results:** (1) Compared with control group, the model group rats showed an obviously decreased preference for sucrose solution (P<0.01) and a significantly increased water consumption (P<0.01), and decreasing trend of scores of crossing and rears in open field test. (2) The model group rats had higher mean unstimulated salivary flow rate (P<0.01) in comparison with control group, and after tongues of rats were stimulated by citric acid filter, the stimulated saliva flow rate was significantly higher (P<0.01) than the unstimulated saliva flow rate in both control group and model group. (3) The discharging frequency of CeA (P<0.01) and IS (P<0.01) in model group increased in comparison with control group, and there was a positive correlation between the discharge frequency of the two nuclei ($r=0.899$, P<0.01). (4) In model group, the phase locking values of delta (P<0.05) and beta (P<0.05) components increased, but those of gamma components decreased (P<0.01), compared with the control group. (5) The model group had higher LF/HF ratio (P<0.05) in heart rate variability (HRV) in comparison with control group. **Conclusions:** CUMS-induced increase of salivary flow rate in rats may involve the CeA - IS pathway excitation mechanisms.

Keywords: Chronic psychological stress; Salivary flow rate; Central amygdala nucleus; Inferior salivatory nucleus; Neural network oscillation; Rat

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P1-11 突触局部的 mRNA 乙酰化修饰调节神经可塑性

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突触可塑性是突触传递强度随内外环境变化发生适应性变化，对于学习记忆、感觉适应、技能获得等众多生理功能至关重要。短期突触可塑性的机制主要涉及突触蛋白的翻译后修饰和快速功能调节，被认为与记忆的获得有关。长期突触可塑性的发生则依赖突触蛋白的合成和突触数量的增加，被认为是长久性记忆巩固的重要条件。以往的研究大都聚焦在神经活动通过激活基因转录产生更多的 mRNA, 进而翻译出更多的蛋白质-即蛋白质的从头合成。近年来的研究表明，蛋白质合成的调控还可以发生在转录后的 mRNA 水平，即表观转录。在此，我们发现了一种与学习和记忆相关的转录后调控机制，即 N4-乙酰胞苷（ac4C）mRNA 修饰。ac4C 是目前唯一已知的 mRNA 乙酰化形式，在不同物种中高度保守。我们使用成年小鼠海马作为学习和记忆的脑区, 进行了 ac4C-RIP seq、mRNA-seq 及 TMT 蛋白质组。结果显示，在测序的 mRNA 中，大约 40%的 mRNA 可以发生 ac4C 修饰，ac4C 主要发生在翻译起始位点附近，且 ac4C 丰度与 mRNA 及蛋白质的表达水平正相关。我们对成年小鼠使用 Morriz 水迷宫进行学习和记忆行为训练，并发现记忆形成后，突触中的 ac4C 水平动态增加，但在小鼠海马的组织匀浆样品中没有增加。利用对照组和训练组小鼠的突触小体组分进行 ac4C-RIP seq 联合 mRNA-seq，我们进一步确定了学习和记忆调控的突触 ac4C-mRNA，即 synaptic ac4C-epitranscriptome (SAE)，其中许多 ac4C-mRNA 编码了在突触中新合成的对学习和记忆至关重要的蛋白质。最后，我们使用 Cre/loxp 策略在成年小鼠海马中敲除 N-乙酰转移酶 10（NAT 10），这是目前唯一已知的 ac4C 修饰酶，结果发现损害了突触中局部蛋白质合成和学习记忆的能力。综上，这些结果揭示了一个表观转录机制，即动态 mRNA 乙酰化，在突触局部的调控学习和记忆方面的重要作用。

关键词：ac4C; 神经可塑性; 学习记忆

P1-12 Synapse elimination by phagocytic astrocytes in a Parkinson's disease mouse model

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Abstract: Objective Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by alterations in synaptic function and circuit remodeling. However, the pathological role of reactive gliosis in PD remains controversial. Astrocytes are considered to play dominant roles in eliminating synapses by phagocytosis during the activity-dependent circuit remodeling processes. Therefore, in the present research, we study the role of astrocytes synapse elimination by phagocytosis in PD. **Methods** First, we establish the hemi-parkinsonian mouse with 6-OHDA. Then, immunostained brain sections were imaged on a Leica confocal microscope taking up to 30 z stacks with a 63x oil objective. $GFAP^+$ astrocytes structures were 3D-reconstructed using the surface rendering function in Imaris and synapsin (SYP) puncta inside the astrocytes were quantified using the mask function. **Results** (1) Activated astrocytes accumulated markedly in the substantia nigra pars reticulata (SNr) in the model ($p<0.05$). (2) The SYP density in SNr was not significantly changed after two weeks of 6-OHDA injection ($p>0.05$). (3) The activated astrocytes of SNr phagocytosed SYP^+ presynapse structures in the model. And compared to unlesioned side, astrocytic phagocytosis of SYP in SNr was significantly increased in the lesioned side ($p<0.01$). **Conclusion** Reactive astrocytes in SNr contribute substantially to synapse elimination of hemi-parkinsonian mouse with 6-OHDA.

Keywords: synapse elimination; astrocyte; Parkinson's disease; basal ganglia; 6-OHDA

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P1-13 Nano-selenium alleviates LPS-induced microglia activation and dopaminergic neuronal damage

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Abstract: Objective: Selenium (Se) is an essential element for human health that can be obtained in nature through several sources. Nanoparticles based on Se (SeNPs) are less toxic than inorganic and organic Se. The anti-inflammatory effects of nano-selenium in peripheral

inflammation have been increasingly confirmed, but few studies have investigated the effects of nano-selenium on neuroinflammation. This study aimed to investigate the role of Cs4-SeNPs, a new type of nano-selenium, in lipopolysaccharide (LPS)-induced neuroinflammation, neuronal damage and behavioral dysfunction, as well as underlying mechanisms. **Methods:** Quantitative reverse transcription-polymerase chain reaction was used to evaluate the expression of pro-inflammatory mediators and cytokines. Western blotting was conducted to assess the protein expressions of iNOS, COX-2, TLR4, p-NF-κB and TH. Rotarod test and pole test were used to detect motor coordination ability. **Results:** We showed that Cs4-SeNPs inhibited LPS-induced production of proinflammatory factors, including TNF-α, IL-1β, iNOS and COX-2 in BV2 cells by suppressing the TLR4-mediated NF-κB signaling pathways. In the LPS-induced Parkinson's disease (PD) mouse model, Cs4-SeNPs treatment ameliorated LPS-induced motor incoordination and dopaminergic neuronal loss. Moreover, Cs4-SeNPs significantly inhibited TLR4-mediated NF-κB pathway activation and decreased proinflammatory cytokine levels as well as microglial activation. **Conclusion:** This study suggests that Cs4-SeNPs exerts anti-neuroinflammatory effect in LPS-induced neuroinflammation by modulating TLR4 signaling pathway both in vitro and in vivo. Selenium nanoparticles therapy may be a potential therapeutic strategy for the treatment of neuroinflammation-related diseases.

Keywords: nano-selenium; inflammation; microglia; Parkinson's disease

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P1-14 Oxytocinergic modulation in mouse medial prefrontal cortex

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Oxytocin (OT) is a multifunctional endogenous neuropeptide and OT mainly targets oxytocin receptor (OxtR) to modulate neuronal activity. OT neurons widely project to many brain regions, including the medial prefrontal cortex (mPFC). Although previous studies reported the expression of OxtRs in glutamatergic projection neurons and somatostatin (SST) interneurons, the expression pattern of OxtRs and modulatory role of OT in mPFC remain largely unknown. Utilizing fluorescence in situ hybridization (FISH), we find that *Oxtr* mRNA is mainly expressed in excitatory pyramidal neurons and SST inhibitory neurons in layer 2/3 (L2/3) and L6. Compared to

the excitatory neurons, inhibitory neurons have a higher density of *Oxtr* mRNA. With OxtR-Cre; Ai3 reporter mice, we also find OXTR neurons are distributed in L2/3 and L6, while SST-OXTR neurons are mainly in L2/3. With *in vitro* electrophysiological recording, we assessed neural activity changes following OT administration via current injection. We observed that the majority of pyramidal neurons located in L2/3 exhibit inhibition upon administration of oxytocin, resulting in a decrease in their firing rate, resistance, and resting potential. The excited neurons, however, are distributed across all layers with an increased firing rate, resistance, and resting potential. These characteristics have no difference between subregions or gender. Our study indicates that the precise distribution of OXTR and its spatially specific regulation might be a fundamental part of the physiological function in mPFC.

Keywords: oxytocin receptor; medial prefrontal cortex; layer specificity;

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P1-15 阿司匹林保护大脑缺血再灌注损伤的神经机制

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缺血性中风是导致全球死亡和残疾的主要原因。阿司匹林作为一线抗血栓药物，可以抑制血小板聚集，防止血栓形成，预防卒中发生。除此之外，阿司匹林已被证实可以在缺血再灌注（I/R）损伤中保护神经元免于兴奋毒性死亡。然而，其内在的神经保护机制仍旧不清楚。

在本工作中，我们通过质谱发现阿司匹林给药可以提高小鼠脑内蛋白的乙酰化修饰水平，通过 KEGG 分析发现，这些乙酰化升高的基因在神经元死亡相关的细胞缺氧死亡（HIF-1）和神经坏死（Necroptosis）信号通路中显著富集，其中 CaMK2α、CaMK2β 和 CaMK2δ 同时出现在两条信号通路中。我们通过结构模拟预测乙酰化后对三个基因功能的影响，发现钙调蛋白激酶 II α（CaMK2α）的赖氨酸 42 位点（K42）乙酰化修饰对蛋白功能的改变最大。通过进一步实验发现，阿司匹林给药后大脑皮层神经元胞浆中的 $K42^{AC}$-CaMK2α 蛋白发生显著上调，而突触中的 $K42^{AC}$-CaMK2α 蛋白变化不大。我们通过乙酰化蛋白标准品滴定的方法，进一步计算出阿司匹林给药可以使大脑皮层胞浆中大约 12%的 CaMK2α 蛋白发生 K42 乙酰化。我们通过进一步的功能实验发现，K42 乙酰化会破坏 CaMK2α 和 ATP 之间的结合，

抑制 CaMK2α 的激酶活性，12%的 $K42^{AC}$-CaMK2α 足以使整体 CaMK2α 的激酶活性降低 40%。

为了验证 $K42^{AC}$-CaMK2α 是否参与了阿司匹林对脑缺血的保护作用，我们在阿司匹林给药过程中脑室注射干扰肽抑制 $K42^{AC}$-CaMK2α。实验发现抑制 $K42^{AC}$-CaMK2α 会显著削弱了阿司匹林的神经保护作用。为了进一步研究 $K42^{AC}$-CaMK2α 是否可以发挥对脑缺血的保护作用，我们使用密码子扩展技术（genetic code expansion）在小鼠大脑皮层内过表达 $K42^{AC}$-CaMK2α，和对照组小鼠（过表达 CaMK2α）相比，过表达 $K42^{AC}$-CaMK2α 的小鼠在脑缺血后死亡率降低，梗死面积减少，认知功能改善。以上结果说明，$K42^{AC}$-CaMK2α 的发生对于阿司匹林发挥神经保护作用而言是必要的。

综上，由于 CaMK2α 特异性表达于大脑皮层的兴奋性神经元，在血小板里不表达，我们的研究结果揭示了阿司匹林保护脑缺血的神经保护机制。

关键词：阿司匹林，缺血性卒中，神经保护，钙调蛋白依赖性激酶

Neural mechanisms of aspirin protection against cerebral ischemia-reperfusion injury

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Ischemic stroke is the leading cause of death and disability worldwide. Aspirin, as a first-line antithrombotic drug, inhibits platelet aggregation, prevents thrombosis, and prevents stroke. In addition to this, aspirin has been shown to protect neurons from excitotoxic death in ischemia-reperfusion (I/R) injury. However, its intrinsic neuroprotective mechanism remains unclear.

In the present work, we found by mass spectrometry that aspirin administration increased the level of acetylation modification of proteins in mouse brain, and KEGG analysis revealed that these genes with elevated acetylation were significantly enriched in neuronal death-associated cell hypoxia death (HIF-1) and neuronal necrosis (Necroptosis) signaling pathways, in which CaMK2α, CaMK2β, and CaMK2δ appeared in both signaling pathways. We predicted the effects of acetylation on the functions of the three genes by structural simulations and found that the acetylation modification of the lysine 42 site (K42) of calmodulin kinase II α (CaMK2α) had the greatest alteration in protein function. Through further experiments, it was found that $K42^{AC}$-CaMK2α protein in the cytosol of neurons in the cerebral cortex underwent significant up-regulation after aspirin administration, whereas $K42^{AC}$-CaMK2α protein in the synapses was little changed. We further calculated that aspirin administration resulted in K42 acetylation of approximately 12% of CaMK2α proteins in the cortical cytoplasm by titration of acetylated

protein standards. We found by further functional experiments that K42 acetylation disrupts the binding between CaMK2α and ATP and inhibits CaMK2α kinase activity, and that 12% $K42^{AC}$-CaMK2α is sufficient to reduce overall CaMK2α kinase activity by 40%.

To verify whether K42AC-CaMK2α is involved in the protective effect of aspirin against cerebral ischemia, we inhibited K42AC-CaMK2α by ventricular injection of interfering peptide during aspirin administration. We found that the inhibition of $K42^{AC}$-CaMK2α significantly impaired the neuroprotective effect of aspirin. To further investigate whether $K42^{AC}$-CaMK2α could exert a protective effect against cerebral ischemia, we overexpressed $K42^{AC}$-CaMK2α in the cerebral cortex of mice using the codon expansion technique (genetic code expansion) and compared it with control mice (which overexpressed CaMK2α), mice overexpressing $K42^{AC}$-CaMK2α had lower mortality, reduced infarct area, and improved cognitive function after cerebral ischemia. These results suggest that the occurrence of $K42^{AC}$-CaMK2α is necessary for aspirin to exert its neuroprotective effects.

In summary, because CaMK2α is specifically expressed in excitatory neurons of the cerebral cortex and is not expressed in platelets, our findings reveal a neuroprotective mechanism of aspirin protection against cerebral ischemia.

Keywords: Aspirin, Ischemic stroke, Neuroprotection, Calmodulin-dependent kinase

P1-16 GHSR1a deletion-mediated autophagic dysregulation promotes neurodegeneration in Parkinson's disease

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Parkinson's disease (PD) is an age-related neurodegenerative disorder, characterized by the gradual, irreversible loss of dopaminergic neurons in the substantia nigra (SN), leading to decreased dopamine content in the striatum. Our previous studies showed that plasma ghrelin levels were significantly reduced in early-stage of PD patients. And the administration of exogenous ghrelin could antagonize 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity, inhibit the activation of caspase-3 to protect MES23.5 cells from apoptosis induced by rotenone. As a brain-gut peptide composed of 28 amino acids, ghrelin acts primarily through the activation of growth hormone secretagogue receptor (GHSR1a).

GHSR1a belong to G protein-coupled receptors, which are highly expressed not only in the

hypothalamus and pituitary gland, but also in the SN, cortex, hippocampus and ventral tegmental area. It is worth noting that the probability of circulating ghrelin entering the brain is very low, and in this case, relatively low ghrelin cannot target most of the GHSR1a in the brain. So, what roles can such highly expressed GHSR1a play in the brain?

Here, we observed that GHSR1a knockout could aggravate dopaminergic neurons degeneration in MPTP-induced PD mice models, which was related to the over-initiation of autophagy but the inhibition of lysosomal degradation ability. Besides, as a subunit of mTORC1, DEPTOR was overexpressed in GHSR1a knockout mice (*Ghsr*$^{-/-}$ mice), subsequently positively regulating autophagy and enhancing autophagy initiation. As a result, the damaged mitochondria could not be effectively eliminated due to lysosomal dysfunction, which ultimately exacerbates the process of apoptosis and then intensified the damage of nigral dopaminergic neurons. Mechanistically, DEPTOR was transcriptionally regulated by KLF4, and dopaminergic neurons-specific knockdown of KLF4 effectively alleviated the neurodegeneration in *Ghsr*$^{-/-}$ mice. The present study expands our current knowledge about the implications of GHSR1a in the neurodegeneration of PD and provides a new theoretical basis for the treatment of PD.

Key words: Parkinson's disease; GHSR1a; autophagy; KLF4; DEPTOR

P1-17 Berberine hydrochloride ameliorates pruritus by inhibiting MrgprB$_2$ receptor on mast cell

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Background: Berberine hydrochloride (BBR) is a conventional component in Chinese medicine, and is characterized by a diversity of pharmacological effects, including anti-inflammation, antitumor and immunoregulatory. However, the cellular and molecular antipruritic mechanisms of BBR remain to be explored.

Objection: In oder to explore the effects of BBR in pruritus and determine whether its antipruritic effect is related to MrgprB$_2$ receptor.

Methods: In this study, the mice were divided into control group, model group, model group

with low, medium and high doses (50mg/kg, 100mg/kg and 150mg/kg, gavage) of BBR. The antipruritic effects of BBR were evaluated by itch behavioral experiments. The relationship between the antipruritic mechanism and mast cell was studied by H&E and toluidine blue staining. In vitro, the effects of BBR on $MrgprB_2$ were studied by calcium imaging, electrophysiological and HEK transfection experiments and molecular docking.

Results: Treatment of mice with BBR attenuated pruritus induced by Compound 48/80 through inhibiting mast cell degranulation. In addition, BBR could inhibit the calcium influx and the voltage-dependent currents induced by $MrgprB_2$ activation in mast cell in vitro. We also found BBR could attenuate the calcium influx in $MrgprB_2/X_2$ overexpressing HEK293 cells induced by Compound 48/80 and PAMP-12. Moreover, molecular docking results showed that BBR had affinity to $MrgprB_2$ protein.

Conclusion: These results indicated that BBR alleviated pruritus by suppressing $MrgprB_2$ receptor on mast cell.

Keywords: Berberine hydrochloride, Antipruritus, Mast cell, $MrgprB_2$

P1-18 Astrocyte-derived apolipoprotein D is essential for neuronal survival in Parkinson's disease

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Abstract: It was reported that increased immunostaining for apolipoprotein D (Apo D) of glial cells surrounding dopaminergic (DAergic) neurons was observed in the brains of Parkinson's disease (PD) patients, as well as elevated levels of Apo D in the plasma. In the present study, we observed that Apo D levels released from astrocytes were increased in PD both *in vivo and in vitro*. There were up-regulated expression levels of Apo D in the SN and plasma of PD model mice, and the levels of Apo D also increased in MPP^+-treated C6 cells and its culture medium. When co-cultured with astrocytes, due to the increased release of astrocytic Apo D, the survival rate of primary cultured ventral midbrain (VM) neurons was significantly increased with

1-methyl-4-phenylpyridillium ion (MPP^+) treatment compared with that of the control. Increased levels of TAp73 and its phosphorylation at Tyr99 in astrocytes were required for the increased Apo D levels and its release. Conditional knockdown of TAp73 genes in the nigral astrocytes *in vivo* could aggravate the neurodegeneration in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated PD mice. This study demonstrated that oxidative stress promotes the secretion of Apo D from astrocytes, and the crosstalk of the DAergic neurons and astrocytes plays an important role in the protection of Apo D in PD.

Keywords: Parkinson's disease; apolipoprotein D; TAp73; astrocytes

P1-19 海马脑区 AdipoR1 神经元活性对 METH 成瘾行为的影响及机制

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摘要：毒品成瘾是以强迫性觅药和持续性渴求状态为特征的慢性复发性脑疾病。干预记忆再巩固过程、破坏病理性情感记忆，是消除毒品渴求、预防复吸的潜在策略，但机制不明。脂肪组织分泌的脂联素及其受体信号系统在众多毒品成瘾行为中发挥重要作用。利用 CPP 成瘾复吸模型、行为学、光/化学遗传学、神经电生理、形态学以及神经分子生物学技术，阐明海马 DG、CA1 脑区 AdipoR1 神经元活性对 METH 成瘾记忆再巩固的影响，实验发现，甲基苯丙胺（METH）成瘾位置偏好（CPP）模型血液中脂联素表达降低，海马齿状回脂联素受体 AdipoR1 特异性表达降低，过表达 AdipoR1 或脂联素受体激动剂 AdipoRon 可降低小鼠 METH 诱导的 CPP 行为，以上结果提示脂联素/AdipoR1 途径参与 METH 成瘾记忆行为，实验将解析脂联素/AdipoR1 途径参与调控 METH 成瘾记忆再巩固的分子机制，为预防和治疗 METH 复吸提供新的实验依据和思路。

关键词：位置偏好行为，海马 DG、CA1 脑区，AdipoR1 神经元，脂联素

P1-20 The role of CRF receptor1 in the hippocampal DG on spatial learning and memory in the chronic stress model of rats

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Abstract: Objective Chronic stress (CS) is ubiquitous in the life, and as its key regulator,

corticotropin-releasing factor (CRF) participates in the learning and memory alteration induced by CS. As the entry point of information into the hippocampus, the hippocampal dentate gyrus (DG) encodes and processes new information and plays an essential role in learning and memory. In addition, evidence have shown that CRF and its receptor 1 (CRFR1) are expressed in the DG. In this study, we investigated the role of CRFR1 in the DG on spatial learning and memory in a rat model of CS established by chronic unpredictable stressor. **Methods** Male SD rats (300-350 g) were randomly divided into control (CON) and CS groups, and rats in the CS group were randomly given one of the seven different stressors daily for 30 days. The spatial learning and memory abilities of the rats were examined by Morris water maze (MWM); the levels of corticosterone (CORT) and CRF were measured using ELISA; the expression of CRFR1 in the DG was observed by immunohistochemical staining and western blot (WB). Next, the role of CRFR1 in spatial learning and memory of CS rats was examined by microinjection of its antagonist (R121919) into the DG 30 min before the behavioral test. The intracellular levels of glutamate (Glu) in the DG were measured by *in vivo* microdialysis and HPLC; the expression of glutamatergic AMPA receptors (AMPAR) in the DG was observed by WB. **Results** (1) CORT and CRF levels were significantly increased, and the expression of CRFR1 was significantly increased in the DG in the CS group; (2) CS significantly impaired the spatial learning and memory, and microinjection of R121919 in the DG significantly attenuated the spatial learning and memory impairments in CS rats; (3) CS significantly inhibited the response of Glu in the DG during spatial learning process, and it was recovered by local microinjection of R121919 in the DG; (4) CS significantly decreased the expression of AMPAR in DG, and it was significantly reversed by local microinjection of R121919. **Conclusion:** Over-activation of CRFR1 in the DG involves in CS-induced spatial learning and memory impairments in rats via inhibiting the activity of Glu-AMPA receptor system.

Keywords: Chronic stress; Corticotropin releasing factor receptor 1; Spatial learning and memory; Hippocampal dentate gyrus

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P1-21 NR2A 特异性拮抗剂 NVP-AAM077 对大鼠海马空间学习和记忆能力的影响

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目的 谷氨酸能信号通路是中枢系统中最重要的兴奋性传导系统，也是海马完成学习记忆的关键途径。N-甲基-D-天冬氨酸受体（NMDAR）是谷氨酸的代谢型受体，主要是由NR1和NR2亚单位组成的四聚体结构，其中NR2A亚单位在海马的学习记忆中发挥重要作用，其分布异常参与多种疾病的发生发展过程。本研究通过海马微量注射NR2A特异性拮抗剂NVP-AAM077，探讨NR2A在大鼠的空间学习记忆中的作用，为NVP-AAM077及其它NR2A的靶点药研究提供神经药理学数据。**方法** 3月龄雄性SD大鼠随机分为行为学训练（training）和未训练（non-training）两大组，两大组的大鼠随机分为对照组（Vehicle）、利用脑部微量注射法向海马内注射NVP-AAM077（NVP）组，分别用水迷宫实验检测大鼠的空间学习记忆能力，Western blot 检测NR2A、脑源神经营养因子（BDNF）表达；然后利用脑部微量注射法向训练组注射NVP的大鼠海马内注射整合应激反应抑制剂（ISRIB），检测大鼠海马的转录激活因子4（ATF4）表达及真核转录起始因子2α（eIF2α）磷酸化水平以及空间学习记忆能力。**结果** 行为学训练结果显示，与non-training比较，行为学训练促进大鼠海马NR2A和BDNF表达；但海马内注射NVP-AAM077的大鼠（NVP组）海马的NR2A和BDNF表达显著减少；与Vehicle比较，海马注射NVP的大鼠空间学习记忆能力显著下降；WB检测发现，注射NVP大鼠海马的磷酸化eIF2α和ATF4表达显著增多；利用脑部微量注射法向训练组注射NVP大鼠的海马内注射ISRIB 显著抑制海马ATF4表达，并翻转注射NVP引起的大鼠空间学习记忆损伤。**结论** 海马内注射NVP抑制海马DG的NR2A通路激活并损害大鼠空间记忆，这种作用主要与海马ISR有关。

关键词： NVP-AAM077；NMDA 受体 2A 亚单位；海马；空间学习和记忆；整合应激反应

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P1-22 慢性压力导致小鼠抑郁和痛敏后大脑皮层神经细胞形态和信号特征的研究

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抑郁症是一种常见的精神疾病，患者最常见的表现是快感缺乏和绝望。同时伴随着认知

功能缺陷，表现为注意力、执行力、情景记忆能力和处理日常事务的速度下降。《2022 年国民抑郁症蓝皮书》指出“我国成人抑郁障碍终身患病率为 6.8%，其中抑郁症为 3.4%，目前我国抑郁症患者为 9500 万，每年自杀的人数中 40%为抑郁症患者”。 抑郁症成因复杂且危险因素繁多，我们日常生产生活中面对的各种压力也是导致抑郁症的潜在因素，慢性不可预知压力模型可模拟人类在日常生产生活活动中面临的各种压力。本课题组研究表明：1. 雄性 C57 小鼠在经历十天慢性不可预知性压力处理后，实验组小鼠在强迫游泳实验（对照组：n=8、实验组：n=6、$P < 0.0001$）和悬尾实验（对照组：n=8、实验组：n=7、$p=0.0024$）中的不动时长都高于对照组，而且实验组小鼠与对照组相比其对机械刺痛的敏感程度更高（对照组 W0：n=8、实验组 W0：n=7、$P < 0.0001$）。这些结果表明连续十天的慢性不可预知性压力使小鼠出现了抑郁样行为，且该模型导致的小鼠抑郁在两周内不会恢复，但是两周之后实验小鼠的绝望行为和痛敏均得到缓解。2. 急性脑切片免疫荧光染色发现实验组小鼠前扣带皮层（ACC 区）和初级躯体感觉皮层（S1 区）中小胶质细胞和 C-fos 的密度均要高于对照组小鼠。3. 前扣带皮层显微注射顺行不跨突触 GFP 病毒后在躯体感觉皮层观察到荧光信号，说明可能存在 ACC→S1 抑郁相关神经信号通路。

关键词：抑郁症 慢性不可预知性压力 前扣带皮层 初级躯体感觉皮层 信号通路

P1-23 人源 α-突触核蛋白通过铁死亡造成运动功能障碍

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α-突触核蛋白是一种与多种神经退行性疾病相关的蛋白质，已被发现在大脑中积聚并导致神经功能紊乱。然而，在神经退行性疾病中的相关机制仍不清晰，为了更好地表征 α-突触核蛋白相关疾病的分子机制，我们建立了一种在初级运动皮层中，利用 AAV 过表达人源 α-突触核蛋白的小鼠模型。通过在体双光子钙成像、分子生物学、电生理和行为学的方法，我们发现在模型小鼠运动皮层中，锥体神经元出现过度兴奋，这是受到 PV 抑制性中间神经元输入减少的影响。进一步的分子机制分析表明，人源 α-突触核蛋白的聚集激活了铁死亡和神经炎症，导致 PV-Ins 丢失并造成运动功能受损。综上所述，我们的研究为铁死亡在与 α-突触核蛋白相关的神经退行性疾病的发病机制提供了新的见解。

关键词：α-突触核蛋白，运动皮层，铁凋亡

P1-24 Chemokine receptor CXCR2 in primary sensory neurons of trigeminal ganglion mediates orofacial itch

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The CXCR2 chemokine receptor is known to have a significant impact on the initiation and control of inflammatory processes. However, its specific involvement in the sensation of itch is not yet fully understood. In this study, we aimed to elucidate the function of CXCR2 in the trigeminal ganglion (TG) by utilizing orofacial itch models induced by incision, chloroquine (CQ), and histamine. Our results revealed a significant up-regulation of CXCR2 mRNA and protein expressions in the primary sensory neurons of TG in response to itch stimuli. The CXCR2 inhibitor SB225002 resulted in a notable decrease in CXCR2 protein expression and a concomitant reduction in scratch behaviors. Distal infraorbital nerve (DION) microinjection of a specific shRNA virus inhibited CXCR2 expression in TG neurons and reversed itch behaviors. Additionally, the administration of the PI3K inhibitor LY294002 resulted in a decrease in the expressions of p-Akt, Akt, and CXCR2 in TG neurons, thereby mitigating pruritic behaviors. Collectively, we report that CXCR2 in the primary sensory neurons of trigeminal ganglion contributes to orofacial itch through the PI3K/Akt signaling pathway. These observations highlight the potential of molecules involved in the regulation of CXCR2 as viable therapeutic targets for the treatment of itch.

Keywords: CXCR2, trigeminal ganglion, orofacial itch, incision, virus

P1-25 Effects of exercise intervention on anxiety/depression-like behaviors in obesity model rats

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Abstract: Objective: To investigate the effects of exercise intervention on the anxiety/depression-like behaviors and neuronal discharges of basal lateral amygdala (BLA) and lateral habenula medial (LHbM) in obesity model rats. **Method:** Male SD rats (*n*=53) were randomly divided into a normal group, a model group (rats were fed a high-fat diet for more than 60 days.), and a model+exercise intervention group (model rats were fed a high-fat diet for 60 days followed by an exercise intervention of 5 times/week, 40 min/session, for a total of 28 days.). Normal rats were also subjected to the environmental intervention treatment of staying on a stationary animal treadmill for 5 times/week and 40 min/time for a total of 28 days. Behavioral observations were conducted through open field and elevated cross maze experiments, and a multi-channel physiological recorder was used to record the discharge signals of rat BLA and LHbM binuclear neurons. **Results:** (1) In the elevated cross maze experiment, compared to the normal rats (*n*=23), the modeling rats (*n*=30) showed a significant decrease in total distance, entries in zone center, entries in zone open arms, time in zone center, time in zone open arms, and distance in zone center (all $P<0.01$); Compared with the model group (*n*=9), the entries in zone open arms ($P<0.05$), distance in zone center ($P<0.05$), time in zone close arms ($P<0.05$), and time in zone open arms ($P<0.05$) of the model+exercise intervention group rats (*n*=7) were significantly increased. (2) In the open field experiment, compared with the normal group, the total distance, entries in zone center, time in zone center, and distance in zone center of the model group were significantly reduced (all $P<0.05$); Compared with the model group, time in zone center ($P<0.05$), distance in zone center ($P<0.05$) of the model+exercise intervention group were significantly increased. (3) Compared with the normal group, the firing frequency of BLA neurons in the model group was significantly reduced ($P<0.05$), while there was no significant change in the model+exercise intervention group. (4) There was no significant difference in behavioral data between the normal group of rats before and after environmental intervention. **Conclusion:** The preliminary results suggest that obesity model rats may exhibit anxiety/depression-like behaviors, which may be partially relieved by an exercise intervention.

Keywords: Obesity; Anxiety/depression-like behaviors; Basal lateral amygdala; Animal running platform

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P1-26 Preliminary observation of effects of riluzole combined with composite pseudostellaria granule on denervated skeletal muscle atrophy

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Abstract Objective To observe the effects of riluzole combined with composite pseudostellaria granule (CPG) on denervated skeletal muscle atrophy by combining Chinese and western medicine. **Methods** Forty-eight male SD rats (200-220g) were randomly divided into six groups: normal, sham operation, model, CPG, riluzole, and combined group (n=8 each group). The model rats were prepared by cutting off the right tibial nerve of rats, and identified by tibial function index (TFI). After six weeks of treatment with drugs, the rats were sacrificed, their bilateral gastrocnemius muscles were taken to measure wet weight, and the total protein content of BCA was quantitatively detected by colorimetric method. **Results** (1) The TFI of the rats in the sham operation group was lower than that in the normal group (P<0.05), while that in the model group, CPG group, riluzole group and the combined group was significantly lower than that of the normal group and sham operation group (P<0.01). Compared with the model group, the TFI of the modeling side in the CPG group was increased (P<0.05), while that in the riluzole group only showed an increase tendency ($P>0.05$). The TFI of the modeling side in the combined group was similar to that in the model group (P>0.05). (2) The residual rate of wet weight of gastrocnemius muscle in sham operation group was similar to that in normal group (P>0.05), but that in the model group, CPG group, riluzole group and combined group was significantly lower than that in the normal group and sham operation group (P<0.05). (3) The total protein content of BCA in the sham operation group was similar to that in the normal group (P>0.05), while that in the model group was significantly lower than that in the normal group and the sham operation group (P<0.01).And that in riluzole group was higher than that in the model group (P<0.05), while that in the modeling side of the rats in the CPG group and the combined group was similar to that in the model group (P>0.05). **Conclusion** The preliminary results suggest that the rat denervated skeletal muscle atrophy model is successfully prepared, and riluzole had a certain atrophy-delaying effect. The effects of composite pseudostellaria granule combined with riluzole

need further study yet.

Key words: Tibial nerve; Denervation; Muscle atrophy; Riluzole; Composite pseudostellaria granule; Integrative medicine

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P1-27 Effects of mirtazapine combined with saikosaponin D on depression-like behaviors in CUMS rats

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Objective: To observe the effects of mirtazapine (MTP) combined with saikosaponin D (SSD) on depression-like behaviors in chronic unpredictable mild stress (CUMS) rats. **Methods:** Fifty-four male SD rats (150-180g) were randomly divided into control group (*n*=8) and modeling group (*n*=46). Four weeks of continuous CUMS and solitary rearing were used to prepare the CUMS model rats, and the model rats were identified by the sucrose preference test. The successful modeling rats were stratified and randomly divided into the model group (*n*=7) and the MTP group (5mg/kg/d, *n*=7), low-dose SSD group (LDSSD, 0.75mg/kg/d, *n*=8), high-dose SSD group (HDSSD, 1.5mg/kg/d, *n*=8), LDSSD+MTP group (*n*=8), and HDSSD+MTP group (*n*=8). The drugs were used in 5 treatment groups and equal amounts of saline were given in the control and model groups by intraperitoneal injection for 2 weeks. Afterwards, open field test and sucrose preference test were employed to detect the treatment effects. **Results:** (1) After modeling, compared with the control rats, the sucrose preference index (SPI) decreased in the modeling group ($P<0.01$); the total distance of open field exercise and the number of cross-grids in the central area decreased ($P<0.01$). (2) After the drug and saline intervention, the SPI of the control, model, and HDSSD+MTP groups was similar to that before drug administration, while the SPI in the other 4 groups was increased compared with that before drug administration ($P<0.05$); the SPI of the model group was decreased compared with the control group ($P<0.01$), and the SPI of the LDSSD+MTP group ($P<0.01$) and the remaining 4 groups ($P<0.05$) was significantly elevated

compared with the model group. (3) After drug and saline intervention, the total distance of movement in the open field experiment in the model group was reduced compared with the control group (P<0.01), and that in the 5 groups of drug intervention was increased compared with the model group (P<0.05), but the HDSSD group and HDSSD+MTP group were reduced compared with the control group (P<0.05 and P<0.01). The number of cross-grids of the central area in the model group decreased compared with the control group (P<0.05), and there was a tendency to increase in all drug treatment groups compared with the model group. **Conclusions:** The preliminary results suggest that mirtazapine and saikosaponin D may improve the depression-like behaviors of CUMS rats to different degrees, but the synergistic effect need further study yet.

Keywords: Mirtazapine; Saikosaponin D; Chronic mild unpredictable stress (CUMS); rats

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P1-28 枸杞糖肽缓解由氧化应激和铁凋亡导致的焦虑疾病

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枸杞糖肽是一种天然的具有免疫活性的糖蛋白，具有抗氧化抗衰老的功效，特别在神经退行性疾病中具有神经保护的作用。但枸杞糖肽能否通过减轻细胞氧化反应从而预防神经精神疾病还需要进一步研究。为了研究枸杞糖肽作用的生理机制和预防焦虑症的机制。我们采用慢性压力应激焦虑小鼠模型，给予焦虑小鼠连续 7 天的枸杞糖肽灌胃给药治疗，并对其胶质细胞和神经元细胞进行构建，在体钙信号记录以及相关蛋白分子检测等手段进行验证。结果表明，枸杞糖肽可以通过降低 mPFC 脑区的脂质过氧化物堆积，预防铁凋亡的发生，保护神经元和胶质细胞等方式缓解小鼠焦虑样行为。总体来说，枸杞糖肽可以保护神经元，预防慢性压力导致的焦虑，为天然植物药理研究的发展提供参考。

关键词：枸杞糖肽，慢性压力应激，铁凋亡，脂质过氧化

P1-29 HDAC6 调控 HSP90-HSF1 影响 APP/PS1 转基因小鼠海马组织病理学及认知行为学功能的变化

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目的：探讨组蛋白去乙酰化酶（HDAC）6 通过修饰热休克蛋白（HSP）90 和热休克转录因子 1（HSF1）影响阿尔茨海默病转基因动物模型海马组织中病理性标记物 Aβ 寡聚体和 Tau 磷酸化（p-Tau）水平及其认知行为学功能的变化。**方法**：（1）将 APP/PS1 转基因小鼠（6 月龄）随机分为 5 个实验组，各组分别经侧脑室（*i.c.v.*）注射生理盐水（NS）、HDAC6 特异性抑制剂 Tubastatin A hydrochloride（TSA，1μM）、HDAC6 激动剂 Theophylline（Theo，150 μM）、HSP90 抑制剂 ganetespi（Gane，14 μM）、以及预先应用 Gane 再注射 TSA 联合用药，每只均 2.5 μl；以 C57BL/6J 小鼠（6 月龄）分别 *i.c.v.*注射等量的 NS、TSA、Theo、Gane 等 4 个对照组，每组均 8 只。Morris 水迷宫检测小鼠的认知行为学能力；Western blot 或免疫组织化学检测小鼠海马组织 HDAC6、HSP90、HSF1、$A\beta_{1\text{-}42}$、Tau 和 p-Tau 水平；qRT-PCR 检测海马组织 *hdac6*、*hsp90* 和 *hsf1* mRNA 的表达；尼氏染色检测小鼠海马神经细胞形态和数量的变化。（2）将小鼠海马神经细胞 HT22 随机分为空载对照组和 $A\beta_{1\text{-}42}$ 干预组，在 Aβ 干预基础上再分为 HSP90 敲低、HSP90 过表达、HSF1 敲低和先敲低 HSF1 再过表达 HSP90，共计 6 组。Western blot 检测各组细胞 HSP90、HSF1、$A\beta_{1\text{-}42}$、Tau 和 p-Tau 水平；免疫荧光检测各组 HSP90、HSF1 的表达；qRT-PCR 检测各组细胞 *hsp90*、*hsf1*mRNA 的表达。 **结果**：（1）APP/PS1 转基因小鼠海马组织中 HDAC6 和 $A\beta_{1\text{-}42}$ 和 p-Tau 的表达水平均升高，而 HSP90 则降低；抑制 HDAC6 可上调 APP/PS1 小鼠海马组织 HSP90 和 HSF1 的表达而下调 $A\beta_{1\text{-}42}$ 和 p-Tau 的表达，同时改善小鼠的认知行为学功能（$P<0.05$ 或 $P<0.01$）；激动 HDAC6 则相反；而预先抑制 HSP90 再应用 HDAC6 抑制剂则没有引起 HSP90 和 HSF1 表达的升高以及 $A\beta_{1\text{-}42}$ 和 p-Tau 的水平的降低，同时小鼠的行为学功能也没有明显提升（$P>0.05$）；4 个对照组比较上述指标均没有明显变化（$P>0.05$）。（2）$A\beta_{1\text{-}42}$ 干预组神经细胞 HDAC6 和 $A\beta_{1\text{-}42}$、p-Tau 的表达水平均升高，而 HSP90 则降低，同时细胞活性和突起均减少（$P<0.05$ 或 $P<0.01$）；过表达 HSP90 可上调 HSF1 的表达、降低 $A\beta_{1\text{-}42}$ 及 p-Tau 的水平，同时增加细胞活性和突起的数量（$P<0.05$ 或 $P<0.01$）；敲低 HSP90 则引起相反的效应；先敲低 HSF1 再过表达 HSP90，则没有引起明显的 HSF1 和 $A\beta_{1\text{-}42}$、p-Tau 的表达水平以及细胞功能及突起的变化（$P>0.05$）。 **结论**：HDAC6 可能通过调控 HSP90 影响转录因子 HSF1 的表达，进而影响转基因小鼠海马组织中 Aβ 寡聚体的形成和 Tau 蛋白磷酸化水平以及小鼠的认知行为学功能变化。

P1-30 KDM4A in the dorsal root ganglia contributes to the development and maintenance of neuropathic pain via regulation of CCL2 in rats

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Objective The lysine specific demethylase 4A (KDM4A) has been demonstrated as a

coregulator of neuropathic pain by promoting neuroinflammation. Increasing evidence reveals that C-C Motif Chemokine Ligand 2 (CCL2) participates in neuroinflammation, which plays an important role in the development and maintenance of neuropathic pain. However, it is still unclear whether CCL2 is regulated by KDM4A in neuropathic pain.

Methods The neuropathic pain was conducted by spinal nerve ligation (SNL) of the lumbar 5 nerve root in rats. Immunofluorescence, Western blotting, qRT-PCR and chromatin immunoprecipitation (ChIP)-PCR were performed to investigate the underlying mechanisms.

Results L5 SNL significantly increased KDM4A and CCL2 expression in the ipsilateral L4/5 dorsal root ganglia (DRG) after SNL. DRG microinjection of KDM4A siRNA, as well as prior microinjection of AAV2-KDM4A into the DRGs of rats following SNL elevated the paw withdrawal threshold (PWT) and paw-withdrawal latency (PWL) compared with that of the SNL group. Microinjection of AAV2-KDM4A decreased the expression of CCL2 in DRGs. ChIP-PCR showed that SNL-induced increased binding of signal transducer and activator of transcription 3, STAT3 with CCL2 promoter was repressed by the treatment of microinjection of AAV-EGFP-KDM4A shRNA.

Conclusions These results suggest that KDM4A may contribute to neuropathic pain by regulating the expression of CCL2 in DRGs.

Keywords: Neuropathic pain, KDM4A, Spinal nerve ligation, Dorsal root ganglia, CCL2

P1-31 Electro-acupuncture modulating corticostriatal dysfunction induces time-dependent motor improvement in Parkinsonian rats

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Motor impairments in Parkinson’s disease (PD) are associated with corticostriatal dysfunction including increased glutamate transmission and aberrant beta synchronized oscillations. Although electro-acupuncture (EA) has shown promise in improving motor deficits in PD, the underlying mechanisms are unclear. In this study, we used a rat model of PD with a unilateral lesion of the medial forebrain bundle by 6-hydroxydopamine toxin injection to assess the effects of EA stimulation on motor symptoms, corticostriatal glutamatergic synaptic transmission and the electrophysiological activities in the motor cortex and striatum during and after EA application. We found that high frequency (100 Hz) EA produced a time-dependent improvement in motor symptoms, attenuated glutamate release, and reduced spine pathology,

without restoring striatal dopamine levels. EA also decreased aberrant synchronized high beta (25-40 Hz) oscillations in the cortico-striatal circuit. Using chemogenetic tools, we selectively inhibited corticostriatal glutamatergic neurons and found that this alleviated motor symptoms and improved corticostriatal pathological phenotypes in PD rats. Conversely, chronic chemogenetic activation of corticostriatal glutamatergic projection blocked the beneficial effects of EA on motor symptoms and synchronized beta oscillations in PD rats. Our findings suggest that EA exhibits targeted interventions on corticostriatal dysfunction, inducing time-dependent recovery of movement in PD. This study elucidates the potential mechanisms underlying EA treatment for motor symptoms in PD.

Keywords: Parkinson's disease; Corticostriatal glutamate transmission; Beta oscillatory synchronization; Electro-acupuncture stimulation; Spine plasticity

P1-32 Pathological α-synuclein abolishes the maintenance of mitochondrial homeostasis by exosomal hemoglobin under chronic hypoxia

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Hypoxia stress is closely related to the occurrence and development of many central nervous system diseases, but its underlying mechanism is obscure. Hemoglobin is the main protein involved in the transportation and utilization of oxygen. Recent studies have shown that its pathological changes are involved in nerve injury and the progression of hypoxia-related neurological diseases, but its molecular mechanism is still unclear. In this study, we will explore the role and mechanism of hemoglobin abnormal changes in nerve injury under hypoxic stress.

In this study, C57BL mice were used to establish a chronic hypoxic model. We found that chronic hypoxia induced cognitive and motor dysfunction in mice, accompanied by decreased synaptic plasticity, neurodegeneration and neuronal death in cerebral cortex and hippocampus. The results of single-nucleus RNA sequencing of brain showed that the mRNA of hemoglobin subunits was considerably increased in the brain of mice under chronic hypoxia, and this significantly up-regulated hemoglobin transcription was found in endothelial cells, glial cells, etc., but not in neurons. We further found that chronic hypoxia also induced hemoglobin mRNA upregulation in the exosomes of brain tissue. Through the combined analysis of single cell transcriptomics and

exosome transcriptomics, we found that chronic hypoxia-induced cerebral exosomes carrying up-regulated hemoglobin mRNA were also released by non-neuronal cells. Interestingly, further experiments showed that transcriptionally upregulated hemoglobin was mainly expressed in neurons, but not in non-neuronal cells. We found in vitro that hypoxia induces endothelial cells to up-transcribe hemoglobin and release it via exosomes, which are taken up by neurons to express hemoglobin. Although some hemoglobin in neurons was located in the mitochondria, a large amount of hemoglobin remains in the cytoplasm and binds to phosphorylated α-synuclein (p-α-syn), rather than non-phosphorylated α-synuclein. This abnormal distribution of hemoglobin causes dysfunction of the mitochondrial respiratory chain. This abnormal distribution of hemoglobin triggers nerve injury by causing dysfunction of the mitochondrial respiratory chain.

In summary, through single-nucleus transcriptomics sequencing combined with tissue exosome sequencing analysis, this study revealed that the way in which non-neuronal cell exosomes are transmitted in the brain under chronic hypoxia mobilized the expression of hemoglobin in neurons; The abnormal hemoglobin distribution caused by p-α-syn induced mitochondrial and nerve damage. This study provides a new perspective for the role and mechanism of hemoglobin in hypoxic-related nerve injury.

Keywords: α-synuclein, Hemoglobin, Hypoxia, Mitochondrial homeostasis, Nerve injury

P1-33 二肽基肽酶 4 影响阿尔茨海默症学习记忆功能障碍作用及机制

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目的 拟探讨敲除或抑制二肽基肽酶 4（DPP4）改善阿尔茨海默症（AD）学习记忆功能障碍及其调控焦亡信号通路的作用机制。**方法** 7 周龄雄性 C57BL/6J 和 DPP4 基因敲除小鼠（$DPP4^{-/-}$）随机分为四组：C57BL/6J 假手术组（Control 组）、$DPP4^{-/-}$假手术组（$DPP4^{-/-}$组）、模型组（AD 组）、$DPP4^{-/-}$模型组（$DPP4^{-/-}$+AD 组）；侧脑室微量注射 5μl $A\beta_{25-35}$ 进行 AD 造模。Morris 水迷宫实验观测学习记忆能力；培养 HT22 神经元细胞，利用 DPP4 抑制剂西格列汀（Sitagliptin，0.25mM）将细胞分为对照组（Control 组）、正常加抑制剂组（Control+Sit 组）、模型组（AD 组）、模型加抑制剂组（AD+Sit 组）。Hoechst/PI 荧光双染法检测焦亡情况，Western blot 法检测焦亡和记忆相关蛋白的表达水平。**结果** 水迷宫实验显示，与 AD 组相比，$DPP4^{-/-}$+AD 组定位航行实验的逃避潜伏期明显缩短，空间探索实验中穿台次数和目标象限停留时间百分比均显著增多；而 Control 组和 $DPP4^{-/-}$组相比逃避潜伏期、穿台次数、

目标象限停留时间百分比均无明显差异。Western blot 实验结果显示，与 AD 组相比，DPP4$^{-/-}$+AD 组海马组织内 BDNF 蛋白表达明显升高，NLRP3、Caspase-1、GSDMD 等蛋白表达明显减少。Hoechst/PI 荧光双染法实验观察到 HT22 细胞 AD 组细胞焦亡率与 Control 组相比明显升高；与 AD 组相比，AD+Sit 组细胞焦亡率显著降低。同样 Western blot 实验结果显示，与 AD 组相比，AD+Sit 组细胞内 NLRP3、Caspase-1、GSDMD、1L-18、1L-1β 等细胞焦亡相关蛋白的表达显著减少。**结论** 敲除 DPP4 基因可能通过抑制 NLRP3-Caspase-1 细胞焦亡通路作用，改善 AD 小鼠的学习记忆功能障碍。

关键词：二肽基肽酶 4；阿尔茨海默症；学习和记忆；焦亡；

P1-34 ABI3BP 在阿尔茨海默症发生发展中的作用及机制研究

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研究目的：探究 ABI3BP 在 AD 中的作用及机制。

研究方法：蛋白免疫印迹法检测不同年龄段野生型小鼠海马中 ABI3BP 蛋白表达及 3 月龄野生型和 5xFAD 小鼠脑组织中 ABI3BP 的表达；选用 1 月、3 月、6 月、12 月、18 月龄野生型和 ABI3BP$^{-/-}$雄性小鼠，水迷宫以及新事物认知实验检测各年龄段小鼠学习认知能力的差异；免疫组织化学染色检测野生型和 ABI3BP$^{-/-}$小鼠脑组织中 Ki67 和 PCNA 的表达；免疫荧光共染分别检测 Ki67 和 PCNA 与 GFAP、NEUN、IBA1 及 ABI3BP 与 GFAP、NEUN、IBA1 共定位。利用 ABI3BP$^{-/-}$小鼠和 5xFAD 小鼠进行杂交，得到野生型小鼠、ABI3BP$^{-/-}$小鼠、5xFAD 小鼠以及 ABI3BP$^{-/-}$小鼠 5xFAD 小鼠，水迷宫以及新事物认知实验检测 3 月龄 4 种基因型小鼠学习认知能力的差异；硫磺素 S 染色、尼氏染色检测 3 月龄四组基因型小鼠大脑斑块沉积以及神经元数量的差异。

研究结果：ABI3BP 蛋白在 1 月、3 月、6 月、12 月、18 月龄野生型小鼠海马中表达下降，3 月龄 5xFAD 小鼠海马中表达增加；不同年龄 ABI3BP$^{-/-}$小鼠相较于野生型小鼠穿越目标平台的次数和平台区域停留的时间显著增加，认知指数显著增加，逃避潜伏期显著降低两组小鼠在行径距离、速度上没有差异；在野生型小鼠中，ABI3BP 与 GFAP 共定位；与野生型小鼠相比 ABI3BP$^{-/-}$小鼠脑组织中 Ki67、PCNA 表达增多，并与 GFAP 共定位；ABI3BP$^{-/-}$ x 5xFAD 小鼠在穿越目标平台的次数和在平台区域停留的时间显著增加，认知指数显著增加，逃避潜伏期显著降低两组小鼠在行径距离、速度上没有差异；与 5xFAD 小鼠相比，ABI3BP$^{-/-}$5xFAD 小鼠小鼠大脑皮层区和 DG 区斑块数量显著减少。

研究结论：目前，我们的研究发现 ABI3BP 缺失可以改善 5xFAD 小鼠的认知功能，减少 Aβ 沉积。

关键词：ABI3BP；阿尔茨海默病;星形胶质细胞（GFAP）；淀粉样 β 肽类；

P1-35 Electro-acupuncture alleviates corticostriatal circuit dysfunction in Parkinsonian rats

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Motor impairments in Parkinson's disease (PD) are associated with corticostriatal dysfunction including increased glutamate transmission and aberrant beta synchronized oscillations. Although electro-acupuncture (EA) has shown promise in improving motor deficits in PD, the underlying mechanisms are unclear. In this study, we used a rat model of PD with a unilateral lesion of the medial forebrain bundle by 6-hydroxydopamine toxin injection to assess the effects of EA stimulation on motor symptoms, corticostriatal glutamatergic synaptic transmission and the electrophysiological activities in the motor cortex and striatum during and after EA application. We found that high frequency (100 Hz) EA produced a time-dependent improvement in motor symptoms, attenuated glutamate release, and reduced spine pathology, without restoring striatal dopamine levels. EA also decreased aberrant synchronized high beta (25-40 Hz) oscillations in the corticostriatal circuit. Conversely, chronic chemogenetic activation of corticostriatal glutamatergic projection blocked the beneficial effects of EA on motor symptoms and synchronized beta oscillations in PD rats. Our findings suggest that EA exhibits targeted interventions on corticostriatal dysfunction, inducing time-dependent recovery of movement in PD. This study elucidates the potential mechanisms underlying EA treatment for motor symptoms in PD.

Key words: Parkinson's disease; Corticostriatal glutamate transmission; Beta oscillatory synchronization; Electro-acupuncture stimulation; Spine plasticity

P1-36 磁共振弥散张量成像在注意缺陷多动障碍临床应用研究

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目的：使用 MRI 弥散张量成像技术揭示注意缺陷多动障碍（ADHD）儿童的脑白质结构和功能改变。**方法：**临床确诊一组 ADHD 患儿及一组健康对照儿童纳入 MRI 研究，经临

床及影像筛查，采用基于体素及全脑神经纤维束单独成像对比分析。**结果**：ADHD 患儿神经纤维束关联异常，以胼胝体毯部、下额枕束受损较多见。

儿童注意缺陷多动障碍（atltention deficit hyper-activity disorder, ADHD）又称为多动症，是儿童期常见的一类心理障碍。表现为与年龄、发育水平不相称的注意力不集中和注意时间短暂、活动过度和冲动，常伴有学习困难、品行障碍和适应不良。该症于学前起病，呈慢性过程，不仅影响儿童的学校、家庭和校外生活，而且容易导致儿童持久的学习困难、行为问题和自尊心低，此类患儿在家庭及学校均难与人相处。如不能得到及时治疗，部分患儿成年后仍有症状，明显影响患者学业、身心健康以及成年后的家庭生活和社交能力。其发病机制尚未完全了解，诊断主要依赖于行为分析。通过 DTI 脑网络对比分析，对为该类疾病的早期诊断提供了有力证据。

本研究在选择性注意任务中的行为表现比年龄匹配的正常对照儿童神经纤维束有明显异常，但存在一定局限性，首先，ADHD 患者不同亚型之间的行为和神经活动表现可能存在差异，而当前研究中 ADHD 组通过治疗控制的样本量较小，故无法有效的亚组分析，ADHD 疾病本身的复杂性和临床表现的异质性，加上不同研究图像质控标准和分析方法各异，导致研究结果有所差异。其次，神经纤维束异常表现是脑白质发育异常导致，脑灰质激活强度需结合 BOLD、脑电图、脑磁图等检查综合分析，并基于任务难度效应的全脑综合分析更具有全面性。未来需要大样本量、更全面的评价指标以及更完善的多元变量分析策略进行多维度分析，深入探究白质微结构改变与 ADHD 患者行为和认知功能的关系。及时就医，早发现、早诊断、早治疗。一般预后良好，少数受持续至成年。因脑白质神经纤维束具有非常强的可塑性，10 岁以前及时康复治疗，会取得很好的效果，因此平素应注意观察孩子的语言、情绪、行为变化，尽量避免重大生活事件的影响。如孩子出现注意力不集中，活动过度和冲动等疑似情况时，应尽早去医院就诊。

关键词：磁共振扩散张量成像，胼胝体毯部，下额枕束

P1-37 NMDAR 阻断诱导 dCA1 区神经元兴奋性异常于空间行为障碍的相关性

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空间认知行为障碍是精神分裂症(schizophrenia，SZ)临床症状的重要表现之一。目前对于空间认知行为障碍的病理生理机制尚不清楚，缺乏有效的治疗手段。既往研究表明 SZ 患者海马体积减小、细胞间的联系减弱。然而，SZ 海马功能异常与空间认知行为障碍之间的具体相关性尚不清楚。因此，本研究采用虚拟空间定位（virtual spatial location，VSL）任务和神经元在体钙成像技术，探究急性 NMDAR 低功（acute NMDA hypofunction，ANH）模

型小鼠中空间认知行为障碍与海马 dCA1 区神经元兴奋性活动异常的相关关系，并检验了阿立哌唑（aripiprazole，ARI）对其的治疗效果。研究结果发现，ANH 模型鼠存在自发运动的距离和速度增加，空间认知能力受损等行为异常。同时海马 dCA1 区出现神经元兴奋性活动的频率、振幅、半宽增加，神经元活动之间的同步性降低，神经元活动编码空间位置的精确度下降，编码奖励信息的能力降低。给予 ARI 治疗可以降低 ANH 鼠自发运动的距离和速度，缓解空间认知能力障碍。降低海马 dCA1 区神经元活动的频率、振幅、半宽，提高它们的同步性以及编码空间位置和奖励信息的能力。这些结果充分证实了 ANH 鼠空间认知障碍与海马 dCA1 神经元兴奋性活动异常之间的相关性，以及 ARI 的治疗效果，为深入了解 SZ 空间认知行为障碍的病理生理机制和寻找有效的治疗药物提供了实验依据。

关键词：精神分裂症；空间认知；NMDAR 拮抗剂；海马；谷氨酸能神经元；在体钙成像；阿立哌唑

P1-38 TadA orthologs enable both cytosine and adenine editing of base editors

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Cytidine and adenosine deaminases are required for cytosine and adenine editing of base editors respectively, and no single deaminase could enable concurrent and comparable cytosine and adenine editing. Additionally, distinct properties of cytidine and adenosine deaminases lead to various types of off-target effects, including Cas9-indendepent DNA off-target effects for cytosine base editors (CBEs) and RNA off-target effects particularly severe for adenine base editors (ABEs). Here we demonstrate that 25 TadA orthologs could be engineered to generate functional ABEs, CBEs or ACBEs via single or double mutations, which display minimized Cas9-independent DNA off-target effects and genotoxicity, with orthologs B5ZCW4, Q57LE3, E8WVH3, Q13XZ4 and B3PCY2 as promising candidates for further engineering. Furthermore, RNA off-target effects of TadA ortholog-derived base editors could be further reduced or even eliminated by additional single mutation. Taken together, our work expands the base editing toolkits, and also provides important clues for the potential evolutionary process of deaminases.

Key words: TadA orthologs, base editors

P1-39 TadA reprogramming to generate potent miniature base editors with high precision

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Although miniature CRISPR-Cas12f systems were recently developed, the editing efficacy and targeting range of derived miniature cytosine and adenine base editors (miniCBEs and miniABEs) have not been comprehensively addressed. Moreover, functional miniCBEs have not yet be established. Here we generated various Cas12f-derived miniCBEs and miniABEs with improved editing activities and diversified targeting scopes. We found that miniCBEs generated with traditional cytidine deaminases exhibited wide editing windows and high off-targeting effects. To improve the editing signatures of classical CBEs and derived miniCBEs, we engineered TadA deaminase with mutagenesis screening to generate potent miniCBEs with high precision and minimized off-target effects. We showed that newly designed miniCBEs and miniABEs are able to correct pathogenic mutations in cell lines and introduce genetic mutations efficiently via adeno-associated virus delivery in the brain in vivo. Together, this study provides alternative strategies for CBE development, expands the toolkits of miniCBEs and miniABEs and offers promising therapeutic tools for clinical applications.

Key words：miniature base editors, TadA reprogramming

P1-40 外侧臂旁核-下丘脑室旁核兴奋性谷氨酸能神经通路在晕动症发生中的作用

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晕动症（Motion sickness，MS）是由于机体暴露于异常加速度环境下所引起的多系统生理反应。前庭内侧核及脊束核可以接受晕动刺激信号并传递至外侧臂旁核（LPBN）而产生晕动症状。LPBN 是重要的中继核团，同时存在丰富的谷氨酸能神经元。为明确 LPBN 谷氨酸能神经通路在晕动症发生中的作用，本课题开展了以下研究。

研究内容：

1、LPBN 谷氨酸能投射纤维及其与晕动模型大鼠 Fos 蛋白共存观察

LPBN 注射 AAV2/1-CaMKII-EGFP 后，各核团内 EGFP 阳性纤维分布情况及其与晕动刺激 Fos 蛋白免疫荧光共表达情况均存在差异。下丘脑室旁核（PVN）内共标记神经元占比最高。

2、晕动模型大鼠 LPBN、PVN 内 Fos 蛋白与谷氨酸囊泡型转运体共标记观察

LPBN 内 VGLUT（1-3）/Fos 三种共标记神经元在 Fos 阳性神经元总数量中占比分别为 92.8%、95.4%、89.3%；PVN 内 VGLUT2/Fos、VGLUT3/Fos 共标记神经元占比显著高于 VGLUT1/Fos（85.4%，83.1% vs. 1.7%）。

3、光遗传激活 LPBN-PVN 谷氨酸能神经通路

LPBN 注射 ChR2 光敏病毒，在 PVN 核团上方给予 473nm 蓝光间断照射 2h，与对照组相比，光遗传刺激大鼠 PVN 内 EGFP 荧光蛋白表达显著增强、Fos 蛋白表达明显增多；动物摄食量显著降低、粪便颗粒数增加、自发活动显著减少，但是尾部温度无明显变化。

4、晕动模型大鼠 PVN 内重要神经肽与 Fos 蛋白免疫荧光共标记观察

ChAT/Fos、Reelin/Fos 共标记神经元占 Fos 阳性神经元的比例＞90%，CRH/Fos 共标记神经元占比约为 40%，AVP/Fos、OXT/Fos 共标记神经元占比＜5%。

研究结论：

1、晕动症相关核团内 EGFP 投射纤维分布存在显著差异；接受 LPBN 谷氨酸能投射并被晕动刺激激活的神经核团主要为 PVN。

2、光遗传激活 LPBN-PVN 谷氨酸能神经通路，诱发大鼠产生晕动症相关行为改变，包括摄食量减少、自发活动减少、粪便颗粒数增加。但是，未出现类似于晕动刺激后尾部散热增加的表现。

3、LPBN-PVN 谷氨酸能投射纤维与谷氨酸囊泡型转运体 VGLUT2、3 共存；晕动刺激可显著激活 PVN 内 ChAT、Reelin、CRH 阳性神经元。

关键词：晕动症，臂旁核，室旁核，谷氨酸

P1-41 Downregulation of PPP1r17 in the hippocampus drives alcohol-associated behavior in mice

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Alcohol addiction is characterized by persistent changes in motivation, emotion, and decision making. Drug addiction has been characterized as a disorder of synaptic plasticity. This study established two-bottle choice alcohol drinking paradigm to analyzed the mRNA expression profile in the hippocampus of mice, and the key gene protein phosphatase 1 regulatory subunit 17 (PPP1r17) was found. PPP1r17 is the encoded protein is a substrate for cGMP-dependent protein kinase, which is likely involved in human-specific cortical neurodevelopment. Our research examined the role of PPP1r17 in the hippocampus on alcohol-associated behaviors mice. We evaluated the effect of PPP1r17 downregulation using an adeno-associated virus (AAV) containing a short hairpin RNA against PPP1r17. The results show that downregulated PPP1r17 did not affect the exploratory ability and anxiety of mice. In the conditioned place preference paradigm, compared with the alcohol treated group mice, the time in drug-paired side of PPP1r17 knockdown mice was significantly increased during the test period. The results of righting reflex test showed that the sedation latency of PPP1r17 knockdown group was significantly increased than control group, but the duration of alcohol sedation was significantly decreased. Western blot data showed that compared with the control group, the ratio of F-actin/G-actin and p-Cofilin/Cofilin were increased in PPP1r17 knockdown alcohol exposed mice. In addition, p-AKT/AKT, p-GSK-3β/GSK-3β and p-CREB/CREB were all increased, regard as the downstream pathway of PPP1r17. Together, these data suggest that regulation of PPP1r17 in the hippocampus is participate in structural synaptic plasticity alterations, which is influence alcohol-related behavior.

Key words： Alcohol dependence; PPP1r17; Two-bottle choice model; Hippocampus

P1-42 Role of extracellular vesicles of Lactobacillus plantarum on alcohol consumption in Sprague-Dawly Rats

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Alcohol use disorder (AUD) is a significant public health issue, often characterized by repeated alcohol consumption and withdrawal. Alcohol impairs the intestinal barrier, resulting in changes in intestinal permeability and intestinal microbiota composition, which reduces the relative abundance of intestinal lactic acid bacteria. However, whether the gut microbiota affects alcohol consumption remains elusive. Here, utilizing Lactobacillus plantarum-derived extracellular vesicles (L-EVs), we show an underlying mechanism of how gut microbiota regulate alcohol consumption. Both intraperitoneal injection of L-EVs and microinjection of L-EVs into the ventral tegmental area (VTA) reduced alcohol consumption at 72h after withdrawal, similar to the effect of intra-VTA microinjection of brain-derived neurotrophic factor (BDNF). Intriguingly, the microinjection of K252a (an antagonist of Trk B) into VTA reversed the effect of L-EVs on reducing alcohol consumption. Intraperitoneal injection of L-EVs increased the expression of BDNF in VTA of alcohol-dependent rats. Furthermore, L-EVs rescued the low expression of BDNF in alcohol-incubated PC12 cells. Taken together, our findings suggest that L-EVs attenuate alcohol consumption in alcohol-dependent rats by regulating BDNF expression.

Keywords: Alcohol, ventral tegmental area, Lactobacillus plantarum derived extracellular vesicles, brain-derived neurotrophic factor

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P1-43 Effects of calcitonin gene-related peptide on synaptic transmissions in spinal cord motoneurons *in vitro*

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***Objective*:** To observe the effects of calcitonin gene-related peptide (CGRP) on descending pathway and peripheral input synaptic transmissions of neonatal rat spinal cord motoneuron (MN) *in vitro*. ***Method*:** Neonatal Sprague-Dawley rats aged 8 to 12 days old were used to prepare transverse spinal cord slices. Intracellular recording was performed from MN in the ventral horn of the spinal cord slices, and electric stimulation (monopulse, 0.1 to 0.2 ms, 0.1 Hz, 10 to 100 V) was applied to the ipsilateral ventrolateral funiculus (iVLF) and ipsilateral dorsal root (iDR) to induce excitatory postsynaptic potentials (iVLF-EPSP and iDR-EPSP). CGRP was perfused to observe its effects on the synaptic transmissions in spinal cord MNs. ***Result*:** ① In 7 stably recorded MNs, iVLF-EPSP was evoked and 1 μmol/L CGRP was perfused for 15 min. Inhibitory effect on duration of iVLF-EPSP was observed in 5 MNs ($P < 0.05$). ② In 5 stably recorded MNs, iDR-EPSP was elicited and 1 μmol/L CGRP was perfused for 15 min. Inhibitory effect on area under curve ($P < 0.05$) and raise time ($P < 0.01$) of iDR-EPSP was observed in 3 MNs. ③ In 2 stably recorded MNs, the amplitude of iDR-EPSP were decrease after perfusion 1 and 5 μmol/L CGRP for 15 min each, with the inhibition rates of 6% and 36%, respectively. ***Conclusion*:** CGRP may have inhibitory effects on MN synaptic transmissions from descending activation and sensory afferent input pathways.

Keywords: Calcitonin gene-related peptide; Motoneurons; Synaptic transmission; Spinal cord

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P1-44 Activation of TRPV4 induces neuroinflammation through inhibiting the nicotinic acetylcholine receptor α7 subunit

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Transient receptor potential vanilloid 4 (TRPV4) is permeable to calcium ion (Ca^{2+}).

Activation of TRPV4 can mediate Ca^{2+} influx and increase the intracellular Ca^{2+} concentration. TRPV4 is widely expressed in neurons and glial cells in the hippocampus, cerebral cortex, thalamu, etc. Activation of TRPV4 has been shown to induce neurotoxicity. Recent studies have found that activation of TRPV4 can enhance inflammation, but the underlying mechanism is not completely clear. The nicotinic acetylcholine receptor α7 subunit (α7nAChR) plays a crucial role in the anti-inflammatory effect in the central nervous system. Activation of TRPV4 could modulate glutamate receptors and γ-aminobutyric acid receptors, but whether activation of TRPV4 has an effect on α7nAChR remains unclear. The present study examined the effect of TRPV4 activation on α7nAChR and further explored whether this effect was responsible for TRPV4-induced inflammation and neuronal injury. Herein, we found that (1) administration of a TRPV4 agonist GSK1016790A (GSK) markedly inhibited acetylcholine-induced current (I_{ACh}) in hippocampal neurons, which was blocked by a TRPV4 specific antagonist or an α7nAChR specific antagonist. GSK-induced inhibition in I_{ACh} was attenuated by an inhibitor of Ca/calmodulin dependent protein kinase II (CaMKII). The hippocampal levels of NACHO protein and α7nAChR protein on the membrane were markedly decreased in mice by intracerebroventricular injection of GSK. These results indicate that activation of TRPV4 may inhibit α7nAChR function by activating CaMKII, and reduce 7nAChR expression on the cell membrane by inhibiting NACHO expression. (2) More activated microglia were found in the hippocampi of GSK-mice. Moreover, the protein levels of IBa-1 and CD11b markedly increased, and those of of CD206 and ARG1 decreased in the hippocampi of GSK-mice. These changes in GSK-mice were markedly alleviated by administration of an α7nAChR specific agonist DMXB. (3) The hippocampal protein levels of phosphorylated phosphoinositide 3-kinase (p-PI3K) and phosphorylated Akt (p-Akt) markedly decreased, and those of phosphorylated NF-κB p65 subunit (p-p65) and IL-1β increased in GSK-mice. These changes in GSK-mice were markedly attenuated by administration of DMXB. Administration of a PI3K agonist markedly decreased the protein levels of p-p65 and IL-1β in the hippocampi in GSK-mice. Administration of a NF-κB inhibitor markedly decreased the protein level of IL-1β in the hippocampi in GSK-mice. (4) Administration of DMXB markedly increased the number of surviving neurons in the hippocampus of GSK-mice. It is concluded that activation of TRPV4 may down-regulate α7nAChR to increase M1-type microglia activation, inhibit PI3K-Akt signaling pathway resulting in NF-κB activation and inflammatory factors production, which contributes to TRPV4-induced inflammation and neuronal injury.

Keywords: TRPV4, α7nAChR, inflammation, neuronal injury

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P1-45 A central mechanism for generation and maintenance of vigilance state in zebrafish and mice

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Abstract: Neural dynamics underlying internal brain states well orchestrate overt behaviors in animals. Neuromodulators have been frequently characterized as central elements to shape behavior states. However, it remains elusive how neuromodulators interact with activity pattern of neural circuits to implement internal brain states. Here we found that conspecific alarm substance (CAS) could reliably generate and maintain an internal synchronized state and vigilance behavior through persistent and intense activation of 5-HT neurons of dorsal raphe nucleus (DRN) in adult zebrafish. Intensely released 5-HT switched activity pattern of neural circuit in the central zone of dorsal pallium (Dc) (homolog to mammalian cortex) from a desynchronized state into a synchronized state represented by low-frequency high-amplitude neuronal oscillation. This innate 5-HT-driven mechanism controlling vigilance state revealed in zebrafish also applied to mammals. Persistent and intense activation of DRN 5-HT neurons by optogenetics or chemogenetics in mice generated and maintained an internal synchronized state in prefrontal cortex as well as vigilance behavior. Furthermore, we demonstrated that 5-HT drove the internal vigilance state via targeting at *5-HT7a*-expressing excitatory neurons in zebrafish Dc region or mice prefrontal cortex. Genetic ablation or pharmacological antagonism of 5-HTR7 diminished the internal synchronized state and vigilance behavior. Thus, we revealed an ancestral neural mechanism of vigilance across species and this sheds lights on understanding the interplay between neuromodulators and neural circuits to shape behavior states.

Keywords: vigilance; 5-HT; neuromodulator; synchronized state; neuronal oscillation

P1-46 CB1R antagonist NESS 0327 improved the motor dysfunction of MPTP-induced PD mice

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Parkinson's disease (PD) is the second most common neurodegenerative disease. Although

the etiology of PD is not fully elucidated, evidence showed that endocannabinoid system might be involved in the pathogenesis of PD and emerged as a promising target. NESS 0327 is a novel cannabinoid receptor type 1 (CB1R) antagonist with extremely strong affinity for CB1R. However, the role of NESS 0327 in motor dysfunction of PD animal models are still unknown. Therefore, we investigated the possible effect of NESS 0327 on MPTP-induced motor dysfunction and elucidated the possible mechanisms. Our results showed that NESS 0327 (i.p.) for 5 consecutive days could effectively antagonize the prolongation of turnaround time and pole time induced by MPTP. In the open field experiment, NESS 0327 could improve MPTP-induced reduction of total distance and average speed. Moreover, CatWalk gait analysis further confirmed that NESS 0327 could antagonize postural instability induced by MPTP. In addition, we also demonstrated that NESS could inhibit the decrease of TH protein level and TH positive cells in the substantia nigra of MPTP-induced PD mice. In conclusion, our study confirmed that NESS 0327 could improve the motor dysfunction and antagonize the damage of dopaminergic neurons in the SN of MPTP-induced PD model mice. This provides new evidence for targeting endogenous cannabinoids to alleviate motor dysfunction in PD.

Keywords: Parkinson's disease, CB1R, NESS 0327, endocannabinoid

P1-47 Molecular mechanisms of aldosterone-targeting neurons in the nucleus tractus solitarius in mice activated by a low sodium diet and their whole-brain projection

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[Abstract] The nucleus tractus solitarius (NTS) containing 11βHSD2 and MR (Mineralocorticoid receptor) neurons has been recognized as aldosterone-targeting neurons, playing a crucial role in sodium appetite regulation. However, their neuroanatomical basis and the molecular mechanisms responsible for their activation remain poorly understood. This study aimed to discover the brain-wide projection pattern and molecular mechanisms driving the activation of aldosterone-targeting neurons in the NTS. [**Methods]** 11βHSD2-Cre mice received stereotaxic injections of a viral vector specifically targeting the NTS, resulting in the expression of green fluorescent protein in 11βHSD2 neurons. Cryosections of brain tissue were prepared to visualize the entire axonal distribution pattern. 11βHSD2-Cre mice were subjected to either a low sodium diet (0.01% sodium) or a high sodium diet (2% sodium). Fluorescently labeled NTS neurons were isolated for single-cell RNA sequencing to explore their transcriptomic profile and

identify the molecular changes associated with their activation. **[Results]** (1) Low sodium levels induced the activation of 11βHSD2 neurons within the NTS, while high sodium levels suppressed their activity. (2) Aldosterone-targeting NTS 11βHSD2 neurons exhibited extensive axonal projections to the parabrachial nucleus, pre-locus coeruleus, and the ventrolateral bed nucleus of the stria terminalis. (3) Activation of NTS 11βHSD2 neurons by low sodium levels upregulated the expression of select sodium channels (Hcn2 and Scn2), potassium channels (Kcnk9 and Kcnq3), and calcium channels (Cacna1). However, no significant differences were observed in the expression of molecules involved in the peripheral aldosterone-MR signaling pathway, such as Nr3c2, epithelial sodium channels, and Sgk1. **[Conclusion]** Aldosterone-targeting neurons within the NTS display heightened activity in response to low sodium levels, characterized by distinct molecular signaling pathways compared to the peripheral aldosterone regulation system. These neurons exhibit dense axonal projections to the parabrachial nucleus, raphe nucleus, and median raphe nucleus.

Keywords: Nucleus Tractus Solitarius, Aldosterone, Low Sodium Diet, Transcriptome

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P1-48 Dopaminergic neurodegeneration in the substantia nigra is associated with olfactory dysfunction in mice models of Parkinson's disease

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Olfactory dysfunction represents a prodromal stage in Parkinson's disease (PD). However, the mechanisms underlying hyposmia are not specified yet. In this study, we first observed an early olfactory dysfunction in mice with intragastric rotenone administration, consistent with dopaminergic neurons loss and α-synuclein pathology in the olfactory bulb. However, a much severer olfactory dysfunction was observed without severer pathology in olfactory bulb when the loss of dopaminergic neurons in the substantia nigra occurred. Then, we established the mice models by intrastriatal α-synuclein preformed fibrils injection and demonstrated the performance

in the olfactory discrimination test was correlated to the loss of dopaminergic neurons in the substantia nigra, without any changes in the olfactory bulb analyzed by RNA-sequence. In mice with intranasal ferric ammonium citrate administration, we observed olfactory dysfunction when dopaminergic neurodegeneration in substantia nigra occurred and was restored when dopaminergic neurons were rescued. Finally we demonstrated that chemogenetic inhibition of dopaminergic neurons in the substantia nigra was sufficient to cause hyposmia and motor incoordination. Taken together, this study shows a direct relationship between nigral dopaminergic neurodegeneration and olfactory dysfunction in PD models and put forward the understandings that olfactory dysfunction represents the early stage of neurodegeneration in PD progression.

Keywords: Olfactory dysfunction, Substantia nigra, Dopaminergic neuron, Olfactory bulb

P1-49 远隔缺血适应脑保护的内皮祖细胞动员机制

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作为一种机体内源性对抗缺血损伤的保护策略，远隔缺血适应(remote ischemic conditioning, RIC)可通过四肢(骨骼肌)比较耐受缺血的器官进行缺血处理，来保护对缺血缺氧极其敏感的重要器官—脑，因此 RIC 为防治缺血性脑血管病提供了新方法。但 RIC 脑保护起效机制尚不明确，这阻碍了其进一步临床转化。为此，本研究利用小鼠大脑中动脉闭塞致缺血性卒中模型、原代培养脑微血管内皮细胞氧-糖剥夺离体缺血模型和原代培养骨髓内皮祖细胞，借助动物神经行为学、细胞生物学、分子生物学等学科技术，探讨骨髓内皮祖细胞(EPCs)动员在 RIC 脑保护中作用及其可能的分子机制。结果发现：1.单次 RIC 处理显著改善缺血性卒中小鼠神经功能和降低脑梗死体积的同时，循环血 EPCs 持续增多，而阻断 EPCs 归巢则明显削弱 RIC 脑保护作用；2.长期 RIC 通过提高血趋化因子 VEGF 而持续动员骨髓 EPCs 入血；3.缺血性卒中小鼠脑梗死周围皮层和海马 HIF-1α、HIF-2α 的表达均明显增高，提示激活的 HIF 通路可能发挥循环血 EPCs 招募作用；4.生物信息学分析提示 EPCs 归巢入脑后对缺血损伤的脑微血管内皮细胞修复作用的潜在靶点，即 AURKA 和 CENPF。综上，本课题揭示了 EPCs 动员在 RIC 脑保护中的重要作用，并探讨了 EPCs 入脑后修复脑微血管内皮细胞的潜在靶点。所获结果丰富了人们对于 RIC 脑保护机制的认识，并为 RIC 临床应用提供实验依据。

关键词：缺血性卒中，远隔缺血适应，内皮祖细胞，脑微血管

P1-50 Inhibition of SOCS3 signaling in the NTS alleviates hypoventilation in diet-induced obese male mice

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The Central leptin signaling system has been found to facilitate breathing and is correlated with obesity-related hypoventilation. Both the injection of leptin into the nucleus tractus solitarii (NTS) and the activation of leptin receptor–expressing NTS neurons potentiate respiratory drive. Here, we sought to reveal the mechanism underlying the contribution of NTS neurons—in particular, leptin signaling—to hypoventilation in a previously-established diet-induced obesity (DIO) mouse model and to determine whether genetic deletion of SOCS3 in the NTS alleviates hypoventilation in DIO mice. We demonstrated that the number of CO_2-activated NTS neurons was decreased and acid-sensing ion channels were downregulated in DIO mice relative to control lean mice. In addition, NTS leptin signaling was disordered as indicated by the downregulation of phosphorylated STAT3 and the upregulation of SOCS3 in DIO mice. Moreover, the deletion of SOCS3 in the NTS or retrotrapezoid nucleus significantly alleviated the blunted hypercapnic ventilatory response in DIO male mice. In conclusion, we suggest that a disordered leptin signaling system in the NTS contributes to obesity-related hypoventilation, the mechanism of which is probably associated with the reduced chemosensitivity of NTS neurons.

Keywords: Hypoventilation, Chemoreception, Leptin, Nucleus tractus solitarii, Retrotrapezoid nucleus

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P1-51 Effects of adenosine on synaptic transmissions in rat spinal cord motoneurons *in vitro*

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Abstract: ***Objective:*** To observe the effects of adenosine on synaptic transmissions, especially mediated by the spinal intrinsic regulation pathway and descending activation pathway of motoneuron (MN) in spinal cord slices. ***Methods:*** Spinal cord slices were prepared from neonatal SD rats (8~14 days old), and the ipsilateral ventrolateral funiculus (iVLF) and ipsilateral pericentral canal (iPCC) were electrically stimulated (single pulse, 0.1 ~ 0.3 ms, 10 times/min, voltage 15~100 V) to induce excitatory postsynaptic potential (EPSP, iVLF-EPSP and iPCC-EPSP) in MNs. Adenosine at required concentration was perfused and its effects on spinal MN iVLF-EPSP and iPCC-EPSP was observed. ***Results:*** ① In 10 MNs, perfusion of 50 μmol/L adenosine for 15 min depolarized MN with increased membrane resistance ($P < 0.01$ and $P < 0.05$), and reduced the amplitude of AP ($P < 0.01$). ② In 5 MNs, bath of 50 μmol/L adenosine for 15 minutes, reduced the frequency of spontaneous spike discharges ($P < 0.01$). ③ In 8 MNs, after perfusing 50 μmol/L adenosine for 15 minutes, a decrease in amplitude and area under curve of iVLF-EPSPs and iPCC-EPSPs was observed ($P < 0.05$). The apparent association rate constant (K_1), apparent dissociation rate constant (K_2) and apparent equilibrium dissociation constant (K_T) of iVLF-EPSPs and iPCC-EPSPs were not significantly changed by bathing 50 μmol/L adenosine foy 15 minutes ($n = 7$, $P > 0.05$). ④ In 6 MNs with iVLF-EPSPs, the amplitudes of iVLF-EPSPs were concentration-dependently decreased after perfused in turn with 10, 50 and 250 μmol/L adenosine for 15 minutes ($P < 0.01$). In 5 MNs with iPCC-EPSPs, the amplitudes of iPCC-EPSPs were concentration-dependently decreased after perfused in turn with 10, 50 and 250 μmol/L adenosine for 15 minutes ($P < 0.01$). ***Conclusion:*** Adenosine may concentration-dependently inhibit synaptic transmissions of spinal intrinsic regulatory pathway and descending activation pathway to MNs, thereby regulating the output of spinal cord motor control.

Keywords: Adenosine; Spinal cord; Motor neurons; Excitatory postsynaptic potential; Descending activation; Pericentral canal

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P1-52 Effects of 2-AG on peripheral afferent synaptic transmission to spinal cord motoneurons

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Abstract: ***Objective:*** To investigate the effects of 2-arachidonic acid glycerol (2-AG, also known as endogenous cannabinoids) on the postsynaptic potentials (iDR-EPSP) evoked by peripheral afferents in isolated spinal cord motoneurons (MNs) from neonatal rats. ***Methods:*** Transverse slices (400-500 μm) of spinal cord were prepared from 8~14 day-old neonatal SD rats, and the intracellular recording technique of spinal cord MN was applied to observe the effect of 2-AG on the iDR-EPSP induced by electrically stimulating ipsilateral dorsal root (iDR) in MNs. ***Results:*** In 15 MNs, perfusion of 5 μmol/L 2-AG for 15 min induced a depolarizing response with an increase in membrane resistance ($P < 0.01$) and decreased iDR-EPSP amplitude and area under curve (both $P < 0.01$). In 7 MNs, cumulative perfusion of 1, 5, and 25 μmol/L 2-AG for 15 min each induced depolarizing responses and concentration-dependently reduced iDR-EPSP amplitude ($P < 0.01$) and area under curve ($P < 0.05$). The apparent receptor kinetic analysis showed that 25 μmol/L 2-AG reduced the apparent maximum response V_{max} and apparent dissociation rate constant K_2 of iDR-EPSPs (both $P < 0.05$), but tended to increase the apparent binding rate constant K_1 and apparent equilibrium dissociation constant K_T. In 8 same-cell recordings of iDR-EPSP and iDR-IPSP, a trend toward a decrease in iDR-EPSP, iDR-IPSP amplitude, and area under curve was observed by perfusion of 25 μmol/L 2-AG for 15 min. In the 3 MNs with iDR-IPSP 25 μmol/L 2-AG had a tendency to suppress iDR-IPSP amplitude and area under curve. ***Conclusion:*** 2-AG has a concentration-dependent inhibitory effect on peripheral afferent excitatory synaptic transmission to spinal cord motoneurons.

Keywords: 2-Arachidonic acid glycerol; Spinal cord; Motor neurons; Postsynaptic potentials

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P1-53 基于 mTOR 通路探讨半夏白术天麻汤对缺血性脑卒中的保护作用

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目的 基于网络药理学方法探讨半夏白术天麻汤(BBTD)治疗脑卒中的作用机制，并通过动物实验和 Western Blot 等手段验证 BBTD 是否通过 mTOR 通路调控细胞炎症、自噬和细胞凋亡效应从而对抗缺血性脑卒中缺血再灌注损伤。**方法** 通过 TCMSP、TCMID 数据库获得 BBTD 各单味药成分并筛选出其治疗脑卒中的潜在靶点，应用网络药理学分析方法获得蛋白相互作用关系以及靶点参与的信号通路、生物过程，将蛋白相互作用关系导入 Cytoscape 软件并构建网络，应用 CytoHubba 插件筛选出关键靶点。应用 AutoDock Tools、AutoDock Vina 软件将得到的关键靶点与活性成分进行分子对接。通过不同浓度的 BBTD 浓缩提取液对 MCAO 模型大鼠进行干预处理，TTC 染色观察脑梗死面积，Western Blot 检测 mTOR、Bclin-1、caspace-3、IL-1、IL-6 等相关蛋白的表达水平。 **结果** 通过数据库筛选得到 98 个 BBTD 治疗脑卒中的潜在靶点；KEGG 富集通路筛选出靶点参与缺氧诱导因子 1 信号通路、肿瘤坏死因子信号通路等 27 条信号通路；GO 功能富集分析结果表明，靶点参与了上皮细胞自噬、炎症和血管重塑等 163 个生物过程。最终确定关键靶点为 MAPK1、MAPK3、mTOR、TNF 等。BBTD 通过胫骨青霉素、8β-乙氧基苍术内酯III、 香风草甙、菜豆素、3β-乙酰氧基苍术酮、氢化松苓酸、异欧前胡素、甘草酚、反鳕油酸等成分达到治疗脑卒中的效果。TTC 染色结果显示，与模型组相比，药物处理显著降低了 MCAO 模型大鼠的脑梗死面积($P < 0.05$)；Western Blot 检测结果显示，与对照组相比，模型组 mTOR 蛋白表达被抑制，而药物处理后 mTOR 的表达显著升高（$P < 0.05$）；与假手术对照组相比，模型组 IL-1、caspace-3、IL-6 和 Bclin-1 蛋白表达显著升高，而药物处理后其表达量显著下调（$P < 0.05$）。**结论** BBTD 通过多成分、多靶点、多通路干预缺血性脑卒中,其作用机制可能与 mTOR 通路调控的细胞自噬、凋亡和炎症有关。

关键词 急性脑缺血 半夏白术天麻汤 mTOR

P1-54 Effects of ICAM5 on alcohol dependence behavior in mice through remodeling of synaptic structure

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Alcohol dependence (addiction) is a high risk factor for many diseases. Intercellular Adhesion Molecule 5（ICAM5）, a cell adhesion molecule that belongs to the Ig superfamily, is highly expressed in neurons and plays an important role in dendritic spine development, synaptic plasticity, neural circuit formation, and emotion and learning and memory. However, the role of

ICAM5 in drug addiction and related mechanisms still unclear. In our study, we tested the effects of ICAM5 in chronic alcohol exposure mice model, and analyzed the neuronal plasticity changes and possible mechanisms during the test. We previously found the expression of ICAM5 was significantly decreased ($P < 0.001$) in the hippocampus after chronic alcohol exposure, and there was no significant difference in the medial prefrontal cortex and amygdala. Our research pretends to explore whether ICAM5 can affect the behavior of alcohol-addicted mice and the plasticity of hippocampal neurons. Using recombinant adeno-associated viruses to overexpress ICAM5 in the hippocampus, we investigated the NMDAR, PSD-95, and cellular cytoskeleton proteins F-actin/G-actin after alcohol treatment. Western blot analysis demonstrated that protein expression of NMDA receptors (GluN1, GluN2A and GluN2B) in the hippocampus of alcohol-exposed mice were higher than that of the control mice. Further, the expression of these proteins was decreased in ICAM5 overexpressing mice. ICAM5 also regulated the ratio of F-actin/G-actin (dendritic spines cytoskeleton proteins), which might be the key mediator for behavioral changes in mice. Consequently, our results highlight new evidence that ICAM5 may play an important role in the molecular mechanism underlying alcohol reward and preference. ICAM5 induced alcohol drinking behavioral changes in mice were closely related to hippocampal neuron plasticity such as synaptic transmission-related proteins and cytoskeleton proteins.

Keywords: alcohol dependence; ICAM5; synaptic plasticity; hippocampus

P1-55 Cell-specific NFIA upregulation promotes epileptogenesis by TRPV4-mediated astrocyte reactivity

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Background: The astrocytes in the central nervous system (CNS) exhibit morphological and functional diversity in brain region-specific pattern. Functional alterations of reactive astrocytes are commonly present in human temporal lobe epilepsy (TLE) cases, meanwhile the neuroinflammation mediated by reactive astrocytes may advance the development of hippocampal epilepsy in animal models. Nuclear factor I-A (NFIA) may regulate astrocyte diversity in the adult brain. However, whether NFIA endows astrocytes with regional specificity to be involved in epileptogenesis remains elusive.

Methods: Here, we utilize an interference RNA targeting NFIA to explore the characteristics

of NFIA expression and its role in astrocyte reactivity in a 4-aminopyridine (4-AP)-induced seizure model *in vivo* and *in vitro*. Combined with the employment of a HA-tagged plasmid overexpressing NFIA, we further investigate the precise mechanisms how NIFA facilitates epileptogenesis.

Results: 4-AP-induced NFIA upregulation in hippocampal region is astrocyte-specific, and primarily promotes detrimental actions of reactive astrocyte. In line with this phenomenon, both NFIA and vanilloid transient receptor potential 4 (TRPV4) are upregulated in hippocampal astrocytes in human samples from the TLE surgical patients and mouse samples with intraperitoneal 4-AP. NFIA directly regulates mouse astrocytic TRPV4 expression while the quantity and the functional activity of TRPV4 are required for 4-AP-induced astrocyte reactivity and release of proinflammatory cytokines in the charge of NFIA upregulation. NFIA deficiency efficiently inhibits 4-AP-induced TRPV4 upregulation, weakens astrocytic calcium activity and specific astrocyte reactivity, thereby mitigating aberrant neuronal discharges and neuronal damage, and suppressing epileptic seizure.

Conclusions: Our results uncover the critical role of NFIA in astrocyte reactivity and illustrate how epileptogenic brain injury initiates cell-specific signaling pathway to dictate the astrocyte responses.

Keywords: NFIA; TRPV4; Epilepsy; Reactive Astrocyte; Neuroinflammation

P1-56 乙酰水杨酸乙酯保护小鼠大脑缺血再灌注损伤的有效性和安全性研究

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缺血性脑卒中是目前造成全球死亡、残疾的首要原因。溶栓或血栓清除术是常用的治疗策略，但其时间窗口较窄，且往往会造成脑缺血/再灌注（I/R）损伤。神经保护可以改善 I/R 损伤，延长再灌注的时间窗。然而，成功应用于临床的研究很少，因此迫切需要新的神经保护方法。

乙酰水杨酸（阿司匹林）在缺血再灌注的细胞和动物模型上具有神经保护作用，但目前在临床上并未直接应用于神经保护药物，其中主要限制因素是阿司匹林在血脑屏障（BBB）和细胞膜上的渗透性较差，大剂量的阿司匹林服用会增加颅内出血风险。为此，根据阿司匹林的两个活性基团（乙酰基及羧基），再结合我们前期发现的阿司匹林发挥神经保护作用的靶点——乙酰化细胞质中 Ca2+/钙调蛋白依赖性激酶 2a (CaMK2a)的赖氨酸 42 号位点，我们对阿司匹林的衍生物进行筛选，筛选原则是保留乙酰基团以保证乙酰化神经保护靶点的活性，

对于羧基进行酯化替代以改变其膜通透性，以期获得具有神经保护作用的同时通透性高、出血风险低的化合物。我们通过计算机模拟分析相关靶点亲和力及药物毒性评估来比较各阿司匹林衍生物——乙酰水杨酸甲酯（M-ASA）、乙酰水杨酸乙酯（E-ASA）、乙酰水杨酸丙酯（P-ASA），我们最终筛选到阿司匹林衍生物—乙酰水杨酸乙酯。

在小鼠缺血性中风模型中，缺血后和再灌注前腹腔注射一次 E-ASA 可以减少 I/R 损伤。此外，E-ASA 对血小板中的环氧合酶-1（COX-1）活性的抑制作用较低，因此与阿司匹林相比，对小鼠造成的出血风险较小。综上，E-ASA 被证明在小鼠急性缺血性脑卒中具有良好的神经保护作用，同时出血风险较低，有望对临床急性缺血性中风提供一个新的治疗策略。

关键词：阿司匹林，缺血性卒中，神经保护，乙酰水杨酸乙酯

Protection of cerebral ischemia-reperfusion injury in mice by ethyl acetylsalicylate efficacy and safety studies

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Ischemic stroke, a major cause of mortality and disability worldwide, occurs when a blood clot blocks or narrows an artery leading to the brain. Thrombolysis or thrombectomy is the common therapeutic strategy, but it has a narrow time window and often causes ischemia/reperfusion (I/R) injury of the brain. Neuroprotection can ameliorate the I/R injury and extend the time window for successful reperfusion. However, few has translated into clinic successfully and new neuroprotective approaches are urgently needed.

Acetylsalicylic acid (aspirin) is neuroprotective in cells and animal models of ischemia-reperfusion but is not currently used directly as a neuroprotective drug in clinical practice, with the main limiting factors being the poor permeability of aspirin across the blood-brain barrier (BBB) and cell membranes, and the increased risk of intracranial hemorrhage associated with high-dose aspirin administration. To this end, based on the two active groups (acetyl and carboxyl) of aspirin, and in combination with our previous discovery of the target of aspirin's neuroprotective effect - the lysine 42 site of Ca2+/calmodulin-dependent kinase 2a (CaMK2a) in the acetylated cytoplasm - we carried out a screening of aspirin derivatives, with the screening principle of retaining the acetyl group to ensure the activity of the acetylated neuroprotective target, and esterifying the carboxyl group to change its membrane permeability, in order to obtain compounds with neuroprotective effects and at the same time high permeability and low risk of hemorrhage. We compared the aspirin derivatives - methyl acetylsalicylate

(M-ASA), ethyl acetylsalicylate (E-ASA), propyl acetylsalicylate (P-ASA) - by computer simulation analysis of the relevant target affinity and drug toxicity assessment, and we finally screened the aspirin derivatives -Ethyl acetylsalicylate.

In a mouse model of ischemic stroke, a single intraperitoneal injection of E-ASA after ischemic and before reperfusion reduced I/R injury. In addition, E-ASA had a lower inhibitory effect on cyclooxygenase-1 (COX-1) activity in platelets, thus posing less risk of bleeding in mice compared with aspirin. In conclusion, E-ASA was shown to have good neuroprotective effects in acute ischemic stroke in mice with a lower risk of bleeding, which is expected to provide a new therapeutic strategy for clinical acute ischemic stroke.

Keywords: Aspirin, Ischemic stroke, Neuroprotection, Ethyl acetylsalicylate

P1-57 组胺 H4 受体对阿尔茨海默病大鼠内嗅皮层-海马的调节作用及其脑内机制

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阿尔茨海默病（AD）是发病率最高的神经退行性疾病，其主要病理特征是 β-淀粉样蛋白（Aβ）沉积形成的细胞外老年斑和 Tau 蛋白过度磷酸化形成的细胞内神经纤维缠结（NFTs）。该病理变化始于内嗅皮层，随后扩散至海马以及各个脑区。至今，AD 发病机制尚未完全得到揭示。组胺是肥大细胞分泌的一种外周炎症介质，同时也是神经递质，通过 H1-4 受体参与脑内诸多神经功能的调节，并介入多种神经系统疾病的发病机制。组胺 H4 受体（H4R）目前被证实主要表达于小胶质细胞。大量研究表明激活的小胶质细胞介入 AD 发病机制，但目前尚无 H4R 在 AD 中作用的系统研究。

我们先发现 AD 患者前额叶皮层内 H4R 表达较对照组显著增加，且 H4R 的表达与小胶质细胞数量成正相关。成年雄性/老年雌性 Aβ1-42 和 Tau AD 大鼠模型（内嗅皮层注射 AAV-hTau）内嗅皮层和海马内 H4R 表达较对照组显著增加，提示 H4R 很可能介入 AD 发病机制。之后，以 H4R 激动剂 4-Methylhistamine（4-Meh）或拮抗剂 JNJ7777120（JNJ）分别干预两种 AD 大鼠模型，观察改变 H4R 活性对 AD 动物学习记忆行为、内嗅皮层和海马内神经元及胶质细胞形态和功能、及炎症信号传导通路的影响。结果发现：①H4R 配体对成年雄性 Aβ1-42 大鼠动物上述指标的影响未见显著差异；②4-Meh 可通过激活 NFκB 和 ERK

通路介入老年雌性 Aβ1-42 大鼠内嗅皮层的炎症反应；③JNJ 通过抑制 NFκB 和 ERK 通路减轻内嗅皮层-海马通路内 Tau 蛋白引起的胶质细胞的激活，进而具有保护神经元的趋势。本研究显示 H4R 高表达于 AD 主要受累脑区（内嗅皮层与海马），H4R 配体对 Aβ1-42 和 Tau 模型具有与年龄和性别有关的不同调节作用，H4R 拮抗剂有望成为治疗 AD 的新药物靶点。

关键词：组胺 H4 受体 阿尔茨海默病 内嗅皮层 海马 小胶质细胞

P1-58 Anshen Dingzhi Prescription prevents PTSD-elicited neuroinflammation via inactivating FKBP5-IKKα-NF-κB-NLRP3 signaling

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Background: Anshen Dingzhi Prescription (ADP) is an effective formula for the treatment of post-traumatic stress disorder (PTSD) and is widely used in the treatment of neuropsychiatric disorders. Neuroinflammation is closely associated with PTSD; however, it is unclear whether ADP for PTSD is related to neuroinflammation.

Purpose: This study aimed to explore the underlying mechanism of ADP in the treatment of PTSD from the perspective of neuroinflammation via FKBP5-IKKα-NF-κB-NLRP3 signaling.

Methods: A modified Single prolonged stress (SPS) method was used to replicate the PTSD mouse model. Anxiety-like behaviors were detected by open field test and elevated plus maze test, and fear memory test was detected by conditioned fear memory behavioral tests in mice. Changes in the expression of FKBP5-IKKα-NF-κB-NLRP3 signaling proteins and inflammatory factors TNF-α and IL-6 in the hippocampus were detected by western blot.

Results: After SPS modeling in mice, a gradual increase in the expression of inflammatory proteins TNF-α and IL-6 was found in hippocampal on days 1, 7, and 14, which was accompanied by an elevation of the FKBP5-IKKα-NF-κB-NLRP3 signaling proteins. Inhibition of the FKBP5-IKKα-NF-κB-NLRP3 signaling effectively alleviated PTSD-like behavior. ADP significantly reduced the freezing time in fear extinction, increased the movement time and distance in the central region of the open field, and increased the time to enter the open arm in the elevated cross maze in PTSD mice. At the same time, ADP reduced the expression of inflammatory proteins TNF-α, IL-6, and FKBP5-IKKα-NF-κB-NLRP3 signaling proteins in the

mice hippocampus of PTSD.

Conclusion: ADP prevents SPS-induced PTSD-like behaviors by regulating neuroinflammatory via FKBP5-IKKα-NF-κB-NLRP3 signaling.

Keywords: ADP; PTSD; Neuroinflammatory; FKBP5-IKKα-NF-κB-NLRP3 signaling

P1-59 G-1 rescues hippocampal synaptic deficits elicited by PTSD through activating GPR30/BDNF/TrkB signaling

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Background: G protein-coupled estrogen receptor 1 (GPER1, as known as GPR30), is a transmembrane estrogen receptor.G-1 is a GPR30-specific agonist that binds and activates GPR30.Studies have shown that GPR30 activation mediates a variety of signaling pathways, which are ameliorative in many neurological disorders such as AD and VD. Our previous study reported that GPR30 may improve memory in middle-aged mice by activating the BDNF/TrkB signaling pathway. However, whether GPR30 mediates the BDNF/TrkB signaling pathway to affect post-traumatic stress disorder (PTSD) has not been reported.

Purpose: To evaluate the ameliorative effect of GPR30 activation on PTSD-like behaviors in SPS&S mice and to explore the mechanism of action from the BDNF/TrkB signaling pathway.

Methods: Immunofluorescence staining was used to observe the changes of GPR30; a behavioral test method was used to assess the PTSD-like behaviors of single prolonged stress (SPS&S) mice; synaptic changes in the hippocampus of mice were observed by transmission electron microscopy; western blotting was employed to detect the expression of proteins involved in relevant signaling pathways.

Results: Compared with the control animals, the expression level of GPR30 in SPS&S mice was reduced. Meanwhile, SPS&S mice showed obvious fear generalization and anxiety-like behaviors. In contrast, 14 d of continuous G-1 intervention increased the expression of GPR30 and significantly improved the PTSD-like behaviors of SPS&S mice. The number of synaptic structures in the CA1 region of the hippocampus was significantly reduced in SPS&S mice compared with control animals; however, G-1 administration could counteract this effect. Furthermore, the protein expression of BDNF, p-TrkB, PSD95, p-Akt, p-mTOR, and GluN2A was significantly reduced in the hippocampus of SPS&S mice compared to control animals, whereas

GluN2B protein expression was significantly increased; however, these changes in protein expression were reversed following G-1 treatment. Importantly, the TrkB inhibitor ANA-12 inhibited the ameliorating effect of G-1 on PTSD-like behaviors and the increased expression levels of proteins related to the BDNF/TrkB signaling pathway.

Conclusions: Activation of GPR30 improves PTSD-like behaviors in mice, and this effect may be mediated through the BDNF/TrkB signaling pathway to improve synaptic deficits.

Keywords: PTSD; GPR30; BDNF/TrkB; Synaptic plasticity

P1-60 Regulation of mitochondrial signals in PTSD-like behaviors and ameliorative effects of Anshen Dingzhi prescription

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Abstract：Anshen Dingzhi Prescription (ADP) is an important formula for preventing and treating post-traumatic stress disorder (PTSD). Clinical and basic experiments have shown that ADP can improve PTSD-related symptoms. However, the mechanism of its action is still not very clear, and this study aims to investigate the role of AMPK/Sirt1-PGC-1α-dependent mitochondrial function in fear memory and anxiety-like behavior in PTSD, and the action of ADP from this signaling pathway. An SPS mouse model was established to evaluate the changes of AMPK/Sirt1-PGC-1α signals and mitochondrial function. Later, the function of this signaling pathway in fear memory and anxiety-like behavior in PTSD mice was confirmed using the agonists of the pathway. On this basis, the effects of ADP (640 mg/kg/day) with definite therapeutic effects, on mitochondrial structure and function, and this signaling pathway were evaluated. Finally, the possible components of ADP analyzed through bioinformatics were monitored through targeting PGC-1α. Compared to control mice, AMPK/Sirt1-PGC-1α signal pathway in the hippocampus was impaired in SPS mice, accompanied with reduced expression of mitochondrial functional proteins and abnormality of synaptic proteins. The pathway agonists ZLN005 and resveratrol can improve the behavioral function changes of mice caused by SPS, reverse the decline of AMPK/Sirt1-PGC-1α signal protein, mitochondrial functional protein, and the abnormality of synaptic proteins. We have established a fingerprint of ADP, and ADP at a dose of 640 mg/(kg day) can improve fear memory abnormalities and anxiety-like behavior in SPS mice, and repair AMPK/Sirt1-PGC-1α and mitochondrial structure. Through molecular docking

simulation, ADP entering the brain components, malkangunin, ginsenoside Rg5, fumarine, celabenzine, and inermin have strong binding powers with PGC-1α. This study indicates that the mitochondrial dysfunction dependent on AMPK/Sirt1-PGC-1α is an important mechanism for the occurrence of fear abnormailty and anxiety-like behavior in PTSD mice, and ADP may play a protective role in hippocampal impairment in PTSD mice by activating this pathway.

Keywords: PTSD**;** Mitochondrial function**;** PGC-1α**;** Anshen Dingzhi Prescription.

P1-61 参芪益智方通过调节脑周细胞的收缩性来预防 $A\beta_{42}$ 诱导的小鼠记忆损伤

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背景：参芪益智方是中医临床治疗神经系统疾病重要的经验方，广泛用于治疗神经退行性疾病。目的：探讨参芪益智方对 AD 样行为的改善作用以及调控周细胞，减少微血管收缩，改善脑血流量的作用机制。方法：采用 UPLC 建立参芪益智方的指纹图谱；通过行为学测试评估小鼠 AD 样行为；采用透射电镜和 Nissl 染色检测海马的病理学改变；采用 Western blotting 检测相关信号通路蛋白的表达；采用激光多普勒法检测小鼠脑血流量的变化。结果：不同批次提取的参芪益智方溶液相似度大于 0.9。与 Sham 组比，AβO 组小鼠表现出明显的空间记忆和恐惧记忆受损，参芪益智方可明显改善 AD 小鼠记忆受损功能；尼氏染色和透射电镜结果表明，与 Sham 组比，AβO 组海马 CA1 区神经元的数量明显减少，大量细胞器丢失，且模型组脑微血管皱缩变形，血管周围水肿变性，参芪益智方处理后可逆转这些改变;Western blotting 结果表明，与 Sham 组相比，AβO 组小鼠海马 CD31、N-cadherin、PDGFRβ、p-FAK 表达显著增加，参芪益智方处理后可以下调这些蛋白的表达。激光多普勒结果显示，与 Sham 组相比，AβO 组脑血流量明显减少，参芪益智方处理后逆转这一结果。与此同时，PDGFRβ 抑制剂 Sunitinib 对 AD 样小鼠行为与蛋白表达具有改善作用，与参芪益智方作用效应一致。结论：参芪益智方能够改善小鼠记忆受损，可能通过调控 PDGFRβ/FAK/N-cadherin 通路和周细胞收缩，改善脑血流，阻止海马功能损伤起到保护作用。

关键词：参芪益智方、AD、周细胞

P1-62 Expression of TRPC6 in mouse retina and its role in STZ-induced early diabetic retinopathy in mice

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Diabetic retinopathy (DR) is a complication of diabetes mellitus caused mainly by hyperglycaemia. In advanced stages, DR can cause severe and irreversible visual impairment, mainly due to apoptosis of retinal optic nerve cells. Transient receptor potential (TRP) is a class of non-selective cation channels associated with various physiological functions and pathological disease processes. It has been shown that TRPC6 can induce apoptosis or protect neuronal survival in the CNS, but its role in the apoptosis of diabetic mouse retinal neurons is poorly understood. In this study, a diabetic mouse model was established by intraperitoneal injection of STZ, and then we investigated the effect of TRPC6 on the survival of retinal cells with Western blot technology and immunofluorescence staining. We found that the expression levels of TRPC6 and proBDNF proteins were significantly increased in two and three month's diabetic mice. By vitreous injection of TRPC6 agonist, we found that the caspase-3 protein level was increased in 3-month diabetic mice, while, the caspase-3 and proBDNF protein levels were decreased in 3 months diabetic mice by vitreous injection of TRPC 6 antagonist. Immunofluorescence staining results showed that, astrocyte proliferation and ganglion cell apoptosis in 1 or 3-month diabetic mice. These effects were enhanced by TRPC6 agonists and blocked by TRPC6 antagonists in vitreous injection groups. Our results suggest that TRPC6 promotes retinal astrocyte proliferation and induces ganglion cell apoptosis in diabetic mice.

Keywords: TRPC6; diabetic retinopathy; retinal ganglion cells; astrocyte

P1-63 Combined alcohol and cannabinoid exposure leads to synergistic toxicity by affecting cerebellar Purkinje cells

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Combined use of cannabis and alcohol results in greater psychoactive toxicity than either substance alone, but the underlying central mechanisms behind this worsened outcome remain unclear. Here we show that the synergistic effect of Δ9 -tetrahydrocannabinol (THC) and ethanol on motor incoordination in mice is achieved by activating presynaptic type 1 cannabinoid

receptors (CB1R) and potentiating extrasynaptic glycine receptors (GlyR) within cerebellar Purkinje cells (PCs). The combination of ethanol and THC significantly reduces miniature excitatory postsynaptic current frequency in a CB1R-dependent manner, while increasing the extrasynaptic GlyR-mediated chronic chloride current, both leading to decreased PC activity. Ethanol enhances THC actions by boosting the blood–brain-barrier permeability of THC and enriching THC in the cell membrane. Di-desoxy-THC, a designed compound that specifically disrupts THC–GlyR interaction without affecting the basic functions of CB1R and GlyR, is able to restore PC function and motor coordination in mice. Our findings provide potential therapeutic strategies for overcoming the synergistic toxicity caused by combining cannabis and alcohol use.

Keywords: Combined alcohol and cannabinoid, Glycine receptor, Cannabinoid receptor 1, Purkinje cells

P1-64 Correlation between acupoint sensitization and activation of pruriceptor

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Visceral diseases usually accompany with hyperaesthesia phenomenon on the specific parts of the body surface. These parts are also the loci of sensitized acupoints. Meanwhile, spontaneously scratching or pressing on acupoints often arises during visceral diseases as individuals often seeking for pleasure sensation, which may be involved with itch sensation. The newly discovered peripheral itch receptor, dorsal root ganglion neurons which express Mas-gene-related G protein-coupled receptors A3 (Mrgpra3), are the specific candidates for acupoint sensitization. Such receptors turn to be excitative mood during visceral disease, therefore, promotes more scratch and stimulus behavior for regulating inner function. Investigating the dynamic process of itch receptor activation and its correlation with the "opening-closing" attributes of acupuncture points induced by referred hyperaesthesia will provide new avenues for exploring the self-stimulatory healing process triggered by acupoint sensitization.

Keywords: Acupoint sensitization; Pruriceptor; Hyperaesthesia

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P1-65 Astrocytic Nav1.6 knockdown inhibits APP/Aβ abnormal accumulation via autophagy-lysosomal pathway in APP/PS1 mice and reverses its cognitive deficits

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Alzheimer's disease (AD) is the most common neurodegenerative disorder which is pathologically characterized by the deposition of beta-amyloid (Aβ) protein produced by the successive cleavage of amyloid precursor protein (APP). Neurons are the primary source of APP in AD, making the role of astrocytes in APP /Aβ abnormal accumulation greatly neglected and the mechanism of astrocytic dysfunction on it remains unknown. We previously found that the voltage-gated sodium channels (Nav) 1.6 subtype acts a disruptive role in AD, thus we further investigate the role of astrocytic Nav1.6 and its connection with abnormal accumulation APP/Aβ. Adeno-associated virus with the astrocytic promoter and short hairpin against Nav1.6 was used to specifically downregulate astrocytic Nav1.6 in APP/PS1 mice. Astrocytic Nav1.6 knockdown reduced amyloidosis, suppressed glial cell activation with mitigated morphological complexity, improved synaptic function along with morphology, normalized network homeostasis, and restored learning as well as memory in APP/PS1 mice. Mechanistically, downregulation of astrocytic Nav1.6 attenuates reverse Na^{+}-Ca^{2+} exchange current, thereby reducing intracellular Ca^{2+} concentration, which in turn facilitates autophagic flux through AKT/mTOR/ULK pathway, and promotes lysosome targeted APP, ultimately reducing APP/Aβ abnormal accumulation, which might account for the better synaptic and learning ability in APP/PS1 mice. These findings shed light on the functions of astrocytic Nav1.6 in AD pathogenesis and provide a novel therapeutic strategy for the preclinical treatment of AD.

Keywords: Alzheimer’s disease; voltage-gated sodium channels subtype 1.6; Amyloid precursor protein; Aβ; Astrocytes; Autophagy-lysosome pathway.

P1-66 Molecular and cellular mechanisms of the first social relationship: A conserved role of 5-HT from mice to monkeys, upstream of oxytocin

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Maternal affiliation by infants is the first social behavior of mammalian animals. We report here that elimination of the Tph2 gene essential for serotonin synthesis in the brain reduced affiliation in mice, rats, and monkeys. Calcium imaging and c-fos immunostaining showed maternal odors activation of serotonergic neurons in the raphe nuclei (RNs) and oxytocinergic neurons in the paraventricular nucleus (PVN). Genetic elimination of oxytocin (OXT) or its receptor reduced maternal preference. OXT rescued maternal preference in mouse and monkey infants lacking serotonin. Tph2 elimination from RN serotonergic neurons innervating PVN reduced maternal preference. Reduced maternal preference after inhibiting serotonergic neurons was rescued by oxytocinergic neuronal activation. Our genetic studies reveal a role for serotonin in affiliation conserved from mice and rats to monkeys, while electrophysiological, pharmacological, chemogenetic, and optogenetic studies uncover OXT downstream of serotonin. We suggest serotonin as the master regulator upstream of neuropeptides in mammalian social behaviors.

Keywords: 5-HT; serotonin; oxytocin; social behavior; maternal affiliation by infants

P1-67 Calpain 介导 DCC 参与抑郁发生的机制研究

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抑郁症是最为常见的神经精神疾病之一，随着疫情的大流行，抑郁症的发病率显著增加。目前抑郁症机制不清楚，给临床治疗带来巨大挑战，因此找寻新的抗抑郁治疗靶点具有重要意义。结肠癌缺失基因（DCC）被认为是抑郁症的风险基因，但其能否成为抗抑郁的治疗靶点还有待阐明，以及驱动 DCC 分泌增加的上游因素和 DCC 高表达如何导致负性情绪的产生其神经机制仍不清楚。本研究使用习得性无助（LH）构建的小鼠抑郁模型，采用免疫荧光染色、化学遗传学、离体脑片电生理、病毒注射等手段，结果显示 DCC 能够成为抗抑郁的治疗靶点，钙蛋白酶（Calpain）介导的 SCOP 降解异常，ERK 的异常磷酸化是驱动 DCC 表达上升，mPFC 谷氨酸能神经元兴奋性增加从而引发抑郁的重要原因。本研究不仅有助于理解抑郁症发生发展的理论基础，也将为临床治疗抑郁症提供新的干预靶点。

关键词：抑郁症；Calpain；DCC；谷氨酸能神经元

P1-68 Hap1 调控 GR/CREB/BDNF 信号通路在 APP/PS1 小鼠学习记忆中的作用

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背景：阿尔茨海默病（Alzheimer's disease，AD）是一种发病隐匿的神经退行性疾病，是痴呆症最主要的类型，阐明 AD 的发病机制并确定治疗新靶点具有重大的意义。越来越多证据表明，糖皮质激素受体（Glucocorticoid receptor，GR）在 AD 海马中功能失调，这可能是导致 AD 病理及认知损伤的关键因素。但是 GR 功能失调的分子机制并不清楚。亨廷顿蛋白相关蛋白 1（Huntingtin- associated protein 1, Hap1）是酵母双杂交筛选中发现的第一个与亨廷顿蛋白相互作用的蛋白，具有神经保护作用。大量证据表明，其功能缺失与神经退行性疾病相关。AD 作为常见的神经退行性疾病，Hap1 在 AD 中的作用日益受到重视。本课题组前期结果表明，Hap1 与 GR 存在相互作用，并且可以保护 GR 蛋白水平。因此提出假说：Hap1 可能通过调控 GR 信号影响 AD 的学习记忆。

目的：明确 Hap1 通过调控 GR/CREB/BDNF 信号通路对 AD 模型小鼠 APP/PS1 学习记忆样行为产生影响，评估 Hap1 在 APP/PS1 小鼠学习记忆中的重要作用，为 AD 患者的临床治疗提供新的靶点。

方法：1. 利用 CRISPR/Cas9 基因剪切原理，针对小鼠 Hap1 基因，制备特异性敲低 Hap1 的 gRNA 载体，将构建的质粒包装病毒。2. 通过脑立体定位注射方法，特异性敲低 APP/PS1 小鼠海马内 Hap1 表达，利用行为学检测和高尔基染色法，检测 Hap1 表达下调对 APP/PS1 小鼠学习记忆样行为以及海马树突和树突棘形态的影响。3. 外源性添加 $A\beta_{25-35}$ 感染 N2A 细胞制备 AD 细胞模型。特异性敲低 APP/PS1 小鼠海马区和 AD 细胞模型中的 Hap1 表达，用 western-blot 和 qPCR 方法检测 GR，CREB，BDNF 蛋白水平和 RNA 水平的变化。

结果：动物实验：（1）特异性敲低 APP/PS1 小鼠海马内 Hap1 表达导致小鼠学习记忆样行为缺陷，海马神经元变少以及树突棘密度降低。（2）Western-blot 和 qPCR 实验检测，AD 海马中 Hap1 缺失导致 GR、CREB、BDNF 蛋白水平和 RNA 水平降低。细胞实验：通过质粒转染敲低 AD 细胞中 Hap1 表达后，细胞内 GR、CREB、BDNF 的蛋白水平和 RNA 水平均明显下降。

结论：APP/PS1 小鼠海马中 Hap1 降低可导致 GR、CREB、BDNF 表达下调，以及海马组织中神经元减少以及树突棘密度降低，导致 APP/PS1 小鼠的学习记忆损伤。

关键词：亨廷顿相关蛋白 1；神经退行性疾病；阿尔兹海默病；糖皮质激素受体；学习记忆

P2 内分泌代谢

P2-1 Ischemic cardiomyocytes-derived small extracellular vesicles promote cardiac fibrosis

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Myocardial fibrosis is the villain of sudden cardiac death. Myocardial ischemia/reperfusion (MI/R) injury induces cardiomyocyte damage or even death, which in turn stimulates fibroblast activation and fibrosis, but the intercellular communication mechanism remains unknown. Recent studies have shown that small extracellular vesicles (sEVs) significantly contribute to intercellular communication. Whether and how sEV might mediate post-MI/R cardiomyocyte/fibroblasts communication remain unknown. Here, *in vivo* and *in vitro* MI/R models were established. We demonstrate that sEVs derived from cardiomyocyte (Myo-sEVs) carry mitochondrial components,

which enters fibroblasts to initiate myocardial fibrosis. Based on bioinformatics screening and experimental verification, the activating molecule in Beclin1-regulated autophagy protein 1 (autophagy/beclin-1 regulator 1, Ambra1) was found to be a critical component of these sEV and might be a new marker for Myo-sEVs. Interestingly, release of Ambra1^{+}-Myo-sEVs was caused by secretory rather than canonical autophagy after MI/R injury and thereby escaped degradation. In ischemic and peripheral areas, Ambra1^{+}-Myo-sEVs were internalized by fibroblasts, and the delivered mtDNA components to activate the fibroblast cGAS (cyclic GMP-AMP synthase)-STING (stimulator of interferon genes) pathway to promote fibroblast activation and proliferation. In addition, our data show that Ambra1 is expressed on the EV surface and cardiac-specific Ambra1 down regulation inhibits the Ambra1^{+}-Myo-sEVs release and fibroblast uptake, effectively inhibiting ischemic myocardial fibrosis. This finding newly provides the evidence that myocardial secretory autophagy plays a role in intercellular communication during cardiac fibrosis. Ambra-1 is a newly characterized molecule with bioactivity and might be a marker for Myo-sEVs, providing new therapeutic targets for cardiac remodeling.

Keywords: Myocardial ischemia/reperfusion (MI/R) injury; Cardiac fibrosis; extracellular vesicles; Ambra1; secretory autophagy

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P2-2 Vaccarin suppresses diabetic nephropathy through inhibiting the EGFR signaling pathway

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Abstract: Diabetic nephropathy (DN), one of the common chronic complications of diabetes, is the leading cause of end-stage renal disease. Vaccarin, a highly active Chinese medicinal monomer isolated from vaccariae semen, confers protective effects against type 2 diabetes mellitus (T2DM). However, the effects of vaccarin on kidney injury in DN remain unclear. Our study showed that vaccarin ameliorated renal dysfunction and histological damage in diabetic mice through inhibiting renal fibrosis, overproduction of inflammation cytokine and reactive oxygen species (ROS). Additionally, vaccarin treatment significantly suppressed the process of epithelial-to-mesenchymal transition (EMT), a key step for renal fibrosis, in high glucose (HG)-induced HK-2 cells. Mechanistically, the network pharmacology analysis and molecular

docking revealed that epidermal growth factor receptor (EGFR) may be the potential target of vaccarin. In support, the phosphorylated levels of EGFR and its downstream mediator extracellular signal-regulated kinase 1/2 (ERK1/2) were abrogated by vaccarin in diabetic kidneys and HG-treated HK-2 cells. Blockade of either EGFR or ERK1/2 showed similar renal benefits as vaccarin. In conclusion, our results reveal that vaccarin attenuates diabetic renal damage via inactivation of EGFR signaling.

Keywords: Diabetic nephropathy, Vaccarin, EMT, HK-2 cells, EGFR

P2-3 Inhibition of SAT1-mediated ferroptosis arrests loss of retinal ganglion cells in diabetic retinopathy

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It has now become evident that loss of retinal ganglion cells (RGCs) occurs even in the absence of any visible microvascular signs of diabetic retinopathy (DR). As the terminally differentiated cells, death of RGCs will result in irreversible defects in the structure and function of the retina, thus exacerbating the progression of DR. However, the molecular mechanism underlying RGCs death has not been fully elucidated. Here, we demonstrated that ferroptosis, a programmed iron-dependent cell death, as a novel mechanism of RGCs death in a well-characterized diabetes model of ***db***/***db*** mouse. Features of typical ferroptosis, including increased intracellular iron ion levels and lipid peroxidation, accompanied by alterations in characteristic mitochondrial morphology of ferroptosis, have been found in diabetic RGCs. Notably, intravitreal injection of the ferroptosis inhibitor liproxstatin-1 (Lip-1) effectively reduced the death and visual impairment of RGCs in diabetic mice. Mechanistically, *Sat1* (spermidine/spermine N1-acetyltransferase 1), a known ferroptosis-related gene, was significantly upregulated in glucolipotoxicity-challenged primary RGCs by RNA sequencing. Ectopically induced expression of SAT1 led to lipid peroxidation and cell death that can be rescued by Lip-1 upon chronic oxidative stress in a *Sat1* Tet-on RGC cell line. Moreover, intravitreal administration of an siRNA targeting to *Sat1*significantly attenuated the ferroptotic cell death and restored the visual function of diabetic RGCs. As SAT1 is a rate-limiting enzyme involved in conversion of spermidine and spermine to putrescine, we further evaluated whether SAT1-mediated ferroptosis was related to the dysregulation of polyamine homeostasis. A significant decrease in levels of spermidine and spermine was found in diabetic retinas. Of interest, topical ocular administration

of exogenous spermidine protected diabetic RGCs from ferroptotic cell death in a dose-dependent manner. Collectively, our findings provide compelling evidence that ferroptosis is a newly discovered cell death mechanism of diabetic RGCs and Sat1 is novel therapeutic target to counter diabetic RGCs neurodegeneration.

Keywords: diabetic retinopathy, retinal ganglion cells, ferroptosis, SAT1

P2-4 FXR controls insulin content by regulating Foxa2-mediated insulin transcription

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Farnesoid X receptor (FXR) is a nuclear ligand-activated receptor of bile acids that plays a role in the modulation of insulin content. However, the underlying molecular mechanisms remain unclear. Forkhead box a2 (Foxa2) is an important nuclear transcription factor in pancreatic β-cells and is involved in β-cell function. We aimed to explore the signaling mechanism downstream of FXR to regulate insulin content and underscore its association with Foxa2 and insulin gene (*Ins*) transcription. All experiments were conducted on FXR transgenic mice, INS-1 823/13 cells, and diabetic Goto-Kakizaki (GK) rats undergoing sham or Roux-en-Y gastric bypass (RYGB) surgery. Islets from FXR knockout mice and INS-1 823/13 cells with FXR knockdown exhibited substantially lower insulin levels than that of controls. This was accompanied by decreased Foxa2 expression and *Ins* transcription. Conversely, FXR overexpression increased insulin content, concomitant with enhanced Foxa2 expression and *Ins* transcription in INS-1 823/13 cells. Moreover, FXR knockdown reduced FXR recruitment and H3K27 trimethylation in the Foxa2 promoter. Importantly, Foxa2 overexpression abrogated the adverse effects of FXR knockdown on *Ins* transcription and insulin content in INS-1 823/13 cells. Notably, RYGB surgery led to improved insulin content in diabetic GK rats, which was accompanied by upregulated FXR and Foxa2 expression and *Ins* transcription. Collectively, these data suggest that *Foxa2* serves as the target gene of FXR in β-cells and mediates FXR-enhanced *Ins* transcription. Additionally, the upregulated FXR/Foxa2 signaling cascade could contribute to the enhanced insulin content in diabetic GK rats after RYGB.

Keywords: Farnesoid X receptor; Foxa2; Insulin content; Roux-en-Y gastric bypass; Diabetes

P2-5 GPCR 辅助蛋白 MRAP2 介导的 GLP1R 受体信号通路在代谢疾病中的功能探究

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肥胖症是临床常见多发病，病因复杂、减重药物治疗效果有限。下丘脑代谢型 GPCR 中枢调控是研究肥胖发生机制关键突破口。我们前期发现下丘脑神经元中高表达 GPCR 辅助蛋白 MRAP2，其与关键肥胖症治疗靶点 GLP1R 受体在下丘脑中共定位且存在互作，提示 MRAP2 可能参与 GLP1R 介导信号通路。但更为重要的 MRAP2 影响 GLP1R 的功能机制尚未被关注。深入探究 GPCR 调控和作用机理有助于更精准设计个体化 GPCR 靶点药物靶向方案。本研究综合运用单细胞组学、药理功能学、在体基因转染等手段探究 MRAP2 在 GLP1R 信号通路中的调控作用。我们在研究中发现， MRAP2 正调控 GLP1R 的药理学活性，且两者存在生理相关性。此外，MRAP2 通过调控 ERK 信号通路调节 GLP1R 的活性和细胞膜表面运输。我们还发现，MRAP2 的 N 末端是调节 GLP1R 的活性和细胞膜表面运输的主要功能区域。此外，体内实验表明，MRAP2 的下丘脑特异性敲降能够导致小鼠肥胖，能量代谢异常。司美诺肽（MC4R 激动剂）和利拉鲁肽（GLP1R 激动剂）的腹腔给药均能显著降低对照组小鼠食欲和体重，但 MRAP2 下丘脑特异性缺失降低了 GLP1R 活性，从而抑制了利拉鲁肽对 MRAP2 下丘脑敲降组小鼠食欲的急性刺激作用，这提示我们利拉鲁肽作用于中枢 GLP1R 至少是部分通过 MRAP2 发挥作用。综上，本研究从神经元受体及其辅助蛋白角度解析肥胖形成中枢机制，并结合前沿单细胞测序技术揭示了单细胞分辨率下神经元内两者功能相关性。GLP1R 是肥胖症药物开发热门靶点，本研究通过辅助蛋白调控其功能为肥胖症治疗提供新思路。

关键词：肥胖症，下丘脑，单细胞测序，辅助蛋白，胰高血糖素样态 1 受体，利拉鲁肽

P2-6 基于 Micro-CT 和血清非靶向代谢组学方法探究孤立性生长激素缺乏的侏儒大鼠骨微结构受损的机制

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目的：生长激素(GH)/胰岛素样生长因子(IGF1)是影响骨微结构的重要调节因子。生长激素缺乏症(GHD)的临床特征之一是骨密度降低和骨折风险增加。目前对孤立性 GHD 患者（仅 GH 缺乏，其他垂体前叶激素不缺乏）的骨微结构评价不足。本研究通过微计算机断层扫描(Micro-CT)和血清非靶向代谢组学方法，首次在 Lewis 品系侏儒大鼠，一种典型的孤立性 GH 缺乏模型中，探究孤立性 GH 缺乏对骨微结构的影响和可能的作用机制。

方法：测量 Lewis 侏儒纯合子(dw/dw)大鼠(37 周，4 雄 4 雌)、Lewis 侏儒杂合子(dw/+)大鼠(37 周，4 雄 4 雌)的体重、体长(鼻尖到尾尖距离）、左侧股骨质量、直径、和股骨长度。采用 Micro-CT 对左侧股骨的骨微结构进行分析。苏木精&伊红染色(H&E)观察左侧股骨组织学特征。ELISA 法检测血清 IGF-1 和 β-I 型胶原 C- 末端肽(β-CTX)水平。采用全自动生化分析仪测定血清钙(Ca)、磷(P)和总碱性磷酸酶(ALP)水平。采用液相色谱-质谱（LC- MS）方法对大鼠血清进行非靶向代谢组学分析，应用主成分分析法和偏最小二乘判别分析法进行代谢产物分析。通过 KEGG 数据库和 MetaboAnalyst 网站分析代谢物相关代谢通路及生物学意义。

结果：(1)与 dw/+大鼠相比，dw/dw 大鼠体重、体长、左侧股骨质量和长度均显著降低;(2)Micro-CT 结果显示，dw/dw 大鼠骨小梁体积骨密度(Tb.vBMD)减少约 18.0%，骨皮质厚度(Ct.Th)减少约 21.7%($P<0.05$)。这一下降趋势在雌性和雄性均可以发现。此外，dw/dw 大鼠骨体积分数(BV/TV)，骨小梁厚度(Tb.Th)，骨小梁数目(Tb.N)也显著下降;(3) H&E 组织学染色显示，dw/dw 大鼠左侧股骨骨小梁数目更少，分布更稀疏，骨髓脂肪细胞数目更多;(4)dw/dw 大鼠血清 IGF-1 明显降低，血清 ALP 明显升高(P〈0.05)，β-CTX 略有升高（P=0.17），Ca 和 P 无统计学差异;(5)血清 IGF-1 水平与股骨 Micro-CT 检测参数：BV/TV、Tb.vBMD, Tb.Th, Ct.Th 呈正相关;(6)非靶向筛选差异代谢物共 183 个，阳离子模式 134 个，阴离子模式 49 个，其中 2-甲基丁基 β-D-吡喃葡糖苷、甘油磷酸胆碱、醛固酮显著增加;（7）代谢物相关代谢通路结果显示差异的代谢通路主要包括胆汁分泌、类固醇激素生物合成、醛固酮代谢、嘌呤代谢、神经活性配体-受体相互作用等通路。

结论：孤立性 GH 缺乏的 Lewis 品系的侏儒大鼠骨骼微结构受损，骨转换标志物增加，提示 GH/IGF-1 缺乏会导致骨微结构明显破坏。骨微结构的破坏可能与胆汁分泌、类固醇激素生物合成、醛固酮代谢、嘌呤代谢、神经活性配体-受体相互作用等代谢通路异常相关。

关键词：生长激素缺乏；骨骼微结构；Micro CT；非靶向代谢组学

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P2-7 Nerve activity regulates the crosstalk between pancreatic islet β cells and residential macrophages

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Pancreatic islets are richly supplied with nerve fibers from pancreatic neurons and the nervous innervation modulates islet functions. Residential macrophages were discovered in pancreatic islets recent years and they exert a significant impact on the homeostasis and adaptation of pancreatic endocrine cells under normal physiological state or pathological state. Nervous system has been found to have tight morphological and functional relationship with macrophages in GI tract. However, in pancreatic islets, whether pancreatic nerves have any impact on the activity of the residential macrophages and on the macrophage-modulated endocrine cell homeostasis is still unknown. Therefore, in this study, we used neuron-islet complexes to explore the activity of the residential macrophages under nervous control, and investigated the possible communication mechanism between nerves and macrophages.

Method： Experiments were performed in either sex Sprague Dawley rats at an age of seven and eight weeks. After rats being anesthetized with Urethan, pancreas was digested with collagenase V and the neuron-islet complexes and islets were extracted. The immunofluorescent staining of Tuj1 or F4/80 was utilized to determine neurons or macrophages. Nicotinic receptor agonist nicotine tartrate was used to activate neurons, and TNF-α, IL-1β, ATP and insulin were measured with enzyme-linked immunosorbent assay.

Results： The average number of neurons in each neuron-islet complex was 6.17±0.98 and there was no significant difference in the numbers of F4/80 positive cells between the islet group and the neuron-islet complex group. Activating neurons in neuron-islet complexes with nicotine tartrate, insulin and ATP levels were elevated significantly. There was no significant change in islet group with nicotine tartrate. With nicotine tartrate, the pro-inflammatory factors TNF-α and IL-1β were significantly increased in the neuron-islet complex but not in the islet group indicating that the activity of macrophages was enhanced by nerves. ATP has been identified to mediate macrophage activity. Therefore, suramin, a none-selective ATP receptor blocker, was used to block the activation of ATP in macrophages. With the presence of suramin, we discovered that nicotine tartrate failed to increase the TNF-α level or IL-1β level any more in the neuron-islet complexes.

Conclusion： Our results revealed that the neuron excitation enhanced the pro-inflammatory factors secretion from islet-residential macrophages through β cell-ATP-macrophage route, suggesting that nerve activity participates in the process of islet homeostasis by regulating crosstalk between islet β cells and macrophages.

Keywords: pancreatic nerve activity, neuron-islet complex, β cell, macrophage, ATP

P2-8 db/db 小鼠肝脏脂滴和线粒体相互作用机制研究

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目的：最新研究表明肝细胞中脂滴代谢水平与脂滴和线粒体相互作用机制密切相关。本研究对比正常小鼠与 2 型糖尿病模型 db /db 小鼠肝脏脂质沉积程度，旨在探究 2 型糖尿病小鼠肝脏脂质沉积过程中脂滴与线粒体的互作机制。

方法：取 7 周龄 BKS 雄性小鼠为对照组（WT 组，n=9）BKS-db/db 雄性小鼠为实验组（DB 组，n=9），每组随机选取 6 只小鼠眼球取血，检测血脂四项；经生理盐水灌注后，取 3 只小鼠肝脏制作冰冻切片样本，用于油红 O 和 HE 染色；3 只参考 Jennifer 等人棕色脂肪脂滴与线粒体提取方法，取肝脏研磨后 900g 离心，上层白色脂滴层清洗后提取脂滴（Fat layer，FL）；中间层 9000g 离心后取沉淀重悬提取胞浆线粒体（Cytoplasmic mitochondria，CM）。对 FL 和 CM 进行油红 O 和詹姆斯绿染色；免疫印迹法检测 FL 和 CM 中 VDAC、ATGL、Plin5 和 Plin2 在中的表达水平。剩余 3 只小鼠，提取肝脏原代细胞，进行油红 O 和詹姆斯绿染色。

结果：1.与 WT 组相比，DB 组血清中 TG、CHOL、HDL-C 和 LDL-C 浓度显著升高（p＜0.05）；肝脏脂质沉积严重，肝细胞内堆积大量橘红色脂滴且有较多线粒体围绕。2.两组 CM 中线粒体呈绿色，且有少量细小的橘红色脂滴；WT 组 FL 中脂滴小且线粒体少，DB 组 FL 中脂滴较大较多且线粒体含量较多。3.WT 组中 FL 与 CM 相比，VDAC 和 Plin5 表达量显著性降低；Plin2 表达量极显著性升高（p<0.05），DB 组中 FL 与 CM 相比，VDAC 和 Plin5 表达量没有显著性差异（p>0.05）；ATGL 和 Plin2 表达量显著性升高（p<0.05），与 WT 组 CM 相比，DB 组 CM 的 Plin5 表达量显著降低（p<0.05）；Plin2 表达量显著升高（p<0.05），与 WT 组 FL 相比，DB 组 FL 的 VDAC、Plin5、ATGL 和 Plin2 表达量显著升高（p<0.05）。

结论：肝细胞内线粒体或均具备与脂滴相互作用的功能；在 2 型糖尿病小鼠肝脏脂质沉积过程中，线粒体与脂滴的相互作用可能是促进脂滴合成代谢增加和体积扩张的重要机制。

关键词：脂滴、线粒体、肝脏、db/db 小鼠

P2-9 The effects and mechanism of dapagliflozin in regulating fibrogenic factor 21 on white adipose tissue browning

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Purpose: Obesity is associated with various metabolic disorders, imposing a significant

burden on patients and society. The emergence of the "browning" phenomenon in white adipose tissue (WAT) has become a promising therapeutic strategy to counter metabolic dysfunction. The anti-diabetic drug dapagliflozin (DAPA) is believed to promote "browning", but its specific mechanism is still unclear. In this study, we observed the effect of dapagliflozin on regulating fibroblast growth factor 21 to promote "browning" in obese mice and improve metabolic disorders caused by obesity through a combination of in vivo and in vitro experiments.

Method: In vivo experiment: Adult male C57BL/6 mice at the age of four weeks were housed in cages with a temperature of 22-24 ℃, humidity of 50%, and a 12-hour light-dark cycle. They had ad libitum access to food and water. The mice were randomly divided into three groups (n=6): (1) Normal diet (ND) + saline injection, (2) High-fat diet containing 60% kilocalories from fat + saline injection, and (3) High-fat diet containing 60% kilocalories from fat + DAPA injection (HFD+DAPA, 1mg/kg/day). The treatment started from the 5th week and lasted until the 10th week. The mice were weighed weekly, and after the treatment, glucose tolerance tests were performed. The mice were then anesthetized, and blood samples were collected from the orbital cavity. The mice were euthanized immediately after. Liver, epididymal white adipose tissue (eWAT), inguinal white adipose tissue (iWAT), and brown adipose tissue (BAT) were collected for mRNA or Western blot experiments. H&E staining and immunohistochemical analysis were performed. In vitro experiment: 3T3-L1 cells were induced to differentiate into mature adipocytes, and cells were collected for qPCR, Western blotting, immunofluorescence, mitochondrial staining, Oil Red O staining, CCK8 assay, and validation of signaling pathways after different treatment methods during the induction process.

Results: (1) Dapagliflozin can improve obesity induced by HFD in mice; (2) Dapagliflozin can regulate browning of white adipose tissue both internally and externally, as well as activate brown adipose tissue; (3) Dapagliflozin can regulate the levels of fibroblast growth factor 21 (FGF21) and its receptor complex internally and externally, and promote browning by targeting FGF21; (4) Dapagliflozin may partially promote browning through the FGF21-LKB1-AMPK signaling pathway.

Conclusion: Dapagliflozin can improve metabolic disorders caused by obesity by promoting "browning" through the upregulation of fibroblast growth factor 21 (FGF21). We found that dapagliflozin regulates the molecular targets and mechanisms of thermogenic markers expression in 3T3-L1 cells, at least through the FGF21/AMPK pathway. This mechanism may contribute to improving glucose metabolism and weight management in obese diabetic patients. Further research is necessary to fully understand the molecular mechanisms involved and explore the clinical significance of these findings.

Keywords: Dapagliflozin, obesity, FGF21, White adipose tissue browning, LKB1, AMPK

P2-10 维生素 D 缺乏对肥胖小鼠脂代谢的影响

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研究目的：目前，我国居民超重和肥胖的问题日趋严重，超重和肥胖的患病率分别为34.3%和 16.4%。肥胖可引起机体脂代谢紊乱及炎症并危害人类健康。临床数据显示，肥胖患者体内的维生素 D 含量普遍较低，患维生素 D 缺乏症的风险也远高于正常人群。维生素 D 水平与机体脂代谢密切相关，而维生素 D 缺乏是否会加重肥胖引起的脂代谢紊乱还有待探究。本研究的目的是通过构建肥胖和维生素 D 缺乏小鼠模型，来探究维生素 D 缺乏对肥胖小鼠脂代谢的影响。

研究方法：3 周龄 C57BL/6J 雄鼠 24 只，分为对照组（C）、高脂组（HF）、维生素 D 缺乏组（VDD）和高脂维生素 D 缺乏组（HV），分别喂养普通饲料（1000IU VD/kg，脂肪供能 10%），高脂饲料（1000IU VD/kg，脂肪供能 60%），维生素 D 缺乏饲料（0 IU VD/kg，脂肪供能 10%）和高脂维生素 D 缺乏饲料（0 IU VD/kg，脂肪供能占 60%）。12 周后，记录小鼠体重并检测各项血脂指标。使用 SPSS26.0 软件进行单因素方差分析、LSD 事后检验，以 $p<0.05$ 表示具有统计学差异。

研究结果：1、 VDD 组（16.10±2.37nmol/L）和 HV 组（18.72±1.24 nmol/L）小鼠的 25（OH）D 水平均＜50nmol/L，HF 组和 HV 组小鼠体重均高于 C 组小鼠 20%，判定肥胖和维生素 D 缺乏小鼠模型构建成功。2、血脂方面：（1）TC：与 C 组小鼠（2.48±0.22 mmol/L）相比，VDD 组（3.30±0.60 mmol/L, $p<0.05$）、HF 组（4.16±0.69 mmol/L, $p<0.01$）和 HV 组（4.49±0.39 mmol/L, $p<0.01$）小鼠明显更高。与 VDD 组小鼠相比，HF 组($p<0.05$)和 HV 组($p<0.01$)小鼠明显更高。（2）TG：与 C 组小鼠（0.90±0.15mmol/L）相比，VDD 组小鼠（1.14±0.18 mmol/L, $p<0.05$）明显更高，而其他组之间无显著性差异。（3）LDL：与 C 组小鼠（1.35±0.24 mmol/L）相比，HF 组（3.56±0.79 mmol/L, $p<0.01$）和 HV 组（2.59±0.30 mmol/L, $p<0.05$）小鼠明显更高。与 VDD 组小鼠（1.88±0.28 mmol/L）相比，HF 组小鼠明显更高（$p<0.05$）。（4）HDL：各组小鼠之间均无显著性差异。

研究结论：肥胖和维生素 D 缺乏均可引起机体脂代谢紊乱，但二者的联合并未产生叠加效应，这是否与时间长短及机体的代偿反应有关，还有待于进一步探究。

关键词：肥胖，维生素 D 缺乏，脂代谢

P2-11 草鱼 glp-1r 克隆、序列分析及其基因表达的调节

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胰高血糖素样肽 1（GLP-1）通过与其受体（GLP-1R）特异性结合在血糖调节方面发挥重要作用。为研究 GLP-1R 在鱼体内的生理功能，从草鱼前肠中克隆了 GLP-1R 基因。草鱼 GLP-1R 基因 cDNA 序列全长为 2651bp，编码 523 个氨基酸，在 N 端具有 19 个氨基酸残基的信号肽序列，24 个磷酸化位点、3 个 N 糖基化位点、7 个跨膜区，是一种不稳定的疏水性 G 蛋白偶联受体；氨基酸多序列比对及系统进化树分析结果显示，其与金鱼 *glp-1r* 亲缘关系最近；二级及三级结构分析结果显示，螺旋和 loop 区是草鱼 GLP1R 的主要结构元件，且以 α-螺旋为主，其亚细胞定位在质膜。Real-time PCR 结果表明，草鱼 glp-1r 在多个组织中均有表达，但在前肠和脑中表达最高。葡萄糖腹腔注射实验结果表明，草鱼血浆葡萄糖在 1h 达到峰值，3h 恢复到基础水平；草鱼前肠钠依赖型葡萄糖转运蛋白 1（*sglt1*）和葡萄糖转运蛋白 2（*glut2*）在 1h 的表达水平显著高于 0h 和 3h，而 *glp-1r* 的表达水平却随着葡萄糖的注射而显著降低。这表明 GLP-1R 在鱼类中的作用可能与在哺乳动物中截然不同，在鱼类中并不起降血糖的作用。本研究结果初步阐明了 GLP-1R 在鱼类中的生理功能，为探究 GLP-1R 调节鱼类糖代谢的机制提供理论依据。

关键词：草鱼；*Glp-1r*；鉴定；表达分析

P2-12 LIPC-514C/T 多态性与运动干预 PDM 人群健康体适能疗效的关联研究

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目的：研究肝脂肪酶基因（Hepatic lipase deficiency gene，LIPC）多态性与运动干预糖尿病前期（PDM）人群健康体适能变化敏感性的关联，寻找与糖代谢异常运动敏感性相关的分子标记。

方法：2022 年 1 月至 9 月期间，招募 32 名 PDM 患者，进行为期 12 周中等强度有氧（运动强度：40-59%VO_2max；运动方式：健身操；运动频率：3 次/周；运动时间：40-60 min）结合抗阻运动（运动强度：50%-69%1RM；运动方式：弹力带；运动频率：2 次/周；运动组数：10-15RM，2-3 组）干预。运动干预前后测试最大摄氧量、握力、纵跳、俯卧撑、身体成分、坐位体前屈及空腹血糖（FPG）、糖化血红蛋白（HbA1c），应用 SNP 微阵列芯片对唾液 LIPC-514C/T 位点进行解析，使用 SPSS26.0 对比不同 LIPC-514C/T 基因型 PDM 患者健康体适能疗效指标的差异。

结果：（1）LIPC-514C/T 位点 CC 基因型占 37.5%，CT 基因型占 50.0%，TT 基因型占 12.5%，CT/TT 占 62.5%，基因频率分布符合 H-W 平衡（P>0.05）。（2）运动干预前，LIPC-514C/T 基因型与健康体适能、FPG、HbA1c，均无统计学差异（P>0.05）。（3）12 周运动干

预后 FPG、HbA1c、体重、BMI、内脏脂肪重量均较干预前明显下降（P<0.05），肌肉重量、最大摄氧量、握力、纵跳、俯卧撑、坐位体前屈较干预前明显增加（P<0.05）。（3）运动干预前后 CC 型 FPG、体重、BMI、肌肉重量、内脏脂肪重量、握力变化差值明显大于 CT/TT 型（P<0.05），其余指标无差异（P>0.05）。

结论：12 周中等强度有氧结合抗阻力量训练可改善糖尿病前期患者血糖和健康体适能水平，LIPC-514C/T 位点 CC 型运动干预的敏感性优于 CT/TT 型，LIPC-514C/T 位点可用于评价糖代谢异常人群运动干预疗效的分子标记。

关键词：LIPC；基因多态性；糖尿病前期；健康体适能；运动敏感性；遗传标记

P2-13 Roux-en-Y Gastric bypass surgery improves metabolism by up-regulating Nesfatin-1 and activating AMPK/PGC-1α/UCP1 pathway to induce white fat browning

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Background Roux-en-Y Gastric bypass surgery (RYGB) is a promising treatment for obesity and type 2 diabetes mellitus (T2DM) that effectively ameliorates glucose and lipid metabolism disorders. One of the key physiological processes involved is the transformation of white fat into brown fat, known as white fat browning, wherein UCP1 and PGC-1α play essential roles as markers. Previous research has revealed that RYGB significantly promotes white fat browning, thereby enhancing brown fat thermogenesis and improving glucose and lipid metabolism. Nevertheless, the underlying mechanisms warrant further investigation. Notably, our research group has observed a significant increase in the brain-gut peptide Nesfatin-1 following RYGB surgery. Hence, we hypothesize that metabolic surgery augments white fat browning and brown fat thermogenesis through Nesfatin-1 upregulation and the activation of the AMPK/PGC-1α/UCP1 pathway.

Methods Male C57 BL/6J mice were fed a high-fat diet for 21 days to establish an obese mouse model with type 2 diabetes. A control group was also established. After successful modeling, the mice were divided into different groups: model, sham operation, RYGB, Nesfatin-1,

and metformin positive control groups. Weekly assessments of body weight and food intake were conducted, and oral glucose tolerance tests (OGTT) and insulin tolerance tests (ITT) were performed to monitor blood sugar levels. Plasma and triglyceride changes, serum Nesfatin-1, insulin, and related hormones were measured. Histomorphological analyses of adipose tissue evaluated morphological changes, while molecular biology assays assessed white fat browning and heat production indicators like PGC-1α and UCP1. Additional groups were established to explore the signaling pathway: blank control, surgery, and Nesfatin-1 inhibitor + surgery groups. Tissue samples were processed, and Western blot experiments detected PGC-1α, UCP1, and other white fat browning and heat production indicators.

Results The obese type 2 diabetes model mice exhibited significantly higher body weight and blood glucose levels compared to the control group. Following RYGB surgery in the model group, the mice showed marked improvements in body weight, OGTT, and ITT levels, and Nesfatin-1 expression was significantly up-regulated ($P<0.05$, $P<0.01$). Additionally, HE staining of white fat revealed characteristics associated with brown fat. Western blot experiments demonstrated significant upregulation of PGC1-α and UCP1 protein expression in white fat ($P<0.05$, $P<0.01$).

Conclusion RYGB stimulates white fat browning and brown fat thermogenesis through the upregulation of Nesfatin-1 and activation of the AMPK/PGC-1α/UCP1 pathway.

Key words: metabolic surgery; white fat; brown fat; Nesfatin-1

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P2-14 RYGB surgery suppresses ferroptosis via the PI3K / AKT / mTOR signaling pathway to improve nonalcoholic fatty liver disease

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Background: With the global prevalence of obesity and the associated metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) has become one of the most common chronic liver diseases. Abnormal lipid peroxide metabolism, accumulation of reactive oxygen species (ROS) and ER stress are often considered central factors in the development of NAFLD. Ferrotosis is the first form of cell death in NAFLD. It (Ferrotosis) is a new non-apoptotic cell death characterized by abnormal increased concentration of intracellular iron, abnormal accumulation of reactive oxygen species (ROS), and inhibition of lipid peroxide scavenger GPX 4. Existing studies suggest that ferroptosis of hepatocytes and hepatic macrophages may contribute to the development of NAFLD. Inhibition of intrahepatic ferroptosis may be a new therapeutic approach for treating NAFLD. There are no clear drugs for the treatment of NAFLD, and metabolic surgery is a very effective method. Gastric bypass surgery (RYGB) is the "gold standard" procedure for weight loss and diabetes mellitus, which can affect the lipid accumulation in the liver by changing the physiological changes of the gastrointestinal tract, and then improve NAFLD. Although the improvement effect of RYGB surgery on NAFLD is very significant, the mechanism is not well defined. In previous studies, we found that the PI3K / AKT / mTOR pathway plays a crucial role in lipid metabolism, and we found that the ferroptosis inhibitor GPX 4 is activated after intracellular activation of this signaling pathway.

Objective: To investigate whether RYGB improves NAFLD by inhibiting intrahepatic cell ferroptosis and to investigate whether it is related to the PI3K / AKT / mTOR signaling pathway.

Methods: After 4 to 5 weeks old C57BL / 6J males for 16 weeks of high-fat diet, the surgical group and metformin group were treated for one month. Normal control group, sham surgery group, gastric bypass surgery (RYGB) group, and metformin positive control group were established. Test the body weight; Specific gravity of the liver body, Liver pathological changes were observed with hematoxylin-eosin (H & E) staining and oil red O staining; Blood glucose detection using an oral glucose tolerance test (OGTT), Insulin levels were measured by using an insulin tolerance test; The liver and serum levels of malondialdehyde, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) / high-density lipoprotein cholesterol (HDL-C) were determined by ELISA; Index of liver injury, alanine transaminotransferase (ALTase), aspartate transaminotransferase (ASTase), and uric acid serum levels, Glucose, leptin, and adiponectin serum levels; The expression of GPX 4 was detected by immunohistochemistry and immunofluorescence; Western Blot Determine the expression levels of GPX 4, COX 2, ACSL 4, PI3K, AKT, and mTOR; The mRNA of the proinflammatory cytokines TNF- α, IL-1 β, and IL-6 was detected quantitatively; Iron ion concentration.

Results: After induced by high-fat diet caused NAFLD model. Higher blood glucose concentration and higher serum TG, TC, SF, and FFA concentrations; higher TG and TC content in the liver. After RYGB, the obese phenotype of NAFLD mice was significantly improved; hepatic steatosis decreased significantly; serum TG, TC, SF, FFA levels and liver TG and TC concentrations decreased significantly; ALT and AST levels decreased significantly; glucose tolerance improved without affecting food intake; and insulin resistance was improved significantly. This suggests that RYGB effectively improved the pathological manifestations and associated metabolic indicators of NAFLD. The expression level of markers such as the ferroptosis inhibitor GPX 4 was significantly altered in hepatocytes and hepatic macrophages, and the PI3K / AKT / mTOR signaling pathway was activated. This suggests that RYGB may inhibit ferroptosis through the PI3K / AKT / mTOR signaling pathway.

Conclusion: RYGB surgery may inhibit ferroptosis through PI3K / AKT / mTOR signaling pathway, which provides a new rationale for explaining the treatment of metabolic surgery for NAFLD.

Key words: NAFLD, RYGB, and ferroptosis

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P2-15 RYGB surgery improves obese type 2 diabetes by inhibiting jejunal GLUT 2 levels with Nesfatin-1

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Objective： Roux-en-Y gastric bypass (RYGB) is a classic metabolic procedure for obesity and type 2 diabetes, but the mechanism is unclear. The level of the gastrointestinal hormone

Nesfatin-1 increased significantly after RYGB surgery. The purpose of this study is to elucidate the specific mechanism by which RYGB suppresses glucose transporter 2 (GLUT 2) expression of the jejunum by upregulating Nesfatin-1, reducing glucose absorption and thereby improving obesity and reducing blood glucose.

Methods: A C57BL / 6J mouse model of obesity with type 2 diabetes was established on high-fat diet for 16 weeks. They underwent sham surgery, RYGB surgery and Nesfatin-1 subcutaneous pump, and normal control group was treated for 8 weeks. During this period, body weight, OGTT, ITT and food intake were measured, and after 8 weeks, the level of glucose and lipid metabolism and GLUT 2 in jejunum.

Results: Both RYGB and Nesfatin-1 groups could effectively improve glucose and fat metabolism and reduce body weight in obese mice induced by HFD. The results of OTT and IGTT experiments showed that the blood glucose level was significantly reduced in the RYGB and Nesfatin-1 group mice, suggesting improved glucose uptake in insulin target organs. The jejunal morphology changes observed by H & E staining significantly increased the number of small intestinal villi in the RYGB and Nesfatin-1 groups compared with the sham group. The results of immunohistochemistry experiments showed that GLUT 2 was highly expressed in the apical membrane of small intestinal epithelial cells of the jejunal group, while the expression of GLUT 2 decreased after RYGB surgical treatment or Nesfatin-1 given by buried pump. Further, GLUT2mRNA expression in the epithelial cells of the jejunum by RT-PCR, and GLUT 2 protein content by Western Blot showed that the GLUT 2 expression decreased in the RYGB and Nesfatin-1 groups compared with the sham group.

Conclusion: RYGB surgery inhibited the expression of jejunal apical membrane GLUT 2 by increasing Nesfatin-1, thus reducing small intestinal glucose absorption, improving glucose metabolism and systemic insulin resistance, reducing blood glucose and improving obesity in diabetic mice.

Key words: gastric bypass surgery, Nesfatin-1, apical membrane GLUT 2, glucose metabolism, improvement of obesity

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P2-16 Effect and mechanism of vertical sleeve gastrectomy in improving skeletal muscle insulin resistance in mice with polycystic ovary syndrome by regulating IGF-1

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Background This study aims to investigate the effect and mechanism of Vertical Sleeve Gastrectomy (VSG) on improving skeletal muscle insulin sensitivity in a mouse model of Polycystic Ovary Syndrome (PCOS). PCOS is a common endocrine disorder in women, characterized by obesity and insulin resistance (IR). VSG is a highly effective bariatric surgery known for achieving long-term weight loss and improving insulin resistance in patients with type 2 diabetes mellitus (T2DM). Insulin-like polypeptide substance (IGF-1) plays a crucial role in enhancing skeletal muscle insulin sensitivity. While previous research has shown that VSG surgery can up-regulate IGF-1 levels, the specific mechanism by which it improves skeletal muscle insulin resistance remains unclear. By intervening in the PCOS mouse model through VSG surgery, this study aims to elucidate the impact and underlying mechanism of VSG in enhancing skeletal muscle insulin sensitivity by regulating IGF-1.

Methods C57 BL/6J female mice aged 4 to 5 weeks were used to establish a PCOS model by administering letrozole (1 mg/kg/d) combined with a high-fat diet for 21 days. A control group was also established. After successful modeling, the mice were divided into four groups: PCOS model group, Vertical Sleeve Gastrectomy (VSG) operation group, metformin positive control group, and sham operation group. Various measurements were taken, including body weight and food intake, oral glucose tolerance test (OGTT), and insulin tolerance test (ITT) to assess glucose metabolism. Additionally, ELISA kits were used to measure serum IGF-1 and other related hormones. Skeletal muscle tissue morphology was analyzed using HE staining and Masson staining. Changes in indicators like IGF-1, GLUT4, and FOXO1 were detected using Western Blot and qPCR methods. To investigate the role of IGF-1 through the IGF1R-PI3K-Akt and IGF1R-Ras-MAPK signaling pathways, C2C12 cell lines were cultured in high-glucose DMEM

(containing 15% FBS) and combined with palmitic acid to induce insulin resistance models. The CCK8 method was used to assess the effect of palmitic acid on C2C12 cell proliferation. The cell groups were categorized as follows: blank control group, insulin resistance (IR) group, IGF-1 agonist+IR group, and IGF-1 inhibitor+IR group. Real-time PCR was used to measure GLUT4 mRNA expression, and Western Blot was utilized to assess the expression of IGF-1, GLUT4, FOXO1, and other factors.

Results After VSG treatment, mice in the PCOS model group showed significant improvements in body weight, OGTT, and ITT levels. Additionally, their skeletal muscle fibers exhibited a well-organized and compact structure with reduced collagen fibers. Furthermore, the levels of IGF-1 and GLUT-4 in skeletal muscles were significantly increased, along with up-regulated protein expression. Conversely, FOXO1 protein expression was decreased. qPCR results indicated a significant up-regulation of IGF-1 and GLUT4 gene mRNA expression, while the mRNA expression of the FOXO1 gene was significantly down-regulated. In the cell experiments, adding an IGF-1 agonist to the culture medium reduced glucose concentration in the supernatant and caused obvious muscle cell contractions under the microscope. Compared to the IGF-1 agonist+IR group, the IGF-1 inhibitor+IR group showed significantly decreased expression levels of IGF-1, GLUT4, p-IRS-1 protein, and GLUT4 mRNA. Conversely, the expression level of FOXO1 protein was significantly increased.

Conclusion VSG surgery improves skeletal muscle insulin resistance in PCOS mice, potentially through the IGF1R-PI3K-Akt and IGF1R-Ras-MAPK signaling pathways.

Key words: vertical sleeve gastrectomy; IGF-1; skeletal muscle insulin resistance;

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P2-17 神经肽 CRF 参与高原低氧下炎症反应

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低氧是高原环境的主要特征，在高原低氧环境中，机体会出现功能失调。人类从平原前往高原地区，容易发生急性高原反应，严重者会发展成高原脑水肿和肺水肿，危及生命。高原低氧引起的免疫功能失调与高原低氧相关疾病的发生发展密切相关，但其机制未被完全阐

述清楚。应激调节激素促肾上腺皮质激素释放因子 CRF 及其受体 CRFR1 和 CRFR2 在各类免疫细胞中表达，参与调节多种免疫炎症反应。实验室已证明 CRFR1 参与调节高原低氧炎症反应。高原低氧下 CRF 通过作用于哪些免疫细胞引起免疫功能变化，需进一步研究。脾脏是机体最大的次级免疫器官，在局部和全身性免疫调节中发挥重要作用，研究急慢性低氧对脾脏生理功能的影响，可以为进一步揭示高原低氧影响免疫系统功能的相关分子机制奠定基础。而小胶质细胞是大脑常驻巨噬细胞，能够通过与星形胶质细胞相互作用显著影响神经炎症过程，二者又是神经血管单元和血脑屏障的组成部分。实验室前期工作证明 CRF 激活小胶的炎症反应，小胶和星胶共同参与高原脑水肿的发生。研究 CRF 神经元、小胶和星胶在大脑中的分布，探究急性低氧暴露后小胶和星胶在大脑中的变化，有助于阐明它们在高原低氧脑水肿发生中的作用和机制。

我们通过构建小鼠低氧模型，利用转录组测序、流式细胞术、免疫组化和单细胞测序技术，探究急慢性低氧对中枢和外周免疫功能的影响以及 CRF-CRFR1 信号通路在其中的作用。研究表明急性低氧暴露可能增强脾脏造血功能，破坏 DNA 损伤修复系统，抑制 T 细胞介导的免疫功能。慢性低氧可能抑制机体血管生成，抑制炎症反应。急性低氧导致脾脏 CD4+ T / CD8+ T 下调，可能增加感染性疾病的易感性。CRF - CRFR1 参与急性低氧诱导的脾脏 CD11b+ F4/80+巨噬细胞炎症反应。急性低氧后下丘脑炎症反应部分通过 CRF - CRFR1 调节，各脑区的小胶和星胶增多，提示它们可能参与高原低氧诱导的炎症反应和血脑屏障破坏。

关键字：低氧，CRF，免疫，炎症反应，小胶质细胞，星形胶质细胞

P2-18 视前正中核在精氨酸加压素诱导升温中的作用及机制研究

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精氨酸加压素（Arginine vasopressin，AVP）是由下丘脑室旁核、视上核神经元合成的一种九肽物质，发挥激素和神经递质的作用。传统观点认为 AVP 具有降低体温的作用。但最近有研究报道，侧脑室给予 AVP 会引起体温升高，作用靶区和具体机制尚不清楚。视前正中核（Median Preoptic nucleus MnPO）在体温调节中发挥重要作用。本研究中，我们利用脑立体定位技术向 MnPO 微量注射 AVP 及相关受体阻断剂，观察棕色脂肪温度、核心温度变化情况。我们发现 MnPO 注射 AVP 可先引起小鼠棕色脂肪温度升高，继而核心温度升高，且具有剂量依赖性。此外，我们发现 Glu 受体阻断剂、AVP V_{1a} 受体阻断剂可完全阻断 AVP 的升温效应，但 AVP V_{1b} 受体阻断剂、催产素受体阻断剂、$GABA_A$ 受体阻断剂不能阻断 AVP 的升温效应。我们还利用免疫组织化学双标染色发现，MnPO 表达谷氨酸受体的神经元同时

也表达 AVP V_{1a} 受体。这些结果表明，AVP 可能通过激活 MnPO 神经元 AVP V_{1a} 受体和 Glu 受体诱导小鼠棕色脂肪产热，从而引起小鼠核心温度升高。

关键词：精氨酸加压素 视前正中核

P2-19 Paeoniflorin relieves arterial stiffness induced by a high-fat/high-sugar diet by disrupting the YAP-PPM1B interaction

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Rationale: Arterial stiffness is closely associated with metabolic syndrome, which is a group of cardiovascular risk factors. High-fat/high-sugar (HFHS) diet enhances transforming growth factor (TGF)β-activated Smad2/3 phosphorylation in arteries. previous research showed that PPM1B is a YAP-bound phosphatase that is translocated into the nucleus to dephosphorylate Smads in response to TGFβ. However, this process is inhibited by YAP by the removal of the K63-linked ubiquitin chain of PPM1B at K326. Therefore, effective inhibition of the interaction between YAP and PPM1B can effectively inhibit the development of arterial stiffness.

Objective: To identify a potential inhibitor of the YAP-PPM1B interaction from a library of 1,045s FDA-approved drug.

Methods and Results: We found that paeoniflorin showed no significant cytotoxicity and inhibited the YAP-PPM1B interaction at a median inhibitory concentration (IC50) of 4.797μM. Biolayer interferometry experiments demonstrated a binding between paeoniflorin and the YAP-CC domain with an affinity of 4.05e×10-5M. Moreover, surface plasmon resonance analysis of PPM1B proteins covalently immobilized on a CM5 sensor chip, which was first saturated with YAP-CC domian peptide before the addition of paeoniflorin, revealed the inhibitory effect of paeoniflorin on the interaction between peptide and PPM1B. Immunoprecipitation analysis showed that paeoniflorin significantly reduced the YAP-PPM1B interaction, suggesting that paeoniflorin inhibited the PPM1B-YAP interaction.

Conclusions: Our research shows that paeoniflorin disrupted the interaction of YAP and PPM1B and subsequently inhibiting the prolonged activation of the TGF-β pathway.

Key words: Arterial stiffness;PPM1B;YAP; Paeoniflorin

P2-20 Increased COX6A2 promotes pancreatic β-cell apoptosis via modulation of Cyclophilin F

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Pancreatic β-cell apoptosis plays a key role in the development of type 2 diabetes. COX6A2 (Cytochrome c oxidase subunit Ⅵ A2), one of the subunits of cytochrome c oxidase, is expressed in β-cells, but its function is not fully understood. We, for the first time, found that COX6A2 expression is increased in diabetic β-cells. It is noteworthy that overexpression of COX6A2 promoted β-cell apoptosis; by contrast, decreased COX6A2 suppressed β-cell apoptosis and hyperglycemia in diabetic GK rats, suggesting that COX6A2 is implicated in the regulation of β-cell apoptosis in diabetes. Further studies found that increased COX6A2 bound to and upregulated Cyclophilin F expression, thereby promoting the release of cytochrome c from mitochondria to cytoplasm and hence β-cell apoptosis. These results will shed light on revealing the molecular mechanisms of COX6A2-mediated β-cell apoptosis in type 2 diabetes.

Keywords: β-cell apoptosis, COX6A2, type 2 diabetes

P2-21 Nesfatin-1 改善 DSS 诱导的小鼠溃疡性结肠炎

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Nesfatin-1 是一种胃分泌的厌食神经肽，据报道它可以抑制食物摄入和改善糖脂代谢。实验室前期研究发现 Nesfatin-1 对高脂饮食小鼠小肠远端粘膜屏障具有保护作用，然而其对结肠炎的影响尚未系统深入的探索。本研究以葡聚糖硫酸钠诱导（Dextran Sulfate Sodium Salt，DSS）的溃疡性结肠炎小鼠为模型，探究 Nesfatin-1 对溃疡性结肠炎症状的改善作用。将 32 只 C57BL/6 小鼠随机分为 4 组，即对照组、结肠炎组、低剂量组（30μg/kg）和高剂量组（60μg/kg），低剂量和高剂量组在造模前提前给药 7 天，对照组小鼠常规饲养及饮水，其他三组每天在饮用水中添加 2%的 DSS 构建溃疡性结肠炎模型，造模持续 7 天。实验结束后收集小鼠结肠组织和粪便样品，进行病理学评价和肠道菌群分析。结果显示，与对照组相比，腹腔注射 Nesfatin-1 低剂量和高剂量组均能够缓解小鼠体重降低，增加小鼠结肠长度，显著改善小鼠疾病活动指数评分。此外，Nesfatin-1 处理的结肠组织炎症 M1 型促炎极化基因（Il1β、Il6、Tnfα、Mcp1）显著降低，M2 型抑炎极化基因（Il10、Arg1）显著增加。结肠组织病理

学结果显示，Nesfatin-1 处理显著降低小鼠结肠组织病理学评分，炎症 F4/80 染色显著减少，杯状细胞显著增加。总之，Nesfatin-1 能改善 DSS 诱导的小鼠结肠炎，其机制可能与抑制结肠局部炎症、保护杯状细胞和影响肠道菌群有关，本研究可能为溃疡性结肠炎提供新的治疗靶点。

关键词：Nesfatin-1 内分泌激素 结肠炎 杯状细胞 肠道菌群

P2-22 对羟基苯甲酸依赖肠道微生物改善粘膜屏障缓解结肠炎

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炎症性肠病（IBD）是一种慢性肠道炎症性疾病，其特征是肠道炎症细胞浸润和肠黏膜损伤。饮食对于 IBD 发病机制的影响尚未完全清楚。对羟基苯甲酸（p-hydroxybenzoic acid，HA）是一种主要肠道菌群的代谢物并可从日常膳食中获得，在本研究中，我们探讨了 HA 对 DSS 诱导结肠炎的治疗效果。HA 干预有效缓解了 DSS 诱导的结肠炎，减轻了炎症，增强了黏膜屏障功能，具体表现为杯状细胞数量和 MUC2 的增加。这些作用很大程度上依赖于肠道微生物，因为使用抗生素处理明显减弱了 HA 改善结肠炎的作用。另一方面，用 HA 治疗后的结肠炎小鼠的肠道微生物移植明显减轻了 DSS 诱导的结肠炎。综上所述，我们的研究表明，HA 通过以肠道微生物为依赖方式改善黏膜屏障来改善 DSS 诱导的结肠炎。这项研究为预防和治疗 IBD 提供了新的膳食干预思路。

关键字：结肠炎，杯状细胞，肠道微生物，黏膜屏障，对羟基苯甲酸

P2-23 肝脏 LGR4 加重胆汁淤积引起的肝损伤

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摘要：目前对胆汁淤积引起的肝损伤的机制研究仍不够全面，临床治疗干预策略十分有限。富含亮氨酸的重复 G 蛋白偶联受体 4 (LGR4)，又称为 GPR48，对于细胞保护和细胞增殖至关重要，但其在胆汁淤积肝损伤中的作用尚不明确。在本研究中，我们发现 LGR4 在胆汁淤积性肝损伤中的新功能。在胆管结扎（BDL）诱导的胆汁淤积性肝损伤模型中，肝脏 LGR4 的表达显著下调。肝细胞中的 LGR4 敲低 (*Lgr4-LKO*)显著减轻 BDL 诱导的肝损伤，*Lgr4-LKO* 小鼠肝脏坏死面积减小、纤维化程度减轻、肝损伤酶和总胆红素水平降低，血浆和肝脏中的总胆汁酸水平显著降低。然而，巨噬细胞中的 LGR4 敲低 (*Lgr4-MKO)*则对

BDL 诱导的肝损伤没有显著影响。肝细胞中 LGR4 敲低显著降低 BDL 诱导的 S1PR2 表达和 AKT 磷酸化。重组 Rspo1 和 Rspo3 增强了 TCA 诱导的肝细胞中 S1PR2 表达和 AKT 磷酸化。通过特异性 AKT 或 S1PR2 抑制剂抑制 S1PR2-AKT 信号传导，可阻止肝细胞中 Rspo1/3 诱导的胆汁酸分泌增加。因此我们的研究表明，肝细胞中的 Rspo-LGR4 信号通过 S1PR2-AKT 依赖性方式增强胆汁酸的产生，从而加重胆汁淤积性肝损伤。

关键词：胆汁淤积性肝病，肝细胞，巨噬细胞，LGR4，S1PR2

P2-24 ***Discovering protective effects of adaptive IDH2 upregulation in diabetic retinopathy***

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Background: Diabetic retinopathy (DR) is a crucial ocular complication caused by diabetes mellitus (DM), eventually leading vision loss. Its pathogenesis is too intricate to fully understand. Here, we aimed to explore the mechanisms underlying DM-induced retinal damage and suggest some potential treatments. **Methods:** Two gene microarrays of retinal tissues of type 1 and type 2 DM mice were downloaded from Gene Expression Omnibus. After quality control, the data of gene expression were dimensionally reduced and clustered. Gene set variation analysis (GSVA) and gene set enrichment analysis (GSEA) were used to uncover the enriched pathways. The random Forest algorithm was applied to identify key genes. The human retinal ARPE-19 cells were treated with H_2O_2 and Methylglyoxal (MGO) to simulate oxidative status in diabetes. The cellular protection of ketoglutarate and sulfur were then examined, in the aspects of cell viability, intracellular reactive oxygen species, as well as expression and location key proteins. **Results:** Both type1 and type 2 diabetic status were able to make well-separated clusters of gene expression. The gene sets of Glutathione Metabolism and Glyoxylate and Dicarboxylate Metabolism were positively enriched, while Sulfur Metabolism was negatively enriched in the diabetic retinal tissues. The random Forest algorithm revealed the significance of isocitrate dehydrogenase 2 (IDH2) gene. Induction of oxidation with H_2O_2 or supplementing glucose metabolite MGO both reduced the viability of ARPE-19 cells. However, the damage was alleviated by the treatment with Ketoglutarate or sulfide/sulfane sulfur. The cytoprotection induced by sulfur was attributed to activation of nuclear factor erythroid-2-related factor 2 (Nrf2). **Conclusion:** Diabetes of type 1

and type 2 disrupt the metabolism of glutathione in retinal tissues. Manipulating the pathway of Nrf2-Idh2 is a promising therapeutic approach for DR.

Keywords: Diabetic retinopathy, Gene set analysis, Isocitrate dehydrogenase 2, Reactive sulfur, Nuclear factor erythroid 2-related factor 2

P2-25 Distal segments of cilia in chemosensory neurons regulate pathogen avoidance and innate immunity in *Caenorhabditis elegans*

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Abstract Pathogen avoidance behavior is a typical host-microbe interaction in many species. In *Caenorhabditis elegans*, multiple chemosensory neurons participate in this behavior. Some chemosensory neurons possess cilia with distal segments exposed to the external environment. However, the mechanisms of neuronal cilia involved in pathogen avoidance remain unclear. Here we found that *osm-3(p802)* mutants lacking the distal segments of cilia in chemosensory neurons exhibited slow avoidance to pathogen *Pseudomonas aeruginosa* PA14 exposure. We also observed that the diminished pathogen avoidance in *osm-3* mutants may be resulted from the reduced intestinal colonization of PA14. Furthermore, we found that the enhanced resistance to PA14 exposure is dependent of the classical p38 MAPK pathway. Based on our RNA-seq profile of *osm-3* mutants, we identified three genes regulated by *osm-3* gene are involved in neuronal cilia-mediated pathogen avoidance. Collectively, we highlighted the role of distal segments of cilia in chemosensory neurons on regulation of both pathogen avoidance and innate immunity in *Caenorhabditis elegans.*

Key words: cilia; pathogen avoidance; *Pseudomonas aeruginosa*; innate immunity;

RNA-sequencing

P3 应用生理

P3-1 Preliminary study on kidney hypoxia adaptation mechanism of Pikas（Ochotona curzoniae） based on UHPLC-QE-MS

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Abstract: The plateau pika is a rodent unique to the Qinghai-Tibet Plateau and fully adapted to the extreme environment of the plateau. There are few studies on the kidney adaptation mechanism of plateau Pika. UHPLC-QE-MS method was used to analyze the renal differential metabolites and key pathway analysis (enrichment analysis and topological analysis) of pika at different altitudes, and it was hypothesized that there may be potential mechanisms of kidney hypoxia adaptation in Pika at different altitudes. In this study, 8 plateau pika were captured in Guoluo area (MD group) at an altitude of 4360m and 8 in Menyuan Area (MY group) at an altitude of 2900m, respectively. Kidney tissue samples were taken and univariate statistical analysis, including t test, UHPLC-QE-MS method, was used. Multivariate statistical analysis included principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA) to identify the differences of metabolites in each group. OPLS-DA replacement test was used to evaluate the statistical significance of the model. Volcanic, bubble and rectangle maps were used to analyze the differential metabolites and pathways. The results showed that PCA and OPLS-DA model discriminant analysis showed that renal metabolites in both groups showed obvious cluster type distribution. The levels of adenosine, ribose, adenine, diosgenin, micrine hydrochloride, quinoline alkaloids, carnosol and astaxanthin in MD group were significantly higher than those in MY group. In MY group, hydrogen sulfide, arachidonic acid, epoxyeicosatrienoic acid, histamine, coumarin and Alamandine were significantly decreased (VIP > 1.5, $P < 0.05$). The above differential metabolites may suggest that it may be a biomarker of hypoxia adaptation. Topological analysis of the biosynthesis pathways of valine, leucine and

isoleucine showed significant influence factors. The enrichment of pantothenate and coenzyme A biosynthetic pathways was significant. These pathways may be involved in the plateau adaptation mechanism of Pika. This study verified the above hypothesis, and there were significant differences in renal metabolites of pika at different altitudes, which might be related to the adaptation of pika to low oxygen environment at high altitude.

Keywords: High altitude hypoxia; Pika; Kidney; UHPLC-QE-MS; Metabolic pathway

Acknowledgement: Thanks to all members of the Plateau Medical Research Center of Qinghai University for their help in the experiment.

P3-2 Characteristics of renal mitochondrial hypoxia adaptation in plateau pika at different altitudes

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Objective: To investigate the mitochondrial adaptation characteristics of pika at different altitudes. **Methods**: According to the different elevations, the plateau pika were divided into the elevation group of 4360m (Mado Star Sea) and the elevation group of 2900m (Laji Mountain, South). Mitochondrial oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) levels and mitochondrial hydrogen peroxide (H_2O_2) levels were determined by high resolution mitochondrial respiration apparatus. **Results**: The hemoglobin content of 4360m group was significantly lower than that of 2900m group ($P<0.05$). The kidney state 4 respiratory rate of mitochondrial respiratory chain complex I (CI-LEAK), state 3 respiratory rate of mitochondrial respiratory chain complex I (CI-OXPHOS) and state 3 respiratory rate of mitochondrial respiratory chain complex I+II(CI+II-OXPHOS) in the 2900m group, the electron transport capacity of respiratory chain complex I+II (CI+II-ETS) and the electron transport capacity of respiratory chain complex II (CII-ETS) were both higher than that of 4360m group, but the coupling rate was lower than that of 4360m group ($P<0.05$). The renal mitochondrial CI-LEAK, CI+II-OXPHOS and CI+II-ETS in the 2900m group were higher than those in the 4360m group. The mitochondrial state 4 respiratory rate (FAO-LEAK) of the kidney in the 2900m group with palmitate carnitine and malic acid as substrates was higher than that in the 4360m group. The respiratory rate of fatty acid metabolism pathway state 3 (FAO-OXPHOS) in the mitochondria of

the kidney of the 2900m group with palmitic acid carnitine as the substrate was higher than that of the 4360m group. During state 4 respiration (LEAK) of respiratory chain complex I, state 3 respiration (OXPHOS) of respiratory chain complex I, state 3 respiration (OXPHOS*) of respiratory chain complex I+II, and electron transfer (ETS) of respiratory chain complex I+II, the H_2O_2/O_2 flow ratio (ΔH_2O_2) of 2900m group was lower than that of 4360m group. **Conclusion**: Different altitude pikas have different kidney mitochondrial adaptation characteristics.

Keywords: Altitude; Plateau pika; Kidney; Mitochondria

Acknowledgement: Thanks to all members of the Plateau Medical Research Center of Qinghai University for their help in the experiment.

P3-3 Study on metabolic mechanism of Brown adipose tissue（BAT）in pika adapting to extreme plateau environment

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AIM: To explore the metabolic changes and mechanism of Brown adipose tissue (BAT) of pika in adapting to the extreme environment at high altitude byUHPLC-QTOFMS metabonomics. **METHODS:** Sixteen pikas were captured from Guoluo area (4360m) in Qinghai Province (MD group) and Menyuan area (2900m) in Haibei Prefecture (MY group); respectively. Metabolites in BAT samples of the two groups were determined by UHPLC-QTOF-MS, using Simca software to perform Principal Component Analysis (PCA) and Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) on the metabolic profile features of BAT, combined with t-test, volcanic map analysis and KEGG metabolic pathway analysis of differential metabolites, besides a bubble map was constructed. **RESULTS:** The discriminant analysis results of PCA and OPLS-DA patterns showed that both groups of BAT metabolomics showed significant clustering distribution. It was identified that 107 differential metabolites between MD group and MY group pikas have significant changes. Among them, Glucose 6-phosphate, cholic acid, ADP ribose, adenosine, Deoxycytidine, L-phenylalanine, phosphocreatine, folic acid, Prostaglandin, PC (o-18:0/18:0), PC (o-16:0/20:0), PC (22:0/15:0), PE (24:0/16:0), CDP Ethanolamine levels were significantly up-regulated in MD group， Norepinephrine, stearic acid, urea, ornithine, Propylthiouracil, Riboflavin, flavone, PC (14:0/14:00 0) The levels of PE (15:0/16:0) and PE (22:6 (4Z, 7Z, 10Z,

13Z, 16Z, 19Z)/16:0) were significantly reduced. The enrichment pathway analysis of the screened differential metabolites found that BAT metabolism was related to Phenylalanine, pentose phosphate pathway, tyrosine, Tryptophan and other metabolic pathways. **CONCLUSION:** This study verifies that BAT of pikas have a series of metabolic changes in order to adapt to highland cold and hypoxic environment of the Qinghai-Tibet Plateau, and these metabolites can be used as representative biomarkers of BAT metabolism in plateau native animals.

KEY WORDS: UHPLC-QTOP-MS; High altitude hypoxia; Pikas; Brown Adipose Tissue（BAT）;Metabolomics

P3-4 绞股蓝皂苷的抗缺氧活性及其物质基础研究

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高海拔暴露及呼吸功能障碍疾病引起的氧气利用度降低会导致机体生理及病理学变化，严重者甚至危及生命健康。绞股蓝皂苷（GPs）是药食同源植物绞股蓝（*Gynostemma pentaphyllum*）中的有效成分，具有多种生物活性。我们探索了 GPs 在抗缺氧方面的活性及其物质基础。在 PC12 缺氧细胞模型上，研究发现 GPs 可以通过减少 ROS 和 Ca^{2+}的释放量，增强 SOD 活力，改善线粒体膜电位，从而显著改善缺氧诱导的细胞损伤，维持细胞的正常生理功能。在动物水平上，研究发现 GPs 灌胃处理显著延长了 C57BL/6 小鼠的在密闭瓶中的存活时间，并增强小鼠的运动能力。同时，GPs 处理有效保护了低压缺氧模型小鼠的记忆功能，并通过激活 ERK、Akt 和 CREB 信号通路增加了海马神经元活力。进一步对 GPs 进行化学成分研究，发现 5 个具有抗缺氧活性的单体化合物，其中 GP-14 表现出显著的抗缺氧活性。在 PC12 及原代神经元缺氧细胞模型上，GP-14 处理显著抑制缺氧诱导的细胞凋亡，并减轻原发性神经元损伤。在 LPS 联合低压低氧诱导的小鼠高原脑水肿模型上，GP-14 逆转了缺氧诱导的海马 CA1 区 NeuN 阳性神经元丢失，并通过 Akt 和 ERK 信号通路发挥神经元保护作用；此外，GP-14 通过抑制 NF-κB 信号通路的激活，抑制全身性及神经性炎症，同时，有效逆转了 ZO-1 水平的降低，对血脑屏障完整性具有保护作用。该研究为新型抗缺氧药物研究提供了关键物质基础。

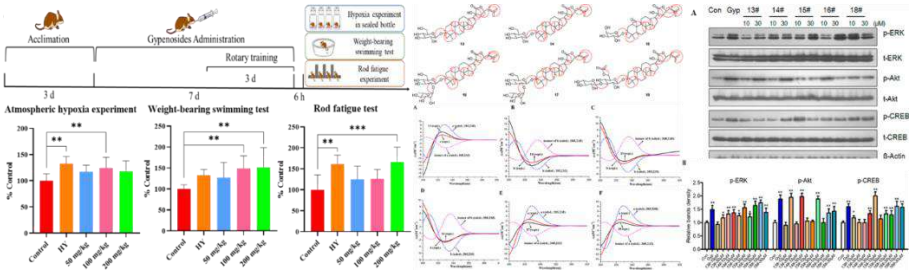


图 绞股蓝皂苷的抗缺氧活性及其物质基础研究

关键词：缺氧，绞股蓝皂苷，GP-14，PI3K-Akt，NF-κB

致谢：本项目受到国家自然科学基金面上项目、中国科学院西部之光项目的资助。

P3-5 深地高温环境下机体急性热应激的多组学研究

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目的：深地空间是除了地表空间外，继太空空间、海洋空间之后的人类可开发的第四大空间。高温高湿是深地环境中引起人体不适但又无法规避的关键环境因素，随着掘进深度的增加，地层每下降 100m，地温升高 2-3℃。本研究拟在深地高温环境下，采取多组学手段，揭示机体热应激前后血液中蛋白质、mRNA 和小分子代谢物的时序变化，探索机体急性热应激的响应机制。

方法：纳入 24 位国家矿山应急救援芙蓉队队员作为受试者。受试者在 50℃高温地下巷道内静息 30 分钟以进行急性热应激。在不同时间点（基线、急性热应激后 5 min、30 min、1 h 和 24 h）采集受试者的静脉血标本，并进行血浆蛋白组学、代谢组学、外周血单核细胞转录组学和外周血中性粒细胞转录组学检测和分析。同时，在急性热应激前后进行心脏彩超及肺功能检测。

结果：（1）血液中数千种分子在急性热应激前后发生表达改变，并呈现出不同的时间变化趋势。这些分子涉及免疫应答、凝血、能量代谢、酸碱平衡、氧化应激等多种生物学过程。（2）相互作用分析和关联分析提示 HSP90AB1、PF4 和 THBS1 等分子可能是急性热应激的潜在调节因子。（3）相关性分析发现，整合素 α5 和肌酸激酶等血液分子能预测急性热应激前后心肺功能参数的变化。

结论：本研究揭示了深地高温环境下机体急性热应激的关键调节因子及生物标志物。这些结果阐释了急性热应激后分子层面的变化，可为建立急性热应激的调控和干预策略提供理论支撑，对深地高温环境下的健康保障具有重大意义。

关键词：深地医学，热应激，蛋白质组学、代谢组学、转录组

P3-6 外源性 EPO 改善慢性间歇性低氧诱导神经元损伤的作用研究

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慢性间歇性低氧（chronic intermittent hypoxia, CIH）作为阻塞性睡眠呼吸暂停（obstructive sleep apnea, OSA）的核心病理机制，可引发氧化应激和炎症反应，进而导致神经元损伤及突触可塑性障碍。然而，目前关于 CIH 诱导神经元损伤的确切分子机制尚不明确，尚无针对性治疗药物。促红细胞生成素（EPO）作为肾脏中产生的一种造血生长因子，具有抗炎、抗氧化、抗凋亡和促进血管生成等作用。而且，脑内以缺氧依赖性方式局部产生的 EPO 可以旁分泌或自分泌方式发挥明显的神经保护作用。以往研究发现，与低氧相比，CIH 暴露后 EPO 水平特异性下调，提示 EPO 可能与 CIH 诱导神经元损伤密切相关。因此，本研究建立 CIH 暴露 HT22 细胞模型，明确 CIH 暴露不同时间点（0，3，6，12，24，48 h）EPO 及其受体 EPOR 的表达水平，探讨外源性 EPO 对 CIH 诱导神经元损伤的保护作用机制。研究结果发现，CIH 暴露 12，24 及 48 h 可引起 HT22 细胞活性明显下降。EPO 及 EPOR 表达水平在 CIH 暴露 3，6h 升高，而在 24, 48h 下降。提示，CIH 暴露早期 EPO/EPOR 水平适应性升高，而伴随暴露时间延长表达明显下调。外源性给予 EPO 可明显增加 HT22 细胞活性和线粒体膜电位水平，降低氧化应激和细胞凋亡，促进 PI3K、AKT 表达及 JAK2-STAT5 磷酸化，上调 Nrf-2、HO-1、Bcl-2/ Bax 表达，下调 caspase-3 活化水平。本研究明确了 CIH 条件下 EPO 的时间表达模式，确定了 EPO 表达下调与 CIH 诱导神经元损伤密切相关。外源性 EPO 可通过激活 PI3K-AKT 及 JAK2-STAT5 信号通路抑制 CIH 诱导的氧化应激和细胞凋亡，发挥神经元保护作用，为 OSA 合并认知障碍患者提供了潜在的特异性治疗策略。

关键词：慢性间歇性低氧；氧化应激；细胞凋亡；EPO

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P3-7 p53 乳酸化修饰在低氧诱导神经炎症中的机制研究

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目的：低氧上调小胶质细胞糖酵解水平，增加乳酸生成，赖氨酸乳酸化修饰（Kla）升高。而 Kla 在低氧诱导神经炎症过程中的作用尚不清楚。我们通过蛋白乳酸化修饰组学分析

观察到小胶质细胞 p53 赖氨酸乳酸化修饰（p53Kla）在低氧诱导的神经炎症中显著上调。本研究主要探讨 p53Kla 在低氧诱导小胶质细胞炎症反应中的影响及机制。

材料和方法：将分离的 C57BL/6J 小鼠原代小胶质细胞和 BV2 小胶质细胞分别给予 PBS（对照组）、LPS（100 ng/ml，LPS 组）、缺氧（0.3% O_2，Hy 组）和 LPS 复合缺氧（LPS-Hy 组）处理，通过 RT-PCR 检测促炎因子 mRNA 水平。检测 BV2 细胞 NF-κB 信号通路、p53 和 p53Kla 表达水平，观察细胞形态以及 Kla 和 p53 表达位置。观察添加 Oxamate 对 BV2 细胞促炎因子和 Kla 的影响，以及细胞活力和迁移能力的改变。

结果：1. BV2 细胞蛋白乳酸化修饰组学分析结果显示，LPS 复合低氧刺激后，p53Kla 水平以及 p53 相关信号通路和细胞周期信号通路较 LPS 组显著上调。2. LPS-Hy 组 BV2 细胞在 3 h、6 h、12 h、24 h 均观察到 p53 蛋白水平较其他处理组显著降低，泛乳酸化和 p53Kla 水平明显升高。3. 处理 24 h 后，LPS-Hy 组 BV2 细胞炎症相关蛋白（p-p65、p-IkBα）水平显著升高；原代小胶质细胞和 BV2 细胞促炎因子 iNOS、IL1β、IL6 和 TNFα mRNA 上调。4. 免疫荧光显示小胶质细胞胞体变大，边界不清晰，p53 表达位置呈现由细胞核向细胞质转移的趋势。LPS-Hy 组 BV2 细胞活力显著降低，细胞迁移能力增强。5. Oxamate（20 μm/ml）可以降低促炎因子水平、Kla 水平和细胞迁移能力，提高细胞活力。

结论：低氧复合炎症刺激诱导小胶质细胞 p53 赖氨酸乳酸化修饰升高，导致炎症信号通路激活，促炎因子表达增加，表明 p53 赖氨酸乳酸化修饰参与低氧诱导的神经炎症损伤。

关键词：小胶质细胞，缺氧，神经炎症，乳酸化修饰，p53

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P3-8 Study on physiological predictive factors of acute mountain sickness

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Objectives: The aim of the present study was to evaluate associations between Acute Mountain Sickness (AMS) and resting arterial oxygen saturation (SaO_2) and heart rate (HR) measured at low altitude and three consecutive days after an ascent to high altitude in a population that had previously not been at high altitude.

Methods: A cohort of 801 Han Chinese students (413 male, 388 female) aged 17 to 21 years were followed from low- to high altitude during August and September 2020. The symptoms of

AMS were assessed by questionnaire before leaving the lowlands and on the third day after arrival at the high altitude city of Lhasa at 3,658 m. AMS was defined by the Lake Louise Scoring System (LLSS) (headache and a cumulative Lake Louise Score ≥ 4). Log-risk and Logit-risk models were applied for analysing the independent effects of SaO_2 and HR on the incidence of AMS.

Results: The risk of AMS increased by decreasing SaO_2 levels measured both in the lowlands (risk ratio (RR): 1.16, 95%CI: 1.13-1.20) and on the first day in the highland (RR: 1.19, 95%CI: 1.15-1.22) per a 1% reduction in SaO_2 level. Heart rate and AMS were only weakly associated at any given point in time.

Conclusions: A reduced SaO_2 at both low and high altitude independently increased the risk of developing AMS. As a predictor for AMS, SaO_2 has its limitations, although individuals with a clear reduction in SaO_2 were at an increased risk of AMS.

Key words: acute mountain sickness, arterial oxygen saturation, heart rate

Acknowledgments: We wish to thank all the students who participated in this study and colleagues at the Tibet University Medical College who gave great support in the data collection process.

P3-9 Elevated serum and urinary secreted protein acidic and rich in cysteine (SPARC) levels are novel biomarkers of kidney fibrosis severity

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Running title: Serum and urinary SPARC as biomarkers for kidney fibrosis

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Background: Interstitial fibrosis is the main determinant of the progression of chronic kidney disease (CKD), and noninvasive identification of interstitial fibrosis is a major challenge. We aimed to explore the diagnostic value of serum and urinary secreted protein acidic and rich in cysteine (SPARC) in kidney fibrosis.

Method: 674 renal biopsy CKD patients in 1 clinical center serving as the training cohort (n = 322) and in 3 clinical centers serving as the validation cohort (n = 352). The serum and urinary SPARC levels were measured at the time of kidney biopsy. *In vivo* and *in vitro* kidney fibrosis models were also applied to confirm the role of SPARC.

Results: Increased SPARC expression was found in kidney fibrosis tissues. Higher serum

and urinary SPARC levels were detected in the kidney fibrosis group than nonkidney fibrosis group. The higher levels of serum SPARC were associated with increasing severity of kidney fibrosis. Moreover, the serum SPARC level had a higher area under the receiver operating characteristic curve (AUC-ROC) (AUC 0.86) than urinary SPARC and the estimated glomerular filtration rate (eGFR). The combination of serum SPARC, urinary SPARC and eGFR could increase the AUC-ROC for kidney fibrosis from 0.86 to 0.90. The diagnostic performance of serum or urinary SPARC were consistent in the validation cohort. *In vivo* and *in vitro* kidney fibrosis models also confirmed the upregulation of SPARC expression.

Conclusions: Serum and urinary SPARC levels may be potential biomarkers for kidney fibrosis, which may be helpful for the noninvasive diagnosis of kidney fibrosis.

Keywords: Secreted Protein Acidic and Rich, biomarker, kidney fibrosis, serum, urine

P3-10 Rho 激酶介导的肾内动脉重建增加模拟航天失重肾损伤易感性

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目的：中长期航天失重导致的多系统功能不全，严重影响航天员在轨飞行安全以及返回地面后的远期健康，是航天医学亟需解决的问题。肾脏作为泌尿、内分泌的器官，在多系统功能整体调控中发挥重要作用，但失重后肾脏损伤机制缺乏系统研究。本项目旨在探究模拟失重后肾脏损伤特点以及与 Rho 激酶介导的肾内动脉重建的关系，为防护措施研究提供新靶点。

方法：以 230-240g 雄性 SD 大鼠为研究对象，通过尾部悬吊、后肢卸荷的方式模拟失重。模拟失重以及同期对照 31 天后，检测肾脏 1-α 羟化酶、肾素表达以及血清肌酐、尿素氮变化，观察肾脏功能改变；双侧肾脏缺血（夹闭 27 分钟），再灌注 24h 后，检测血清肌酐、尿素氮、离子变化以及病理切片行 PAS、KIM1 染色等，观察肾脏损伤易感性；超声检测肾脏血流分布以及血管阻力；通过微血管张力检测技术（Wire myograph）结合 Rho 激酶通路激动与抑制实验，检测肾段动脉功能变化以及与 Rho 激酶通路关系。

结果：和对照组（CON）相比，1、模拟失重组（HU）肾脏 1-α 羟化酶表达降低、肾素表达升高；2、缺血再灌注损伤后，HU 组血清肌酐、尿素氮显著升高，病理结果急性肾损伤评分增加，损伤标志物 KIM1 表达升高；3、超声结果显示 HU 肾脏血流分布降低，肾脏血管阻力增加；4、血管功能结果提示 HU 组肾段动脉苯肾上腺素（PE，10^{-9}-10^{-4} M）与氯化钾(KCL，10–100 mM)诱导的收缩反应增强，Rho 激酶激动剂 U46619（10^{-8}–$10^{-5.5}$ M）介

导的收缩反应增强，Rho 激酶抑制剂 Y-27632（3 μM）能够显著降低收缩反应的组间差异；5、蛋白表达检测结果表明 HU 大鼠肾段动脉 Rho 激酶活性增强；6、在体给予法舒地尔（10 mg/kg/d）明显缓解模拟失重导致的动脉反应性以及肾脏损伤易感性变化。

结论：模拟失重 31 天后大鼠肾脏功能失调，肾脏损伤易感性增加，Rho 激酶介导的肾内动脉重建导致的肾脏血流动力学改变可能是肾损伤易感性增加的原因。

关键词：模拟失重；肾损伤易感性；Rho 激酶；动脉重建

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P3-11 脂质组学和质谱成像技术揭示低压低氧对小鼠脑脂质组成的多样性和动态变化的影响

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脂质代谢紊乱参与认知功能损伤的发生发展，高原低压低氧环境不但引起细胞代谢能量改变，也可导致机体脂代谢异常。已有文献报道慢性高原低氧暴露血清中游离脂肪酸、甘油三脂、胆固醇水平增加，并与认知损伤有一定相关性。而对脑组织脂质组的复杂性及其在持续缺氧条件下的变化仍然知之甚少。因此，全面分析小鼠脑脂质组是了解缺氧诱导认知功能机制的重要一步。本研究采用基于 LC-MS 的脂质组学方法和高分辨质谱成像方法，对暴露于模拟海拔 7000 米低氧环境中 1 天、3 天和 7 天小鼠海马组织的脂质组成及脑部脂质空间分布和变化进行了综合研究，HE 染色、Nissl 染色观察脑部神经元形态数量变化情况。研究结果表明低氧暴露引起小鼠认知能力下降，诱发小鼠海马神经损伤，神经细胞数量减少、排列紊乱，脑部脂质组成发生改变。本研究共检测到小鼠海马组织的 20 类脂质，注释了 1142 种分子脂质。脂质的改变是随着缺氧暴露而逐渐发生的，随着缺氧暴露时间的延长，磷脂酰胆碱增加，磷脂酰丝氨酸、磷脂酰肌醇和心磷脂等磷脂减少，并筛选到对低氧敏感的脂质分子，包括 PS(40:6)，PI(38:4)，PC(34:1)，PC(36:1)，PC(32:0)等。该研究揭示了小鼠脑部脂质组成的多样性和动态性，加深了我们对低压低氧暴露过程中脑组织脂质变化规律的认识，有望今后为高海拔低氧暴露与脑保护的策略提供新思路。

关键词：低氧暴露，脂质代谢，脂质组学，质谱成像

P3-12 低氧加重结扎诱发牙周炎小鼠的脑内炎症

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牙周炎是由多种口腔微生物感染牙周组织导致的慢性炎症性疾病，能诱发局部炎症反应，产生炎症因子，进而通过血液循环等多种途径影响神经系统，造成神经炎症等一系列严重后果。随着越来越多的人群前往高海拔地区活动，研究高原低氧环境对牙周炎引发的脑内炎症的影响具有重要意义。本研究采用磨牙结扎建立牙周炎小鼠模型，将小鼠置于模拟海拔6000m 的低压低氧动物舱中分别处理 1 天、3 天、5 天、7 天，检测对照组、低压低氧组、牙周炎组、低氧合并牙周炎组的炎症水平与神经损伤情况。ELISA 检测血清炎症因子 IL-6、TNF-α 水平，qPCR 检测脑内炎症因子水平，免疫荧光染色观察脑部小胶质细胞、星形胶质细胞活化状态，HE 染色、Nissl 染色观察海马区域神经元形态数量变化和脑部病理结构损伤情况。研究结果显示，低氧合并牙周炎小鼠血清和脑内炎症因子上调，海马小胶质细胞数量明显增多、胞体增大、分支变多，神经元凋亡增多。以上结果提示低氧能够加重牙周炎引发的脑内炎症，为罹患牙周炎人群进入高原地区的风险评估提供参考。

P3-13 GP-14 通过 NF-κB 信号通路减轻脂多糖诱导小鼠抑郁样行为

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神经炎症是抑郁症的常见发病症状，与抑郁症的发展密切相关。许多临床抗炎药物通过减轻神经炎症反应从而起到抗抑郁的作用。绞股蓝皂苷及其生物活性化合物绞股蓝皂苷XIV(GP-14)对缺氧诱导的神经元损伤具有保护作用，并且能够减轻高原缺氧性脑水肿。本研究我们观察了 GP-14 对脂多糖(lipopolysaccharide, LPS)诱导的抑郁样模型小鼠的影响。低剂量脂多糖诱导的抑郁样行为是常用的抑郁症模型，连续 7 天腹腔注射 LPS(0.5 mg/kg)诱导小鼠抑郁样行为，同时小鼠灌胃给药 100 mg/kg GP-14。结果显示：GP-14 不仅能减轻 LPS 诱导的抑郁样行为，还能改善小鼠的焦虑样行为。此外，GP-14 还能缓解抑郁小鼠的学习和认知能力下降。ELISA 和免疫荧光染色结果显示，GP-14 可以减低脑内肿瘤坏死因子-α（TNF-α）、白细胞介素-1β（IL-1β）和白细胞介素-6（IL-6）等促炎细胞因子的水平，并抑制了 LPS 诱导的星形胶质细胞的活化，显示了明显的抗炎作用。进一步利用 GP-14 对 C8 细胞和原代星形胶质细胞的预处理可抑制 NF-κB 信号通路的激活，并下调促炎因子的表达。上述结果提示，GP-14 具有显著的抗炎和抗抑郁特性，GP-14 有可能成为一种治疗抑郁症的先导化合物。

关键词：绞股蓝皂苷 XIV，脂多糖，抑郁症

P3-14 缺氧对能量和营养素代谢以及身体成分的影响

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目的 本课题旨在探究缺氧条件下机体能量和营养素代谢以及身体成分变化特点，为针对性的营养保障措施提供实验依据。**方法** 以 19 名健康男性为试验对象，年龄 18-45 岁，平均年龄为（30.42±6.32）岁，平均身高为（175.3±3.89）cm，采用人体成分测试系统和 Breezing Pro 便携式能量代谢测试系统，分别对其进行缺氧前、后体成分和能量代谢变化分析。人体体成分测试系统检测指标包括蛋白质、腰臀比、无机盐、骨骼肌、体重、身体质量指数(BMI)、体脂肪、体脂肪率等；便携式能量代谢测试系统检测指标包括静息代谢（REE）、呼吸商（RQ）、摄氧量（VO_2）、二氧化碳产生量（VCO_2）。**分析结果显示：**缺氧后身体总水分、蛋白质、肌肉量、无机盐、去脂体重、基础代谢率、InBody 评分显著低于缺氧前（$P<0.05$）；缺氧后体脂肪、体脂百分比、腰臀比、脂肪量显著高于缺氧前（$P<0.05$）；缺氧后静息代谢率计算公式预估值显著低于缺氧前（$P<0.05$），而身高、体重、BMI、内脏脂肪、摄氧量、二氧化碳产生量、每分呼吸次数、每分通气量、静息代谢率偏差、呼吸商、静息代谢率实测值及估算总能量代谢率与缺氧前比较,差异均无统计学意义（$P>0.05$）。**结论** 机体能量和营养素代谢、身体成分变化与氧气供应情况密切相关，缺氧时发生明显改变。

关键词：缺氧；能量；营养素；体成分

P3-15 EFTUD2 regulates the apoptosis of NSCs and cerebral cortex development through RNA alternative splicing of Caspase3

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EFTUD2 is a spliceosomal GTPase. Clinically, different EFTUD2 mutations can cause the occurrence of Mandibulofacial dysostosis with microcephaly (MFDM). However, the mechanism of EFTUD2 and its pathogenic mutants in cerebral development remains unclear. In this study, we constructed mice with Eftud2-deficient cerebral cortical stem cells and cortical neural stem cells

expressing human EFTUD2 pathogenic mutant mice using conditional-knockout and *in utero* electroporation. Our work showed that knocking out of Eftud2 in embryonic neural stem cells produces cortical dysplasia and microcephaly-like phenotype in mice. Meanwhile, EFTUD2 pathogenic mutants induces the loss of neurons. The results of RNA-seq and immunofluorescence analysis indicate that the loss of Eftud2 triggers p53-independent apoptosis and lead to cortical developmental disorders. Combined with RNA co-immunoprecipitation, full-length transcriptome sequencing technology and RNA splicing isoform functional verification experiments, we found that Eftud2 directly binds to the RNA of Caspase3 and mediates neuronal cell death and cerebral cortex development by inhibiting p53-independent activation of apoptosis via RNA alternative splicing of Caspase3. In this study, it reveals the mechanism of EFTUD2 in the development of cerebral cortex and the occurrence of MFDM, and provide theoretical basis for clinical diagnosis and treatment of MFDM.

Keywords: EFTUD2; RNA spliceosome; Mandibulofacial Dysostosis with Microcephaly; Cerebral cortex development

P3-16 间断短时供氧防止低压低氧肺动脉高压的应用基础与保障设备研究

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中长期暴露于低压缺氧环境时，可因肺动脉重建致肺动脉高压及右心肥厚，而目前的对抗措施尚不能达到满意效果。供氧是针对缺氧的有效防护措施，我们证实，连续 24 小时海平面水平供氧可以完全防止 5000 米缺氧 14 天所致大鼠肺动脉高压及右心肥厚。但连续供氧在高原缺乏实用性。

受前期模拟失重心血管影响防护工作启发，我们依据航空供氧中生理等效高度原理，观察了短时程供氧对大鼠低压低氧肺动脉高压的防护效果，探讨了其可能机制，同时针对高原供氧要求的实现，研制了相关保障设备。

结果表明，间断短时程供氧可以明显减轻 5000 米暴露所致大鼠肺动脉高压与右心肥厚，而连续的短时程供氧缺乏上述效果。每天均分 3 次，每次 1 小时的海平面水平供氧可明显降低 5000 米 14 天暴露所致大鼠肺右心收缩压的升高、减小右心肥厚指数；每天 3 次，每次 0.5 小时的海平面水平供氧与上诉供氧方案有相近的防护效果；而每天 3 次，每次 1.5 小时供氧或每天 6 次，每次 1 小时供氧的防护效果下降。每天 3 次，每次小时的 3000 米水平供氧无明显防护效果。每天 3 次，每次 1 小时海平面水平供氧可明显降低肺小动脉肌化程度、Ki67 染色

阳性动脉比例与大鼠肺组织及血清 H_2O_2 的水平。胃饲 MitoQ 可降低间断短时供氧的大鼠整体 ROS 水平，并提高对肺动脉高压的防护效果。针对高原氧源缺乏，我们研发了“便携式分子筛制氧充氧系统”与“无源自增压氧烛式制氧充氧系统”，通过同时使用我们研制的“便携式个人供氧呼吸器”，可为高原地区人员每日间断短时海平面水平供氧提供器材物质保证。

结果提示，间断短时供氧可能是一种现阶段有实用价值的高原肺动脉高压防护方法。

关键词：间断短时供氧，低压低氧，肺动脉高压，供氧装备

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P3-17 低氧预适应对急性缺氧小鼠行为学特征的影响

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目的：寻找可用于评价小鼠急性高空或高原缺氧耐力的无创性评价指标，阐明低氧预适应对高原缺氧小鼠行为学特征的影响。

方法：实验一将 6 只 6-8 周龄雄性 C57BL/6J 小鼠随机分为地面组和缺氧组进行旷场实验，每组 3 只。实验二将 50 只 6-8 周龄雄性 C57BL/6J 小鼠随机分为缺氧组、低氧预适应 1d 组、低氧预适应 3d 组、低氧预适应 5d 组，低氧预适应 7d 组，每组 10 只。低氧预适应组小鼠每天置于小动物低压舱舱进行 1h 低氧预适应（4000m）。低氧预适应 7d 组提前 7 天进行预适应，低氧预适应 5d 组提前 5 天开进行预适应，低氧预适应 3d 组和 1d 组类似。预适应结束后于人体低压舱（5000m）进行旷场实验。旷场为四宫格白色盒子，每一格大小为 25cm×25cm×30cm，将摄像机固定在正上方对小鼠进行录像。实验结束后使用 Smart v3.0 软件对数据进行分析。“中心”区域定义为旷场中心 15cm×15cm 的区域。慢速时间占比指小鼠速度小于 1cm/s 的时间占总时间的比例。将所有小鼠放在各自格子的中央后，低压舱开始上升，按照 10m/s 的速度上升至 5000m 后，测量小鼠活动 10min，随后按照 10m/s 的速度下降。

结果：实验一 5000 米缺氧组旷场实验总路程显著低于地面组，慢速时间占比（<1cm/s）显著高于地面组，中央区域时间占比显著低于地面组。实验二低氧预适应各组旷场实验总路程均显著高于缺氧组，慢速时间占比（<1cm/s）显著低于缺氧组。低氧预适应 7d 组旷场实验总路程显著高于低氧预适应 5d、3d、1d 组，慢速时间占比（<1cm/s）显著低于低氧预适应 3d、1d 组。

结论：我们的实验结果表明急性缺氧可明显改变小鼠旷场实验各项指标，提示旷场实验可以作为评价小鼠缺氧耐力的无创性指标。以往的研究提示低氧预适应可以一定程度上提高缺氧耐力，为满足实际需求，我们进一步缩短预适应时间，结果显示单次低氧预适应对次日高空缺氧有一定防护效果，且增加预适应次数可以提高防护效果。

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P3-18 OPG/RANKL/RANK 系统介导模拟失重所致动脉钙化的作用和机制

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血管钙化是在多种因素作用下发生的与骨发育相似的、主动的、高度可调控的复杂病理过程，主要表现为血管壁僵硬度增加和顺应性降低。近期研究发现，长期航天飞行可引起航天员颈总动脉的僵硬度显著增加，这可能会对航天员的健康造成一定威胁，而流体静压消失和血液头向转移引起的动脉跨壁压升高可能是其重建的主要始动因素。**目的：**本研究将模拟失重大鼠整体实验与血管灌流培养实验相结合，观察不同跨壁压条件下动脉的钙化情况及相关信号分子的表达变化。**方法：**建立 4 周尾部悬吊大鼠模型，设立悬吊组（HU 组）和同期对照组（CON 组），观察模拟失重大鼠颈总动脉钙化相关因子 Runx2、BMP2 和 osteocalcin 的蛋白表达变化，以及骨保护素（OPG）、核因子 κB 受体活化因子（RANK）及其配体 RANKL 的蛋白表达变化；建立可以控制流量、压力的血管培养系统，将正常大鼠进行常压（80 mmHg）和高压（150 mmHg）灌流培养 3 天，同时给予 RANKL 抑制剂 OPG-Fc，观察 RANKL 和 RANK 的蛋白和 mRNA 表达变化以及 OPG/RANKL/RANK 系统对钙化相关因子 Runx2、BMP2、osteocalcin 蛋白和 mRNA 表达的影响。**结果：**与对照组相比，HU 组大鼠颈总动脉钙化相关因子 Runx2、BMP2 和 osteocalcin 的蛋白表达增加；HU 组大鼠颈总动脉 RANKL 及其受体 RANK 的蛋白表达显著增加，而“诱饵”受体 OPG 蛋白表达没有显著变化。与常压灌流组相比，高压灌流组大鼠颈总动脉的 RANKL、RANK、Runx2、BMP2、osteocalcin 的蛋白和 mRNA 表达显著增加，给予 OPG-Fc 抑制 RANK 通路可显著抑制高压灌流增强的 Runx2、BMP2 和 osteocalcin 的蛋白表达。**结论：**跨壁压升高是失重引起动脉钙化的始动因素，OPG/RANKL/RANK 系统可能参与介导失重条件下动脉跨壁压升高所致血管钙化的病理过程。

关键词：模拟失重；血管钙化；骨保护素；核因子 κB 受体活化因子；血管灌流培养

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P3-19 胃食管反流病中食管黏膜上皮屏障功能炎症损伤机制探讨

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胃食管反流病中食管黏膜上皮屏障功能的炎症损伤，传统观点认为是从反流的胃酸和胃

蛋白酶等损伤食管上皮及上皮间的连接蛋白开始的，随着反流的发展，炎症反应逐渐发生，“由表及里”。而最新的研究表明，黏膜下层的炎症反应可以发生于未出现黏膜损伤前，反流物在早期可诱导食管黏膜上皮表达并释放大量的炎症趋化因子诱导炎症细胞聚集到黏膜上皮，最后导致食管黏膜屏障的损伤，“由里及表”。对于食管黏膜屏障功能的炎症损伤的分子机制涉及多种炎症相关的信号通路及受体，如核转录因子 κB（Nuclear Factor-kappaB, NF-κB）、缺氧诱导因子（Hypoxia-Inducible factors, HIFs）、瞬时感受器电位香草酸受体-1（Transient Receptor Potential Vanilloid-1, TRPV1)、蛋白酶激活受体-2（Protease-Activated Receptor-2, PAR-2）、人髓系细胞触发性受体-1(Triggering Receptor on Myeloid Cells 1,TREM-1)、G 蛋白偶联受体-84（G Protein-coupled Receptor-84, GPR84）等。因此，理解反流诱导的食管黏膜屏障功能损伤的机制对寻求胃食管反流病的有效干预措施具有重要的临床意义，可以在未来临床治疗中提供依据和思考。

关键词：胃食管反流病；食管黏膜屏障；炎症反应；

P4 中医生理

P4-1 整合网络药理学和代谢组学揭示白藜芦醇对斑蝥素诱导小鼠肾损伤的保护作用机制研究

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从中药斑蝥中提取的斑蝥素（CTD）具有良好的抗肿瘤疗效，但因其较大的肾毒性，限制了其临床应用，而相关的分子机制还不清楚。白藜芦醇（RES）可通过调节炎症、减少氧化损伤和抗细胞凋亡，对多种急性肾损伤具有较好的保护作用，但其作用机制还不清楚。本研究通过建立 CTD 诱导小鼠的肾损伤和 RES 保护模型，测定小鼠的血清生化和肾脏氧化应激指标，对肾脏进行组织病理学和超微结构观察，通过代谢组学测序并结合网络药理学分析，阐明 RES 治疗肾损伤的核心靶点及作用机制，使用分子对接验证靶点的亲和力。结果表明，经 CTD 暴露后，小鼠血清肌酐、尿素氮以及肾脏的氧化应激相关指标出现显著性的升高，肾小球和肾小管上皮细胞出现明显的病理损伤；超微结构观察显示肾小球上皮细胞线粒体明显肿胀，内质网扩张，自噬溶酶体增加；而白藜芦醇可改善 CTD 引起的肾损伤。代谢组学分析表明，CTD 可诱导肾细胞凋亡和氧化损伤，主要通过破坏鞘脂和谷胱甘肽代谢，增加鞘氨醇和鞘磷脂水平，降低谷胱甘肽水平。RES 通过提高甘油磷脂代谢途径中的磷脂酰胆碱、溶血磷脂酰胆碱和溶血磷脂酰甘油的水平，从而调节肾细胞增殖、炎症反应、氧化应激

和细胞凋亡，最终减轻 CTD 诱导的肾毒性。网络药理学分析结果显示，共获得 132 个 RES 治疗肾损伤的靶点，154 个 KEGG 富集信号通路，其中鞘脂代谢和 AGE-RAGE 信号通路是网络药理学与代谢组学的共同信号通路。将网络药理学中确定的潜在靶点与 MetScape 分析中的基因进行匹配，得到了 4 个关键靶点（ALLC、FASN、OLAH 和 NP），相关的差异代谢产物分别是肉豆蔻酸、尿苷聚糖和胸腺嘧啶。分子对接结果显示，这 4 个核心靶点与 RES 有很强的亲和力。本研究从代谢组学和网络药理学揭示了 CTD 诱导肾损伤和 RES 的保护作用机制，为解析 CTD 致肾毒性的机制及临床中降低其肾毒性的治疗方案提供重要的参考。

关键词：斑蝥素；白藜芦醇；肾损伤；代谢组学；网络药理学

P4-2 Involvement of astroglial glutamate-glutamine in the analgesic process of electroacupuncture for chronic neuropathic pain

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Purpose: Based on our previous study, we observed that astrocytes are involved in cumulative analgesia; however, the underlying mechanism remains unclear. Glutamate is extensively recycled between neurons and astrocytes in a process known as the glutamate-glutamine cycle. Therefore, in this study, we investigated the effects of electroacupuncture on astroglial glutamate-glutamine levels in the dorsal horn of the spinal cord in rats with neuropathic pain.

Methods: 48 male SD rats were randomly divided into a normal control group, chronic constriction injury (CCI) group, and electroacupuncture (EA) group. EA was applied to bilateral Zusanli (ST36)–Yanglingquan (GB34). A neuropathic pain model was established using sciatic nerve ligation. Mechanical and thermal pain thresholds of bilateral hind paws were measured. Co-expression of spinal glutamate/aspartate transporter (GLAST) with microglia and astrocytes was detected by immunofluorescence double labeling. Western blotting and PCR were used to detect the protein and mRNA expression of spinal GLAST, glutamate transporter-1 (GLT-1), glutamine synthetase (GS), and p-ERK. The glutamate (Glu) and gamma-aminobutyric acid (GABA) contents in the spinal cord were measured using high-performance liquid phase (HPLC). To further verify the effects of GLAST and GLT-1 in EA analgesia, 30 male SD rats were randomly divided into the following three groups: intrathecal saline injection + EA, intrathecal

GLAST antagonist injection + EA, and intrathecal GLT-1 antagonist injection + EA.

Results: After CCI, both the mechanical and thermal pain scores of the hind paws decreased significantly ($P<0.05$), indicating a significant decrease in mechanical and thermal pain thresholds. CCI also significantly decreased the protein and mRNA expression of GLAST and GLT-1 ($P<0.05$) and slightly decreased the protein and mRNA expression of GS ($P>0.05$) but significantly increased the content of Glu. After EA treatment, the mechanical and thermal pain thresholds of the bilateral hind paws were significantly increased ($P<0.05$), the protein and mRNA expression of GLAST and GLT-1 increased considerably, GS increased slightly, and the Glu content decreased. After intrathecal injection of the glutamate transporter antagonist, both mechanical and thermal radiation pain thresholds of rats were significantly decreased ($P<0.05$), suggesting that the analgesic effect of EA was reversed by the glutamate transporter antagonist.

Conclusion: Repeated EA administration inhibited CCI-induced chronic neuropathic pain in rats, which may be related to the reversal of the decrease in the expression of GLAST and GLT-1 in astrocytes, thereby accelerating the clearance of Glu and reducing its concentration. A possible target of cumulative EA analgesia in glutamate-glutamine is the regulation of glutamate transporters in astrocytes.

Keywords: GLAST, GLT-1, glutamate transporters, chronic constriction injury, electroacupuncture

P4-3 A network pharmacology-based investigation reveals an inhibitory role of Shenqi Fuzheng injection in glioma via the SRC/PI3K/AKT signaling pathway

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Background: Glioma is a primary malignant tumor of nervous system. Shenqi Fuzheng Injection (SFI) is purified and processed from Radix Codonopsis and Radix Astragali, but its anti-tumor effect is not clear.

Methods: Glioma cell lines U87 and T98G were selected, and the inhibitory effect of SFI on glioma cells was detected by CCK8, EdU, colony formation, scratch test and flow cytometry. Subsequently, GL261 cells were injected subcutaneously into the armpit of C57BL/6 mice and treated by intraperitoneal injection of SFI. Screening the possible signal pathways of SFI inhibiting glioma by network pharmacology. The inhibitory mechanism of SFI was verified by protein imprinting experiment.

Results: The results showed that Shenqi Fuzheng injection inhibited the proliferation and

migration of glioma cells. In addition, in vivo studies showed that Shenqi Fuzheng injection significantly reduced the tumor volume in xenotransplantation mouse model. Moreover, the anti-tumor effect of Shenqi Fuzheng injection is related to the down-regulation of SRC, PI3K and AKT in vitro and in vivo.

Conclusion: Our research results show that Shenqi Fuzheng injection has anti-tumor effect by inhibiting SRC/PI3K/AKT signal pathway, and Shenqi Fuzheng injection may be a potential drug for the treatment of glioma.

Keywords: Shenqi Fuzheng injection；glioma；network pharmacology；SRC/PI3K/AKT signal pathway

P4-4 Study on the effect and mechanism of compound kushen injection in regulating of Lung squamous cell carcinoma

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Objective: Lung cancer is one of the most common and deadly cancers worldwide. Currently, specific targeted therapies for squamous lung cancer are few and ineffective, and patients have poor 5-year survival rates. Therefore, there is an urgent need to find an alternative therapy with minimal side effects. Compound kushen injection (CKI), as an adjuvant drug for tumor treatment, has been carried out for its clinical treatment of lung cancer and its complications. However, studies on the molecular mechanism of the efficacy of CKI in the treatment of squamous cell lung cancer have not been reported, which makes the clinical promotion difficult. In this paper, we investigated the therapeutic effects of CKI on squamous cell lung cancer through animal experiments, cellular experiments and network pharmacology, and preliminarily elucidated the molecular mechanism of the efficacy of CKI.

Methods: The human lung squamous cell carcinoma H226 and SK-MES-1 cell lines were selected for the study. CCK8, EdU, clone formation assay and Western blot were used to detect the effect of CKI on the proliferation ability of human lung squamous cell carcinoma cell lines. Hoechst 33342 staining and Annexin V-FITC/PI were used to detect the change of apoptosis ability of human lung phosphor carcinoma cell lines. JC-1 and DCFH-DA, fluorescent probes to observe mitochondrial membrane potential and reactive oxygen species in cells. The cell cycle changes of the two cell lines were determined by flow cytometry. Network pharmacology was applied to screen the targets and signaling pathways of CKI acting on lung squamous cell

carcinoma, and the above results were revalidated by Western blot assay. C57BL/6 mice were used to establish an axillary transplantation tumor model, which was divided into control group and CKI group. The tumor formation time, mean tumor weight, tumor size, vital organ index, and survival status were observed.

Results: CKI inhibited the proliferation of H226 and SK-MES-1 cells, promoted apoptosis, increased the level of ROS in cells, and decreased the mitochondrial membrane potential. Based on the network pharmacology results, it was hypothesized that the ATR/CHK1/TP53 signaling pathway might be involved in the inhibitory effect of CKI on H226 and SK-MES-1 cells. ATR, CHK1 and p-CHK1 were significantly down-regulated and TP53 and p-TP53 were significantly up-regulated after CKI intervention. Animal experiments showed that CKI significantly inhibited the growth of in vivo transplanted tumors.

Conclusion: CKI inhibits the proliferation of lung squamous carcinoma cells and induces mitochondrial apoptosis and cell cycle arrest by blocking the ATR/CHK1/TP53 signaling pathway.

Key words: compound kushen injection; lung squamous cell carcinoma; proliferation; apoptosis; ATR/CHK1/TP53 signaling pathway

P4-5 网络药理学方法联合体外实验初探金水六君煎辅助放化疗治疗恶性黑色素瘤的分子机制

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摘要：目的 网络药理学方法联合体外实验初步探索金水六君煎辅助放化疗治疗恶性黑色素瘤（malignant melanoma，MM）的分子机制。 **方法** 在 TCMSP 数据库中获取金水六君煎的活性成分及靶点，以“malignant melanoma”为关键词在 GeneCards、TTD、OMIM 数据库中获得 MM 相关靶点，得到金水六君煎有效成分-MM 交集靶点；通过 STRING 数据库获取蛋白质互作（PPI）网络，利用 Metascape 数据库进行基因本体论分析（GO）和基因组的京都基因与基因组百科全书富集分析（KEGG）并在 AutoDockTools 软件中进行分子对接；MTT 法检测金水六君煎含药血清对小鼠 B16 黑色素瘤细胞增殖活性影响；蛋白免疫印迹法（Western blotting）检测金水六君煎含药血清对 P38、p-P38、JNK、p-JNK、Beclin1、P62、LC3 蛋白表达调控；透射电镜观察金水六君煎含药血清对 B16 细胞自噬影响。 **结果** 共获得金水六君煎相关靶点 248 个，MM 相关靶点 2147 个,交集靶点 149 个。GO 显示主要生物过程是 DNA 结合转录因子、激酶结合、细胞因子受体结合等；KEGG 显示主要是癌症通路和 MAPK 信号通路，网络拓扑分析显示金水六君煎治疗 MM 的主要有效活性成分是槲皮素、山奈酚、柚皮

素等，主要核心靶点为 AKT1、TP53、JUN 等；核心靶点与有效活性成分分子对接显示结合活性较好。MTT 结果显示，较空白组，金水六君煎含药血清能有效抑制 B16 细胞的增殖且呈浓度依赖性。Western blotting 实验表明，较空白组，中高剂量组能下调 B16 细胞中 p- P38、p-JNK、P62 蛋白表达，上调 LC3Ⅱ、LC3Ⅱ/LC3Ⅰ、Beclin1 蛋白表达。透射电镜下显示金水六君煎含药血清能促进 B16 细胞中自噬体生成，减少黑素体生成。**结论** 金水六君煎的有效成分和药物靶点很多，其治疗 MM 的作用靶点与通路众多，分子机制可能是通过下调 p-P38、p-JNK、P62 的蛋白表达，上调 Beclin1、LC3Ⅱ/LC3Ⅰ的蛋白表达，抑制 P38 通路和 JNK 通路的激活，从而抑制 B16 细胞增殖；同时促进细胞凋亡，激活细胞自噬，发挥抑癌作用。

关键词：网络药理学；金水六君煎；恶性黑色素瘤；增殖；自噬；分子机制

P4-6 新型小檗碱晶体药 BJ 改善化疗所致周围神经病变及代谢综合征

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小檗碱是一种从毛茛科植物中提取出的季铵类生物碱，目前已广泛地将其作为抑菌、抗感染药物来使用。临床上用于治疗某些临床疾病，例如胃肠炎、肿瘤、心律失常、高血脂、神经退行性疾病，肿瘤等方面表现出很好的治疗效果。小檗碱是一种很有前景的药用植物活性成分，然而，小檗碱口服吸收较差、生物利用度低并且大剂量服用时胃肠道反应严重，并引起体重的急速下降，这在很大程度上限制了小檗碱的临床运用。为解决此类问题，课题组通过结构修饰和制剂学的方法制备了 BJ，生物利用度为小檗碱的 308.5 %，并且细胞毒性显著降低，并在不同的模型上验证了 BJ 有效防治化疗药物所致周围神经病变（Chemotherapy-Induced Peripheral Neuropathy，CIPN）性疼痛及高糖高脂性肥胖，BJ 有望成为抑制 CIPN 的首个标准临床用药和安全有效的减肥药。而且，本研究研发的原代神经元细胞高通量 CIPN 筛选模型真正实现了高通量，并且具备灵敏度高、成本相对较低的优点，可成为研究其他周围神经病变的有效手段。本研究中发现了 BJ 作用新机制，揭示了潜在的有效抑制 CIPN 的信号途径，从而为 CIPN 的新药研发提供新靶点和可靠的阳性对照药，并为重大新药创制提供依据。本研究还发现并验证了 BJ 具有新的适应症，能有效治疗高糖高脂性肥胖。

P4-7 疏肝调神夹脊针治疗阈下抑郁：随机对照研究

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目的：阈下抑郁（Subthreshold Depression，SD）是指具有抑郁情绪表现却又未达到抑郁症临床诊断标准的一种介于健康和抑郁症之间的心理亚健康状态。本研究基于疏肝调神原则，比较疏肝调神夹脊针与常规针刺治疗阈下抑郁的临床疗效及对生存质量的影响，以期为阈下抑郁的治疗提供疗效可靠的临床治疗思路。**方法：**将 72 例阈下抑郁患者随机分为观察组和对照组，每组 36 例。观察组采用疏肝调神夹脊针治疗，穴取 T4-5 夹脊、T7 夹脊、T9-10 夹脊、百会、天柱、风池。对照组采用常规针刺治疗，穴取百会、印堂、神门、太冲、内关、膻中。两组均隔日针刺一次，每周治疗 3 次，周日休息，4 周为一疗程，观察两个疗程，共治疗 8 周。在治疗前、治疗 4 周和 8 周后，对两组患者进行流调用抑郁自评量表（CES-D）评价、汉密尔顿-17 项抑郁量表（HAMD-17）评价和世界卫生组织生存质量测定量表简表（WHOQOL-BREF）评价及疗效评价。**结果：**在针刺各时点进行比较，两组患者 CES-D 评分、HAMD-17 评分呈下降趋势，WHOQOL-BREF 评分生理领域、心理领域、社会关系领域、环境领域的四个维度呈上升趋势。治疗结束后，观察组在 CES-D 评分、HAMD-17 评分和 WHOQOL-BREF 评分的四个维度均优于对照组（P＜0.05）。**结论：**两种方法均有助于阈下抑郁的治疗。相对于常规针刺，疏肝调神夹脊针对阈下抑郁患者的治疗有更好的临床效果，能有效改善阈下抑郁患者的抑郁症状，提高患者的生活质量。

关键词：阈下抑郁；疏肝调神；夹脊穴；针刺；临床研究

P4-8 Astrocyte may participate in the protection of moxibustion against blood–brain barrier damage in rats with multiple cerebral infarctions

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Objective: This study aimed to explore the effect of moxibustion at “Baihui” (GV 20), “Shenting” (GV 24) and “Dazhui” (GV 14) in the Governor Vessel on blood-brain barrier (BBB) damage in rats with multiple cerebral infarctions, and to explore the mechanisms.

Methods: Multiple microinfarct (MMI) in rats were used to model vascular dementia (VD). Moxibustion was administered at the Baihui (GV 20), Shenting (GV 24), and Dazhui (GV 14) for 14 days. Oxiracetam was injected intraperitoneally at a dose of 50 mg/kg for 14 days as the

positive control. Learning and memory was evaluated using the Morris water maze (MWM) and new object recognition test. Cerebral blood flow perfusion was detected by laser Doppler imaging. Pathological changes of the hippocampus were detected by HE staining. Blood brain barrier (BBB) permeability was evaluated by Evans blue staining. The expression of glial fibrillary acidic protein (GFAP) and CX 43 were observed by immunofluorescence. Hippocampal GFAP, CX43, platelet derived growth factor receptor β (PDGFR β), Zonula occludens-1 (ZO-1), C3 and S100A10 were determined by Western blot.

Results: MMI in SD rats damaged the learning and memory function and increased the neuronal degeneration in CA1, CA3, and DG regions of the hippocampus, impaired the BBB integrity, and reduced the cerebral blood flow perfusion and increased the brain mass. Notably, GFAP and C3 protein levels significantly increased, but CX43 and PDGFR β significantly decreased in the hippocampus of MMI SD rats. Moxibustion, as well as oxiracetam treatment improved learning and memory function and neuronal degeneration, enhanced BBB integrity, increased cerebral blood flow perfusion and decreased brain mass. Meanwhile, moxibustion treatment decreased GFAP and C3, and increased CX43 protein levels in the hippocampal. Besides, ORC-treat could increase PDGFR β protein levels in the hippocampus. Especially, immunofluorescence showed that moxibustion treatment reversed the MMI induced increase of GFAP and CX43 ratio in the region of vascular structural unit.

Conclusion: Moxibustion at Governor Vessel acupoints could promote cerebral blood flow and repair BBB function in rats with MMI, and astrocyte might participate in the protection.

Keywords: Moxibustion, Vascular dementia, Glial vascular unit, Glial fibrillary acidic protein, CX43

P4-9 Exploring the mechanism of *Gastrodia elata* Blume and its active compounds protects ischemic neuronal injury：network pharmacology and experimental validation

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Abstract: Traditional Chinese medicine embodies thousands of years of knowledge, clinical experience, richness and their medical resources. However, due to the complex composition and unclear mechanism action of Traditional Chinese medicine, the therapeutic ability has been questioned internationally. Stroke is one of the most serious threats to public health in 21st century, neuronal damage following cerebral stroke is the most devastating condition leading to major health concerns. Through hundreds of years clinical practice and experience in China, *Gastrodia elata* Blume and its extracts are quite effective to treat neurological diseases including headaches, dizziness, epilepsy, neuralgia and paralysis. However, its specific mechanism of action remains elusive. In this study, we employed a network pharmacology approach to elucidate the underlying mechanism of *Gastrodia elata* Blume against ischemic stroke, which was later validated by various experiments. Network pharmacology analysis revealed that a total of 72 proteins might serve as targets of *Gastrodia elata* Blume anti-ischemic stroke effects. The enrichment analysis of Gene Ontology and Kyoto Encyclopedia of Genes and Genomes showed that 50 potential targets mainly mapped to mTOR, AKt/PKB, COX, MAPK and other signal pathways. Furthermore, molecular docking results showed that core compounds 4,4'-dihydroxy dibenzyl ether, 4-ethoxymethylphenyl-4'-hydroxybenzylether and suchilactone had the highest number of anti-ischemic stroke targets and showed the strongest binding with targets MAPK10 and PTGS1. By using the oxygen glucose deprivation (OGD) in vitro hypoxia injury model in cell culture (PC12 and cortical neurons), our pharmacological data showed that the main compound in *Gastrodia elata* Blume, parishin and gastrodin, effectively alleviated hypoxic injury of PC12 cells and cortical neurons by inhibiting the phosphorylation of JNK and p38. In summary, this study sheds light on the therapeutic potential of of *Gastrodia elata* Blume against ischemic stroke by using network pharmacology and provides a scientific basis for further studying clinical applications of *Gastrodia elata* Blume.

Keywords: *Gastrodia elata* Blume; Ischemic neuronal injury; Network pharmacology; Parishin; Gastrodin

P4-10 四君子汤对久坐少动模型大鼠股四头肌 PAX7 和 MyoD 的影响

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目的：通过观察四君子汤对久坐少动模型大鼠股四头肌配对盒基因（paired box gene 7，Pax7）和成肌分化抗原（myogenic differentiation antigen，myoD）的影响，从肌肉干细胞角度揭示“久坐伤肉”的科学内涵。方法：18 只雄性大鼠按随机数字表法分为正常组、久坐少动模型组（模型组）、四君子汤治疗组（治疗组），每组 6 只，后 2 组采用束缚左后肢的方法制备久坐少动模型，同时分别灌服等量的蒸馏水和四君子汤，每日 1 次，共 21 天；采用大小鼠抓力仪检测后肢抓力；HE 染色法观察股四头肌组织学变化；ELISA 法检测股四头肌的肌球蛋白和肌动蛋白含量；免疫荧光法检测 Pax7 和 MyoD 表达。结果：与正常组相比，模型组肌纤维变细，左后肢抓力和肌肉湿重降低（P<0.01），肌球蛋白和肌动蛋白水平下降（P<0.05），Pax7 表达降低（P<0.05），MyoD1 表达升高；与模型组相比，治疗组肌纤维较粗，左后肢抓力和肌肉湿重增加（P<0.01），肌球蛋白和肌动蛋白水平上升（P<0.01），Pax7 表达升高（P<0.05），MyoD 表达降低（P<0.05）。结论：四君子汤能够在一定程度上对久坐性肌萎缩，其机制与影响肌肉干细胞的激活与增殖有关。

关键字：久坐伤肉；四君子汤；配对盒基因 7；成肌分化抗原；肌萎缩

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P5-比较生理

P5-1 Transcriptional regulation of retrotransposons by hypoxia

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Retrotransposable elements (RTEs) comprise up to one-thirds of the human genome. RTEs are silenced by DNA methylation and repressive histone modifications in healthy tissues but get unleashed during aging and cancer. RTEs have been believed to promote cancer by inducing genomic instability, but recent evidence demonstrated tumor suppressive roles of RTEs. However, the mechanisms of RTE regulation in tumor development remains unclear.

Hypoxic microenvironment is an important feature of solid tumors. Here, we compared the

response of RTEs and interferon (IFN) to hypoxia in multiple types of cells including human skin fibroblasts (HCA2), two human lung cancer cell lines (H1299 and A549), mouse skin fibroblasts (MSF), human embryonic lung fibroblasts (IMR90), mouse embryonic fibroblasts (MEF), Plateau zokor skin fibroblasts (PZSF) and naked mole rat skin fibroblasts (NSF).

The expression of LINE1 and Alu (two major RTE families) as well as IFNB1 was significantly repressed in HCA2, MSF, H1299 and A549 cells. Dual luciferase reporter assay and flow cytometry demonstrated that hypoxia represses LINE1 5'UTR-driven transcription. On the contrary, LINE1 was activated by hypoxia in IMR90, MEF, PZSF and NSF cells. RNA-sequencing showed that RTEs expression was broadly increased in IMR90 and repressed in A549 at the subfamily level. Interestingly, IMR90 and MEF are fibroblasts isolated during embryonic development, which has a hypoxic microenvironment; PZSF and NSF are fibroblasts from hypoxia-tolerant subterranean rodents.

We propose that downregulation of RTEs by hypoxia in somatic cells contributes to solid tumor refractory, and upregulation of RTEs in subterranean mammals mirrors the antitumor strategies of embryonic cells. We are exploring the molecular mechanisms and epigenetic modifiers behind the hypoxia-regulated RTEs expression. Our work will provide new targets based on epigenetic and retrotransposon reactivation for tumor suppression.

Keywords: Retrotransposons, tumor, hypoxia

P5-2 Multigenerational exposure of cadmium trans-generationally impairs locomotive and chemotactic behaviors in *Caenorhabditis elegans*

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Abstract: Cadmium is a naturally existing heavy metal and a notorious environmental pollutant. While its toxic outcomes and underlying mechanisms remain largely elusive. To explore the behavioral change caused by multigenerational exposure of cadmium to C. elegans, we challenged the C. elegans with cadmium for six generations and observed its impact on animal behaviors. Wild-type worms were randomly divided into two groups, the control and cadmium exposure groups. Locomotive and chemotactic behaviors were observed across six generations. Head thrashing frequency, chemotaxis index, and fold change index were used to evaluate the neurotoxicity of multigenerational cadmium exposure. Multigenerational cadmium exposure can trans-generationally increase the head thrashing frequency of C. elegans during swimming, and

impair the chemotactic behaviors to isoamyl alcohol, diacetyl, and 2-nonanone. Our findings proposed a trans-generationally behavioral impact induced by multigenerational cadmium exposure.

Keywords: Cadmium, Multigenerational, Toxicity, C. elegans, Locomotion, Chemotaxis, Transgenerational

P5-3 内皮素-1 诱导成年雄性斑胸草雀 HVC 缺血损伤致发声障碍模型的建立

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斑胸草雀鸣唱与人类语言相似，是一种通过后天习得的行为。斑胸草雀鸣唱行为的神经机制研究对于理解人类发声技能的学习和维持机制产生了重要的意义。HVC 是斑胸草雀发声通路中最高级的神经核团，在鸣唱学习与产生过程中承担着感觉运动整合的功能，并编码鸣曲成分（音节）的时序信息。研究表明，HVC 遭到破坏会导致斑胸草雀固化的主题曲结构不完整造成胸草雀的发声障碍。而人类发声运动脑区出现缺血性脑损伤会也会导致发声障碍。那么我们考虑使斑胸草雀 HVC 形成缺血性损伤是否会导致原有的固化的主题曲结构不完整。内皮素-1（endothelin-1, ET-1）是一种血管收缩肽，具有强烈持久的缩血管作用，可使局部脑血流量减少促进脑梗死形成,其优点在于该方法可控制脑缺血的位点和范围，已有研究表明 ET-1 直接应用于未成熟大鼠的海马体会导致脑缺血，因此我们选用 ET-1 作为建立斑胸草雀 HVC 缺血损伤导致发声障碍的主要药物。我们首次尝试将 ET-1 应用于斑胸草雀 HVC 中，采用微量注射技术向雄性斑胸草雀 HVC 双侧各微注射 ET-1，诱导斑胸草雀 HVC 形成缺血性损伤。研究结果显示 10 天左右，鸣曲消失，固化的主题曲结构不再出现。因此可以用 ET-1 诱导斑胸草雀 HVC 缺血损伤致发声障碍，进而可以用这个模型来研究缺血性脑损伤所致发声障碍的恢复机制，并为人类缺血性脑损伤所致发声障碍的治疗提供参考和借鉴。

关键词：斑胸草雀；HVC; 内皮素-1；发声障碍；病理模型

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P5-4 Effects of long-term Chlormequat chloride exposure to *C. elegans*

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Chlormequat chloride (CCC) is a widely used plant growth regulator and a newly identified food processing contaminant worldwide. This study focuses on the effects of long-term CCC exposure in *C. elegans* to provide a basis for its risk assessment and safe use. Synchronized *C. elegans* were exposed to 0, 0.05, 0.5, 5, 50, and 500 μg/ml CCC for 72h in nematode growth medium, using lethality, locomotion, reproduction, life span, growth, and chemotactic behavior as the effect parameters to evaluate the effects of long-term exposure. RNA sequencing was performed to detect transcriptomic changes in *C. elegans* treated with 50 μg/ml CCC. Our results showed that all concentrations of CCC significantly impaired the reproduction capacity of *C. elegans*, represented as reduced brood size and progeny number, without affecting the hatchability. The lifespan of *C. elegans* was remarkably reduced in the groups treated with 50 μg/ml and 500 μg/ml of CCC. Comparing with the control group, gene expression profiling showed significant differences, and pathway enrichment analysis revealed changes in gene expression related to RNA synthesis and transport, protein transport, degradation and localization, and nutrient metabolism in CCC-treated *C. elegans*. Screening key gene and related experimental results suggested that the dysregulation of protein degradation-related genes, such as *eel-1*, *rle-1*, and *wwp-1*, may be closely associated with the decreased reproductive ability and shortened lifespan. Taken together, these results demonstrate that long-term CCC exposure may impair reproductive ability and shorten the lifespan of *C. elegans*. The findings of this study have tremendous implications for the risk assessment of CCC in the environment.

Keywords: Chlormequat chloride, *C. elegans*, long-term exposure, Reproductive toxicity, lifespan

P5-5 高原鼢鼠 Epas1 基因变异及肺纤维化保护机制

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摘要：高原鼢鼠(*Myospalax baileyi*，*M.b*)是世居青藏高原的优势地下鼠，能适应洞道中严重缺氧和高二氧化碳的极端环境。为了探究其长期低氧适应性演化机制，本文以平原 SD 大鼠和平原甘肃鼢鼠(*Myospalax cansus*，*M.c*)为对照，利用生物信息学，比较转录组学和原代细胞培养等方法，研究了高原鼢鼠基因 *Epas1*（内皮 PAS 结构域包含蛋白 1，Endothelial PAS domain-containing protein 1，编码低氧诱导因子 2，Hypoxia inducible factor，HIF-2α）的变

异；比较了实验室大鼠和高原鼢鼠及甘肃鼢鼠肺脏组织的基因转录；成功获得了高原鼢鼠的原代肺成纤维细胞；探讨了高原鼢鼠肺成纤维细胞的抗纤维化保护机制。结果表明：（1）高原鼢鼠和甘肃鼢鼠等其他中国地区鼢鼠中，HIF-2α 密码子 480 位点都由保守的苏氨酸（Thr，T）突变为丝氨酸（Ser，S）。（2）S480 变异通过抑制 HIF-2α 的磷酸化水平，提高其蛋白稳定性和转录活性，促进了胶原蛋白（Collagen）家族基因的转录。（3）与甘肃鼢鼠比较，高原鼢鼠肺组织中纤毛运动相关基因呈高表达，而细胞外基质相关基因和免疫炎症相关基因呈低表达。这种转录调节模式同样出现在持续低氧五天（5000 m，10.8% O_2，5 d）的平原 SD 大鼠肺脏组织中。（4）高原鼢鼠肺成纤维细胞暴露于低氧（1%或 0.1% O_2，24 h）不会激活 HIF-2α 蛋白表达；低氧暴露、氧化应激（H_2O_2）和 TGF-β 刺激都不会诱导高原鼢鼠肺成纤维细胞纤维化。结果提示，高原鼢鼠肺组织增强纤毛功能、下调细胞外基质和免疫反应相关基因的转录调节可能是长期低氧环境适应的策略；其 HIF-2α 独特的 S480 变异可能参与肺成纤维细胞抵抗低氧和抗纤维化生成。

关键词：高原鼢鼠；低氧；内皮 PAS 结构域包含蛋白 1；纤维化

P5-6 低氧下骨髓巨噬细胞分泌的 Metrn 调控造血干细胞动员和分化

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造血干细胞（HSC）可以分化成淋巴系、髓系和红系细胞，主要存在于骨髓微环境中，受到微环境中辅助细胞的调节，且处于生理性低氧状态。巨噬细胞可以感受微环境低氧，同时可调节 HSC 功能，然而低氧下骨髓巨噬细胞参与 HSC 功能调节的机制仍不明确。在本研究中，我们首先观察到骨髓巨噬细胞中 Metrn 高表达，并由此提出假设：骨髓巨噬细胞分泌的 Metrn 可能参与了 HSC 稳态调节。进而发现巨噬细胞特异性 Metrn 敲除可以促进 HSC 的增殖和迁移，从而促进 HSC 由骨髓动员进入血液。骨髓低氧环境可通过 HIF-1α 和 YY1 促进 Metrn 表达。转录组测序揭示巨噬细胞特异性 Metrn 敲除后，脂肪酸氧化、磷脂酶 C（PLC）活性激活等途径在 LSK 细胞中上调，而 DNA 模板的转录正调控、B 细胞凋亡负调控等途径在 LSK 细胞中下调。我们进一步发现了 HSC 胞内的 PLC 信号在巨噬细胞特异性 Metrn 敲除小鼠中激活，激活的 PLC 可以通过调节 Nr4a1 和 Alox15 的表达提高 ROS 水平，从而揭示了 Metrn 调控 HSC 动员的胞内信号途径。免疫共沉淀发现 HSC 表面表达的 Htr2b 可与 Metrn 结合。为进一步探究 Htr2b 在 Metrn 调控 HSC 动员过程中的作用，我们构建了造血细胞特异性 Htr2b 敲除模型，并发现 HSC 中 Htr2b 的缺失激活 PLC 信号进而提高 ROS 水平，从而抑制 HSC 的增殖和动员，Metrn 敲降不影响 Htr2b 敲除后 HSC 的增殖。说明 Htr2b 是 Metrn 在 HSC 上的功能性受体。在上述工作基础上发现炎症条件下 Metrn 可抑制 HSC 向髓

系细胞分化。本研究揭示了低氧调控HSC动员的新机制从而提出Metrn阻断可用于改善HSC动员从而获得HSC用于干细胞治疗，并且发现Metrn抑制HSC向髓系分化从而减轻炎症反应。上述工作也揭示生理低氧下骨髓巨噬细胞帮助HSC维持静息的新机制。

关键词：造血干/祖细胞、Metrn、低氧、动员、活性氧

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P5-7 White and brown adipose tissues: the fuel for hibernation

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Hibernation is the most effective energy saving strategies for small mammals. To survive the hibernation season, some hibernators store body fat as the main fuel of hibernation during fattening period. There are 2 types of adipose tissue with opposite functions, the white adipose tissue (WAT) is the energy storing organ and the brown adipose tissue (BAT) burn the lipid through thermogenesis. WAT accumulation affects the survive rate and hibernation expression. WAT dramatically increased by about 10-fold in 2-3 months fattening period with on evidence of obesity-related diseases. However, the underlying mechanism of this impressive adaptation is still unknown. The distribution of WAT is crucial for metabolic health, the visceral fat accumulation is closely related with metabolic disorders. Our recent study shows that, Daurian ground squirrel (*Spermophilus dauricus*), a typical fat-storing hibernator, accumulate subcutaneous WAT before visceral WAT during fattening, the visceral WAT showed hyperplasia rather than hypertrophy during fattening period. This adipogensis pattern provide the insights into metabolic health during fattening. According to our previous observation, the hibernation varies among individuals, some animals just express very shallow torpors during the whole hibernation season. Since BAT is the the most important thermogenic organ and mitochondria is crucial organelle for the thermogenic capacity, we observed the morphological differences of mitochondria among hibernating, euthermia and arousal Daurian gound squirrels. We found that the euthermia squirrels showed decrased mitochondrial cristae density comparing with hibernating and arousal squirrels. Besides, the lipid droplet area is significantly smaller in euthermia squirrels' BAT. These results might be indicating the relationship between BAT mitochondrial morphology and hibernation expression. Above all, as the fuel of hibernation, the accumulation and physiological changes of adipose tissue affect the hibernation profoundly, the underling mechanisms might provide evidences of hibernation initiation and maintenance.

Key words: hibernation, white adipose tissue, brown adipose tissue, Daurian ground squirrel

P5-8 HCAR2 介导低氧促神经干细胞增殖的作用与途径

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我们前期工作表明低氧能通过 HIF-1/BNIP3/mTORC1/自噬途径显著促进大鼠神经干细胞（NSCs）增殖，在本研究中我们利用小鼠低氧模型进一步揭示了 HIF-1 能通过一条新的信号途径诱导自噬，进而促进 NSC 增殖。我们发现烟酸受体 HCAR2 能在 NSCs 中低表达，但在低氧条件下其表达水平显著增加。在低氧下敲低 HCAR2 会抑制 NSC 增殖，而在常氧下过表达 HCAR2 则促进了 NSC 增殖。这些结果表明，HCAR2 介导了低氧促 NSC 增殖作用。随后，我们证明 HCAR2 为 HIF-1 新的靶基因。为了进一步探索 HCAR2 影响 NSC 增殖的信号途径，我们对敲低 HCAR2 后的 NSCs 进行了转录组测序，结果表明敲低 HCAR2 后细胞自噬通路出现显著下调。接下来，我们通过 Western Blot 进行了实验验证，结果显示 HCAR2 的蛋白表达量与细胞自噬活性呈高度正相关，干扰 HCAR2 的表达会影响 NSC 自噬活性。随后，我们在过表达 HCAR2 的 NSCs 中分别施加自噬阻断剂 Baf A1 以及敲低自噬关键分子 ATG7 来抑制自噬，结果发现 HCAR2 促 NSC 增殖能力在自噬被抑制后被明显减弱，进一步证实了自噬是 HCAR2 调控 NSC 增殖的关键途径。总之，本研究揭示了低氧促进 NSC 增殖的一条新的信号通路，这为相关疾病的防治提供了新的干预靶点。

P6-运动生理

P6-1 12 周重组胶原蛋白补充联合有氧运动对去卵巢大鼠肌骨共减的影响

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目的：肌少-骨质疏松又称肌骨共减（ostesarcopenia，OS），以骨和骨骼肌结构功能下降为特征。据报道，胶原蛋白具有防治 OS 的作用，基于基因重组技术的重组胶原蛋白（RHC）倍受关注。本研究旨在探讨不同剂量 RHC 联合有氧运动对去卵巢大鼠 OS 的影响。

方法：81 只 4 月龄 SD 雌鼠分为假手术组（Sham 组，n=9）和去卵巢组（n=72），去卵巢组进行双侧卵巢摘除手术，假手术组去除部分脂肪。术后，大鼠安静饲养 4 个月，去卵

巢组随机分为去卵巢对照（OVX）、L、M、H、中剂量市售胶原蛋白（Ms）、有氧运动（AT）和中剂量 RHC 联合有氧运动（ATM）组。低中高剂量分别为 0.1、0.5、1 g /kg BW/d，运动组进行 12 周跑台运动训练，60 min×5 次/周。末次干预后取材，称取脏器、脂肪、骨骼肌和股骨重，游标卡尺测量股骨长和直径；双能 X 线吸收检测骨密度（bone mineral density，BMD）、体脂率；抓力仪检测前肢抓力；micro CT 检测股骨远端微结构；三点弯曲实验检测股骨力学特性，包括最大载荷和刚度。

结果：（1）相较于 Sham 组，OVX 组 BMD、前肢抓力、股骨系数、最大载荷、刚度极显著降低，体脂率、腹股沟脂肪系数极显著升高（P<0.01）。（2）各组心、肝、脾和肾脏系数均无显著差异（P>0.05），去卵巢各组子宫系数显著低于 Sham 组（P<0.05）。相较于 OVX 组：（3）BMD、前肢抓力在 L、H 和 Ms 组无显著差异（P>0.05），M 和 AT 组显著升高（P<0.05），ATM 组极显著升高（P<0.01）；（4）AT 和 ATM 组体脂率极显著降低（P<0.01）；（5）股骨最大载荷、刚度在 L 和 M 组显著升高（P<0.05），AT 和 ATM 组极显著升高（P<0.01）；（6）腹股沟脂肪系数在 L 和 M 组显著降低（P<0.05），AT 和 ATM 组极显著降低（P<0.01）；（7）AT 和 ATM 组腓肠肌、股四头肌系数和股骨系数极显著升高（P<0.01）。

结论：12 周中剂量 RHC 补充可改善去卵巢导致的 OS，增加骨微结构，提高骨力学特性和肌肉功能，运动联合干预效果更好。

关键词：重组胶原蛋白；有氧运动；去卵巢大鼠；肌骨共减

P6-2 Arterial smooth muscle cell AKAP150 mediates exercise-induced repression of $Ca_V1.2$ channel function in hypertensive cerebral arteries

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Hypertension is a major, prevalent risk factor for the development and progression of cerebrovascular disease. Regular exercise has been recommended as an excellent choice for the large population of individuals with mild to moderate elevations in blood pressure, but the mechanisms that underlie its vascular-protective and antihypertensive effects remain unknown. Here, we describe a mechanism by which myocyte AKAP150 inhibition induced by exercise training alleviates $Ca_V1.2$ channel activity and restores cerebral arterial function in hypertension. Spontaneously hypertensive rats (SHRs) and newly generated smooth muscle-specific AKAP150 knockin (AKAP150 smKI) mice were used to assess the role of myocyte AKAP150/$Ca_V1.2$ channel in regulating cerebral artery function after exercise intervention. Activation of the

AKAP150/PKCα signaling increased $Ca_V1.2$ activity and Ca^{2+} influx of cerebral arterial myocyte, thus enhancing vascular tone in SHRs. AKAP150 smKI mice were hypertensive with higher $Ca_V1.2$ channel activity and increased vascular tone. Furthermore, treatment of angiotensin II resulted in a more pronounced increase in blood pressure in AKAP150 smKI mice. Exercise training significantly reduced arterial myocyte AKAP150 expression and alleviated $Ca_V1.2$ channel activity, thus restoring cerebral arterial function in SHRs and AKAP150 smKI mice. In cultured cerebral arteries, AKAP150 knockdown attenuated $Ca_V1.2$ channel activity and vasoconstricting response. The current study demonstrates that aerobic exercise ameliorates $Ca_V1.2$ channel function via inhibiting myocyte AKAP150, which contributes to reduced cerebral arterial tone in hypertension.

Keywords: aerobic exercise; hypertension; $Ca_V1.2$ channel; AKAP150; cerebral arteries

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P6-3 有氧运动对抑郁症人群睡眠质量干预效果的系统评价和 Meta 分析

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目的：睡眠障碍是抑郁症的常见症状。一旦患者出现睡眠障碍，将会增加抑郁症治疗的困难，降低患者的生活质量，增加患者自杀的风险。运动是改善抑郁症的有效手段，但其机制远未明了。本研究通过系统评价及 Meta 分析评估有氧运动对抑郁症患者睡眠质量的影响。

方法：以“exercise”、“depression”和“sleep quality”为主题词，通过“主题词＋自由词”的检索策略在 PubMed、Web of Science、EMBASE 和 Cochrane Library 等数据库进行检索。检索时限为自建库至 2023 年 5 月 31 日。根据 Cochrane 系统评价“PICOS”原则制定文献纳入和排除标准，由两位作者独立进行文献检索、筛选和数据提取。使用修订的 Cochrane 偏倚风险第 2 版（RoB 2）工具对纳入文献进行质量评估。采用 Review Manger 5.3 和 STATA 17.0 软件进行 Meta 分析。

结果：最终纳入 9 篇随机对照试验文献，其中低偏倚风险 5 篇，中等偏倚风险 3 篇，高偏倚风险 1 篇，总样本量 471 人。结局指标包括抑郁症状、睡眠质量、焦虑症状和生活质量。抑郁症状（I^2=64%）和焦虑症状（I^2=76%）的异质性检验结果较高，故采用随机效应模型计算合并效应量；睡眠质量（I^2=34%）和生活质量（I^2=0%）的异质性检验结果较低，故采用固定效应模型。Meta 分析结果显示，有氧运动可以显著改善抑郁症患者的抑郁症状

[SMD(95%CI)=-0.68(-1.01, -0.36), P＜0.05]；有氧运动可以显著改善抑郁症患者的睡眠质量[SMD(95%CI)=-0.71(-0.90, -0.52), P＜0.05]；有氧运动可以显著改善抑郁症患者的焦虑症状[SMD(95%CI)=-0.68(-1.16, -0.21), P＜0.05]；有氧运动可以显著提高抑郁症患者的生活质量[SMD(95%CI)=0.62(0.34, 0.91), P＜0.05]。以上指标的敏感性分析结果均保持一致，Begg 和 Egger's 检验结果表明数据均不存在明显的发表偏倚（P＞0.05）。

结论：有氧运动能够改善抑郁症患者的抑郁症状、睡眠质量和焦虑症状，并提高患者的生活质量。但考虑到纳入文献的偏倚风险和样本量偏少的问题，本研究结论还需要进一步深入研究证实。

关键词：有氧运动，抑郁症，睡眠质量

P6-4 孕期运动改善高血压子代血管功能的 *Fgf21* 组蛋白去乙酰化机制

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目的：孕期运动可有效降低后代罹患高血压等心血管疾病风险，但其具体机制尚不完全清楚。研究表明，成纤维细胞生长因子 21（fibroblast growth factor 21，FGF21）主要通过与受体 FGFR1、β-klotho 结合发挥作用，其循环水平与血压升高显著相关，但 FGF21 对高血压外周阻力动脉结构和功能的潜在作用尚未阐明。因此，本研究拟观察孕期运动对高血压子代肠系膜动脉结构和功能的影响，并探讨 SIRT1 介导的 FGF21 基因组蛋白去乙酰化在其中发挥的作用。**方法：**怀孕的自发性高血压大鼠（spontaneously hypertensive rat，SHR）以及正常血压对照组大鼠（Wistar-Kyoto，WKY）随机分为安静组（p-WKY-SED，p-SHR-SED）和运动组（p-WKY-EX，p-SHR-EX）。运动组孕期（gestation day，GD1-GD20）进行无负重游泳运动。以胎鼠（胚胎 21 天）和子代 3 月龄（3M）雄性大鼠为研究对象，采用离体微血管环张力测定、Western blotting 、ChIP-seq 和 ChIP-qPCR 等技术检测子代 3M 大鼠肠系膜动脉（mesenteric artery，MA）张力、SIRT1-FGF21 信号相关蛋白表达和胎鼠 FGF21 基因组蛋白乙酰化水平。**结果：**孕期运动可明显降低 p-SHR-EX 组子代 3M 大鼠的收缩压、舒张压、平均动脉压以及 MA 中膜厚度/管腔内径比值（P<0.05）。高血压时，FGFR1 抑制剂 PD166866 介导的血管舒张反应显著减弱（P＜0.05），而孕期运动可有效上调 PD166866 介导的血管舒张作用（P＜0.05）。ChIP-seq 结果显示，*Fgf21* 启动子区存在一个明显的 H3K9ac 富集峰区域；ChIP-qPCR 进一步验证发现，p-SHR-SED 组 *Fgf21* 启动子区组蛋白 H3K9ac 富集水平显著高于 p-WKY-SED 组。孕期运动可显著上调高血压子代胎鼠 MA 中 SIRT1、FGFR1 的 mRNA 和蛋白表达（P<0.05），下调其 *Fgf21* 启动子区 H3K9ac 富集水平，进而抑制 *Fgf21* 基因转录和蛋白表达（P<0.05）；这一趋势在高血压子代 3M 大鼠 MA 中依旧存

在。**结论：**孕期运动可通过上调高血压子代血管中 SIRT1 表达，降低 *Fgf21* 启动子区 H3K9ac 水平，抑制 *Fgf21* 基因转录，下调 FGF21 蛋白表达，进而改善高血压子代成年雄性大鼠血管功能，降低血压。

关键词： 孕期运动；高血压；表观遗传；*Fgf21*；SIRT1

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P6-5 有氧运动改善高脂饮食诱导肥胖小鼠代谢异常的作用机制研究

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研究目的：肥胖通常与许多代谢疾病有关，如 II 型糖尿病、非酒精性脂肪肝和心血管疾病等。迄今为止，大多数研究表明有氧运动对预防肥胖有效。通过脂肪酶催化水解三酰甘油来减少脂肪沉积，这一过程被称为脂解。然而，运动对脂肪分解的影响机制尚不清楚。本研究旨在探讨运动对肥胖小鼠脂肪代谢相关酶的影响。

研究方法：取 C57BL/6J 雄性小鼠 12 只，随机平均分为对照组（Ctrl, n=4）、高脂组（HFD, n=4）和高脂运动组（HFD + EXE, n=4）。12 周运动干预后称重,麻醉后处死。采集血液检测血脂四项即甘油三酯(triacylglycerol, TG)、总胆固醇 (total cholesterol, TC)、低密度脂蛋白胆固醇(Low-density lipoprotein cholesterol, LDL-C) 和高密度脂蛋白胆固醇(High-density lipoprotein cholesterol, HDL-C)。取肝组织，进行 H&E 染色。Western blotting 检测 HSL、MAGL 和 ATGL 蛋白表达。

研究结果：与 Ctrl 组和 HFD + EXE 组相比，HFD 组小鼠体重显著增加($P < 0.001$)。H&E 染色显示，HFD 组脂肪变性明显，分布有大量弥漫性球囊样改变($P < 0.05$ v.s. Ctrl)，肝细胞大小不均，核膜边界不清。与 HFD 组相比，HFD + EXE 组脂肪空泡数量和直径均显著减少($P < 0.05$)。HFD 组 TG 水平显著高于 Ctrl 组和 HFD + EXE 组($P < 0.001$)。HFD + EXE 组 LDL-C/HDL-C 水平显著低于 HFD 组($P < 0.05$)。HFD 组和 HFD + EXE 组 TC 水平均显著升高($P < 0.01$ v.s. Ctrl)。Western blotting 结果显示，HFD + EXE 组脂肪分解酶(ATGL、HSL、MAGL)表达显著上调($P < 0.001$ v.s. HFD)。

结论：肥胖会导致小鼠的脂肪代谢酶（ATGL、HSL、MAGL）表达下降，影响肝脏微结构和糖脂代谢功能，从而进一步加剧肥胖发展。本研究证实，运动能够改善高脂饮食诱导的肥胖及代谢紊乱，但其具体分子作用机制需要进一步探索。

关键字：肥胖；肝脏；代谢；有氧运动；脂肪水解

P6-6 心率监测在体能训练课运动负荷评价中的实践研究

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研究目的：适宜的运动负荷能够有效增强学生身体素质，体育课作为学生参与体育锻炼的重要途径之一，在学生体质健康提升方面发挥着重要作用。新课标（2022 版）对体育课运动强度和练习密度做出明确规定。本研究依照北京市体育课地方标准，通过心率监测了解新课程改革背景下初二学生体能课运动负荷现状，为一线教师体能课教学设计提供参考，促进初中生身心健康发展。

研究方法：选取北京市西城区某中学初二学生作为被试，通过 Polar Verity 心率采集设备监测学生体能课心率，用心率区间和训练冲量(TRIMP)量化不同教学内容体能课(体能课 1：速度练习；体能课 2：速度耐力练习；体能课 3：耐力练习)运动负荷，分析心率、训练冲量、练习密度等指标，探究不同体能课运动负荷变化及相关调控措施。

研究结果：(1) 初二学生体能课平均心率为 140.6 次/min。心率分布在很小强度区间(HR＜120)占比 22.2%，小强度(120≤HR＜140)心率负荷占比 25.9%，中等强度(140≤HR＜160)心率负荷占比 26.5%，大强度(160≤HR＜180)心率负荷占比 16.7%，极限强度(180≤HR)心率负荷占比 4.6%。有效运动负荷占比 77.2%；(2) 不同教学内容的体能课 3 平均心率为 145.35 次/min，体能课 1 为 137.89 次/min，体能课 2 为 137.67 次/min；(3) 体能课男生平均心率为 144.22 次/min，有效运动负荷强度占比 82.63%，累计时长 34.08min。女生平均心率为 136.31 次/min，有效运动负荷强度占比 71.5%，累计时长 28.43min；(4) 体能课平均 TRIMP 值为 100.46；(5) 准备部分平均用时 6.65min，基本部分 33.29min，结束部分 2.05min。

研究结论：初二体能课总体运动强度适宜，有效运动负荷占比较高，以中等强度为主；男生运动强度适宜，女生平均心率稍低于新课标中提出的体育课适宜心率；体能课 TRIMP 值负荷北京市标准；体能课密度较大，练习时间较长；建议适当调整体能课各部分的时间比例，增加结束部分的时长，保证学生能够在下课前恢复至安静心率，有充足的放松时间。

关键词：体能课；初中生；心率；训练冲量

P6-7 UVB 照射改善小鼠自主活动量的神经电生理学研究

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研究目的：UVB（Ultraviolet B）是紫外线中波长在 280nm～320nm 范围内的中频中波，

适量照射是体内维生素 D（Vitamin D，VD）合成的必要条件。VD 作为脑内重要神经小分子物质，在腹侧背盖区（Ventral tegmental area，VTA）多巴胺神经元兴奋性调节中发挥作用。VTA 是脑内 DA 能神经元主要聚集区，构成 VTA-NAc 多巴胺神经通路，参与生物体动机、奖赏等本能行为的调节。规律的身体活动可对机体产生疾病预防与保护的作用，目前，静坐少动成为现代社会的公共卫生问题，寻找激发身体主动运动动机的对策与方法尤为重要。本文将结合神经电生理记录技术观测 DA 神经元在 UVB 照射后行为活动调节中的响应特征。

研究方法：（1）选取 C57BL/6J 雄性（7 周龄）小鼠，随机分为对照组（N=11）、UVB 照射组（N=11），UVB 组每天进行 50mJ/cm^2 的 UVB 照射，连续 4-7 天；（2）采用自主运动跑盘监测系统对行为表征进行 24 小时记录；采用条件位置偏好系统对跑盘偏好情况进行观测；分析运动距离、运动时间、运动次数以及 24 小时运动节律；（3）采用多通道电生理胞外记录技术，记录 VTA DA 神经元电活动特征，结合行为学判断其响应变化；（4）使用 MATLAB 进行统计分析。

研究结果：（1）UVB 照射后小鼠日平均运动距离增长 41%，日平均运动时间增长 63%，日平均运动次数增长 62%；CON 组跑盘偏好得分为 78s，UVB 组为 108s；（2）在 VTA 记录到 DA 神经元平均放电频率范围为 13.5Hz-44.9Hz，动作电位波宽为 0.2ms，波幅为 0.31mv；小鼠自主运动时平均放电频率升高 37%；记录到的神经元对 UVB 响应可分为两类，一类在 UVB 照射时放电频率降低 39%，一类升高 270%。

研究结论：（1）UVB 照射可提高小鼠自主活动量，延长夜间活动高峰期；UVB 组小鼠跑盘偏好得分高于 CON 组；（2）VTA 的不同神经元在身体活动调节中存在不同机制，对 UVB 照射存在不同响应特征，因此，我们将结合神经电化学方法探讨引起神经元电活动变化的神经小分子调节机制。（NFSC:31971095）

关键词：UVB；身体活动；多巴胺；电生理；动机

P6-8 心率监测在高中女子排球实战训练中的应用及评价

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研究目的：2020 年教育部与国家体育总局联合印发《关于深化体教融合 促进青少年健康发展的意见》中提出，鼓励中学建立排球学校代表队，也是全国第一届学生（青年）运动会备受关注的项目。目前科学化训练方面相关研究较少，因此本文对某高中女子排球队训练过程进行心率监测，了解其训练负荷实时情况，为教练员合理安排训练任务实施训练计划提供生理学参考。

研究方法：（1）本文选取 15 名某高中校女排队员作为心率监测被试；（2）采用 Polar FlowSync 心率带作为研究工具，对被试队员训练课实时监测，并对监测结果分析；（3）根据监测队员的最大心率将心率(Beat Per Minute)划分为 5 个等级区间，并采用训练冲量(TRIMP)区间权重因子×持续时间量化训练强度（权重因子分别对应值为 1、2、3、4、5），（4）运用 Excel 对所得数据处理，主要包括平均数、区间个数等描述性统计。

研究结果：（1）被试群体平均年龄 16.4、身高 181cm、体重 67.3kg；训练年限 7.4；（2）一节训练课时间为 3h，包括准备、技术、体能、恢复四个部分，训练中整体最大心率 177 bpm、平均心率 130bpm、最小心率 82bpm，安静心率 42bpm;（2）各专位队员运动负荷强度特征分析显示，主攻 Trimp 值分布 46.8、57.6、329.4、72、0；接应 14.4、68.4、361.8、28.2、0；自由人 25.2、111.6、205.2、115.2、0；副攻 59.4、115.2、129.6、0%、0%；二传 36、187.2、91.8、50.4、0；（3）整体 Trimp 分布 32.4、194.4、113.4、21.6、0，中大强度持续时间 43.2min，Trimp135，占比 24%。

研究结论：（1）训练强度的安排应根据训练周期的特征及需求展开，本监测为赛后恢复期，整体训练强度小；（2）各专位队员表现出不同运动强度分布特征，这是由于训练课内容是模拟比赛情景，接应要承担进攻与防守，因此负荷强度最大；（3）从总 Trimp 值来看负荷强度较小。(NFSC:31971095)

关键词：心率监测；高中；女子排球训练；Trimp；负荷评价

P6-9 有氧运动对尼古丁成瘾戒断小鼠外侧缰核神经元群体编码特征的影响

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目的：改善戒断症状是减少尼古丁复吸的重要策略，外侧缰核（the lateral habenula, LHb）是大脑的反奖赏中枢。本研究以尼古丁小鼠戒断期 LHb 的神经元群体活动变化特征为切入点，在神经网络水平探究运动减少尼古丁复吸的神经生物学机制，为运动防治成瘾提供实验依据。

方法：以 8 周龄、SPF 级、雄性 C57BL/6 小鼠为研究对象。动物房适应性喂养后，行微丝阵列电极埋置术。采用条件性位置偏爱实验构建尼古丁成瘾模型，建模成功后将小鼠随机分为生理盐水安静组（SS 组）、生理盐水运动组（SE 组）、尼古丁安静组（NS 组）和尼古丁运动组（NE 组），随后进行为期 2 周的戒断。在戒断期，运动组进行两周中等强度有氧运动（前 10min 跑台速度为 12m/min，后 50min 跑台速度为 15m/min，坡度为 0，60min/d，5d/w），安静组小鼠自由饮食及进水。采用免疫荧光染色技术检测 LHb c-fos 的表

达，在体多通道神经信号采集技术记录 LHb 局部场电位。统计学检验使用 SPSS 20.0，方差齐则采取双因素方差分析，显著性水平为 $P<0.05$。

结果：①有氧运动降低尼古丁成瘾小鼠在戒断期对药物的渴求度（$P<0.05$）。②有氧运动增强正常小鼠 LHb 的激活程度（$P<0.001$）；有氧运动降低尼古丁成瘾小鼠戒断期 LHb 的异常激活（$P<0.01$）。③有氧运动对尼古丁成瘾小鼠戒断期 LHb 场电位总能量无显著性影响（$P>0.05$）；有氧运动增强正常小鼠 LHb 场电位 theta 频段能量占比（$P<0.01$）；有氧运动降低尼古丁成瘾小鼠戒断期 LHb 异常增高的 theta 频段场电位能量（$P<0.01$）。

结论：尼古丁成瘾戒断期 LHb 神经元被异常激活，表现为 theta 频段神经网络振荡异常增强。有氧运动降低尼古丁成瘾小鼠戒断期 LHb 异常增高的 theta 频段神经网络振荡，这可能是运动改善尼古丁成瘾的中枢机制之一。

关键词：有氧运动，尼古丁，成瘾，外侧僵核，神经网络

P6-10 运动想象联合干预对脑卒中患者上肢功能和日常生活能力（ADL）的影响：Meta 分析

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目的：系统评价运动想象疗法联合保健康复类与联合训练方法对脑卒中偏瘫患者上肢功能恢复以及日常生活能力的影响。

方法：系统检索知网、万方、维普、中国生物医学文献数据库（CBM）、PubMed、Embase、PEDro、Cochrane Library、Web of Science 中关于运动想象疗法改善脑卒中患者肢体功能障碍的随机对照试验，同时追索纳入文献的参考文献，检索时限均为从建库到 2022 年 10 月。由两位评审员对纳入研究进行质量评价和资料提取，对符合标准的 39 项 RCT 进行 meta 分析，统计学分析采用 RevMan 5.4 软件。

结果：在 Fugl－Meyer 量表（FMA）和改良 Barthel 指数（MBI）中，与常规治疗组/单独运动想象疗法相比，运动想象联合保健类更能提高 FMA 和 MBI 分数，差异具有统计学意义（P＜0.05）。亚组分析结果显示，在改善上肢功能方面，运动想象联合保健类对病程 3 个月以下、干预时间 4 周以下的患者更优，联合训练方法类对病程 3-6 个月的患者更优，差异具有统计学意义（P＜0.05）；在改善日常生活能力方面，运动想象联合保健类对病程 3 个月以下、干预时间 6-8 周的患者更有效，联合训练方法类对病程 3-6 个月、干预时间 4 周以下的患者更优，差异具有统计学意义（P＜0.05）；运动想象联合疗法对 55-70 岁的患者比 50-65 岁患者更能提高 FMA 和 MBI 分数，差异具有统计学意义（P＜0.05）。

结论：运动想象联合疗法可明显改善患者上肢功能和日常生活能力，对不同病程、干预时间、脑卒中类型、年龄分段的脑卒中患者效果各不相同。但鉴于纳入研究较少，样本量小，且质量不高，各研究评价方法变异性较大，故仍需更多高质量研究予以验证运动想象疗法的

实施方式与方法对脑卒中患者上肢功能和日常生活能力的康复效果。

关键词：脑卒中患者；运动想象联合；meta 分析；联合保健类；联合训练方法；上肢功能；日常生活能力

P6-11 脂联素对肝脏 PLIN2 降解的调控途径及其与运动减肥促肝脂分解的关系研究

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目的：探讨脂联素（APN）促进肝脏脂解作用与脂滴包被蛋白 PLIN2 降解的关系及调控途径，进而研究运动减肥促进肝脂分解与 APN-PLIN2 途径关系。为脂联素应用和运动减肥机制研究提供理论和实践依据。

方法：选用雄性 C57BL/6 小鼠 52 只，其中 12 只为脂联素敲除小鼠，另外 40 只同窝野生小鼠。敲除小鼠正常饮食，进行脂联素药物干预。野生型小鼠通过高脂饮食造肥胖造模，造模成功后进行运动和脂联素药物干预。运动干预为 8 周有氧运动训练，药物干预为 Acrp30 注射一周。小鼠共分为 7 组，剔除造模失败小鼠，每组 6 只。分别为野生组(WT)、野生给药组(WT+Acrp30)、敲除组($Adi^{-/-}$)、敲除给药组($Adi^{-/-}$+Acrp30)、高脂组(HFD)、高脂给药组(HFD+Acrp30)、高脂运动组(HFD+EXE)。运动和药物干预后取小鼠肝脏，采用 Western Bolt、RT-PCR、Elisa 等方法检测小鼠肝脏中 APN、APNR2、AMPK、p-AMPK、NRF2、HSC70、LAMP2A、PLIN2 和 p-PLIN2 的表达以及肝脏 TG、ATGL，数据使用 SPSS26.0 统计软件分析。

结果：(1)与 WT 组比较，HFD 组小鼠体重升高；$Adi^{-/-}$组、HFD 组小鼠肝脏 TG 水平升高，ATGL 含量下降；肝脏 APN、AMPK、NRF2、HSC70 和 LAMP2A 的蛋白和 mRNA 表达降低，PLIN2 的表达升高，p-AMPK、p-PLIN2 的水平下降(p<0.01)；WT+Acrp30 组小鼠体重、脂体比和肝脏 TG 水平下降，ATGL 含量升高，肝脏 APN、AMPK、NRF2、HSC70 和 LAMP2A 的蛋白和 mRNA 表达升高，PLIN2 的表达降低，p-AMPK、p-PLIN2 水平升高(p<0.01)；（2）与 HFD 组比较，HFD+Acrp30 组、HFD+EXE 组小鼠体重、脂体比和肝脏 TG 水平降低，ATGL 含量升高，肝脏 APN、APNR2、AMPK、NRF2、HSC70 和 LAMP2A 的蛋白和 mRNA 表达降低，PLIN2 的表达升高，p-AMPK、p-PLIN2 的水平下降(p<0.01)；（3）同 $Adi^{-/-}$组比较，$Adi^{-/-}$+Acrp30 组小鼠体重、脂体比和肝脏 TG 水平降低，ATGL 含量升高，肝脏 APN、AMPK、NRF2 和 LAMP2A 的蛋白和 mRNA 表达降低，PLIN2 的表达升高，p-AMPK、p-PLIN2 的水平下降(p<0.01)。

结论：APN 可能通过 AMPK 促进 PLIN2 的磷酸化和通过 NRF2 提高 LAMP2A 的表达促进肝脏 PLIN2 降解，进而促进肝脏脂质分解。运动减肥可以增加肝脏 APN 水平，并通过 APN 促 PLIN2 降解途径促进肝脏脂质的分解。

关键词：脂联素；PLIN2；肝脂分解；运动减肥

P6-12 一流课程建设背景下运动生理学课程建设现状与方向探讨

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目的：教育部开展一流课程建设以来，涌现了一批国家级一流本科课程，其中多所学校的运动生理学课程也获得了这一称号。但一流本科课程建设是一个连续的过程，需要不断的改进与提升。因此本文对现阶段运动生理学国家级一流课程建设现状进行了总结，分析和归纳，探讨其今后的建设方向，为运动生理学课程建设提供依据。方法：主要采用查阅资料、文献、访谈等方法。结果：（1）教育部公布的两批国家一流本科课程中，运动生理学共 8 门，其中线上课程 2 门，线下课程 3 门，线上线下混合式课程是 3 门。（2）获批运动生理学国家一流本科课程学校中，师范类院校 5 所，综合类院校 2 所，体育类院校 1 所。（3）国家级一流运动生理学课程主要使用的教材为人民体育出版社、高等教育出版社出版。课程设计和教学内容安排有着一定的差异，但知识点的相似度较高。（4）国家一流课程线上课程多集中在智慧树、中国大学 MOOC 等线上平台，具有一定的共享使用率。结论：（1）在体育类课程中，运动生理学课程获批国家级一流本科课程比例相对较高，但教学内容有一定的同质性。（2）实验教学内容相对较少，不够系统，建议加强虚拟仿真实验教学课程建设。（3）专业体育院校可以发挥专业优势，提高运动生理学的应用性。

关键词：一流本科课程，运动生理学，课程建设

P6-13 有氧和抗阻运动经 IL-18/IL-18R 信号通路对 SAMP8 小鼠皮肤老化的影响

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目的：探讨有氧运动和抗阻运动经 IL-18/IL-18R 信号通路对 SAMP8 小鼠皮肤老化的影响，为抗皮肤老化以及治疗慢性炎症性皮肤相关疾病提供新思路。

方法：健康雄性 28 周龄快速老化 SAMP8 小鼠 24 只，随机分为模型组（M 组）、有氧运动组（E 组）和抗阻运动组（R 组），每组 8 只，另设 8 只同龄抗老化 SAMR1 小鼠作对照组（C 组）。（1）观察各组小鼠精神状态、活动情况、毛色等一般情况；HE 染色观察皮肤组织形态学变化；MASSON 染色观察皮肤胶原纤维变化；（2）免疫组织化学观测皮肤衰老标志物β-半乳糖苷酶（SA-β-gal）阳性率；（3）ELISA 法检测血清和皮肤炎性指标 IL-18、IL-1β浓度；（4）免疫荧光法双染 IL18、IL18R；（5）实时荧光定量聚合酶式反应（RT-qPCR）检测 *IL-18*、*IL-18R* 基因表达。

结果：（1）在运动干预后期，与 C 组相比，M 组小鼠表现出明显的衰老体征：进食减

少，自主活动减少，毛发干枯无光泽，脱毛严重，抓取时易激惹，相对抓力显著下降（$P < 0.05$）；背部皮肤出现明显的皱纹、弹力减退，皮肤厚度明显变薄；C 组真皮层内可见波浪状胶原纤维,排列紧实、均匀，M 组胶原纤维形态僵硬，可见断裂、排列稀疏、粗细不均；SA-β-gal 阳性染色率增高（$P < 0.05$）；血清和皮肤 IL18、IL-1β增加（$P < 0.05$）；*IL-18*、*IL-18R* mRNA 表达显著增加（$P < 0.05$）。共定位显示 IL-18 与 IL-18R 结合。（2）经 8 周有氧运动和抗阻运动干预后，与 M 组相比，E 组和 R 组衰老体征有明显改善：进食和自主活动增加，脱毛相对较轻，相对抓力显著增高（$P < 0.05$）；背部皮肤出现皱纹减少、弹力增加，皮肤厚度变厚，胶原纤维分布较均匀、排列紧密；SA-β-gal 阳性染色率降低（$P < 0.05$）；R 组血清和皮肤 IL-1β 降低（$P < 0.05$）；E 组和 R 组血清和皮肤 IL18 显著降低（$P < 0.05$）；IL-18、IL-18R mRNA 表达显著降低（$P < 0.05$）。

结论：有氧运动和抗阻运动均能延缓快速衰老小鼠的增龄性皮肤老化，运动上调的 IL-18/IL-18R 信号通路可能是其作用途径。

关键词：IL-18/IL-18R；有氧运动；抗阻运动；皮肤老化；衰老

P6-14 大负荷运动后骨骼肌炎症损伤的关键基因分析及信号通路鉴定

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目的：通过基于生物信息学筛选大负荷运动后腓肠肌差异炎症基因，鉴定运动性骨骼肌损伤过程中炎症反应的关键基因与信号通路。

方法：32 只 SD 大鼠随机分为对照组（C 组，n=8）和运动组（E 组，n=24），E 组进行 90 min 下坡跑，分别于运动后即刻（E0 组，n=8）、12 小时（E12 组，n=8）、24 小时（E24 组，n=8）取腓肠肌，通过 RNA-Seq 转录组测序，使用 DESeq2 R 包分析各组腓肠肌基因表达情况、筛选差异表达基因（Differentially Expressed Genes，DEGs），从 DisGeNET 数据库和 MSigDB 数据库中提取炎症相关基因（Inflammation-Related Genes，IRGs），与各组 DEGs 相交识别获取差异表达炎症相关基因（Differentially Expressed Inflammation-Related Genes，DEIRGs），使用 clusterProfile R 包对各组 DEIRGs 进行 GO 和 KEGG 富集分析。采用 STRING 数据库对各组 DEIRGs 进行蛋白互作网络分析，运用 cytoscape 软件的 cytoDCA 功能筛选出候选 DEIRGs，进行二次功能富集分析，以明确关键信号通路、核心基因。

结果：经整合分析，将筛选出的大负荷运动后腓肠肌各组 DEGs，与 IRGs 相交获得 451 个 DEIRGs，其中 E0 组上调 122 个、下调 57 个，显著富集于 HIF-1 和 JAK-STAT 信号通路，多细胞生物过程的调控、对有机物的反应、细胞对化学刺激的反应等生物过程；E12 组上调 66 个、下调 29 个，显著富集于补体和凝血级联反应、肌动蛋白细胞骨架的调控和 PI3K-Akt

信号通路，对有机物的反应、多细胞生物进程和发展等生物过程；E24 组上调 101 个、下调 76 个，主要富集于 Th17 细胞分化和 HIF-1 信号通路，对有机物的反应、对缺氧的反应等生物过程。筛选出候选差异表达炎症相关基因 *STAT3*、*PPARG*、*KDR*、*HMOX1*、*SERPINE1*、*FASN*、*ITGB2*、*CXCL12*、*AKT1*、*TP53*、*CD4*、*HIF-1A*、*CD44*，显著富集于 HIF-1、Th17 细胞分化、AMPK、JAK-STAT 等信号通路，对缺氧的反应、调节血管生成、免疫细胞过程的调节、细胞迁移调控等生物过程。

结论：多种炎症相关基因参与大负荷运动后骨骼肌炎症损伤过程，核心差异表达炎症相关基因为 *STAT3*、*PPARG*、*KDR*、*HMOX1*、*SERPINE1*、*FASN*、*ITGB2*、*CXCL12*、*AKT1*、*TP53*、*CD4*、*HIF-1A*、*CD44*。关键基因 *FASN*、*STAT3*、*HIF-1A* 可能通过 HIF-1、AMPK、JAK-STAT 信号通路参与大负荷运动造成的骨骼肌早期炎性损伤。

关键词：运动；骨骼肌损伤；差异表达基因；炎症反应

P6-15 Categorical dose-response and interactions in metabolic syndrome risk: Sedentary behavior, cardiorespiratory fitness, and physical activity

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PURPOSE: The objective of this study was to investigate the interplay and collective (cross-sectional) correlations among sedentary behavior (SB), total physical activity (TPA), and cardiorespiratory fitness (CRF) in relation to the risk factors of metabolic syndrome (MS) in Chinese women aged 40-49 years. **METHODS:** A sample of 132 adult women, aged between 40 and 49 years, underwent measurement of SB and TPA using the International Physical Activity Questionnaire (IPAQ) and Sedentary Time Questionnaire (SIT-Q), respectively. CRF was assessed through submaximal cycle-ergometer testing. MS was defined based on the established guidelines for the prevention and treatment of dyslipidemia in Chinese adults. To explore the dose-response relationship, categorical analyses were employed by comparing the regression coefficients associated with different levels of sedentary time (compared to the lowest sedentary time) using multiple regression. Additionally, both CRF and TPA were categorized into four standardized groups each, using the lowest CRF and TPA group as reference categories for analysis. **RESULTS:**(1) Regardless of CRF and TPA, every additional hour SB was associated with the index of lower TG [β= 1.43mmol^{-1}(95% CI = 0.38; 2.47)] and FPG [β= 0.90mmol^{-1}(95% CI = 0.19; 1.61)] at category of SB (>8h/d). The index of LDL-C [β= -0.41mmol^{-1}(95% CI = -0.70; -0.12)] and TC [β= -0.43mmol^{-1}(95% CI = -0.81; -0.05)] were significantly decreased after

adjusting for CRF (>9.7 ml•kg^{-1}•min^{-1}). And the index of TG [β= -0.88mmol^{-1}(95% CI = -1.51; -0.25)], BMI [β= -2.00mmol^{-1}(95% CI = -3.48; -0.50)] and WC [β= -5.18mmol^{-1}(95% CI = -9.77; -0.59)] were also significantly decreased after adjusting for TPA.(2)Compared with the referent group (<2h of sitting per day, high levels of CRF [>30.7 ml•kg^{-1}•min^{-1}]), there were decreased of LDL-C (β= -0.83; 95% CI = -1.50; -0.17) and TC (β= -0.86; 95% CI = -1.67; -0.05) during the daily SB who sat for more than 6h/day but who also reported >30.7 ml•kg^{-1}•min^{-1} of CRF. And compared with the referent (<2h/d and highest quartile of TPA [>17.5 MET-h per week^{-1}]), the index of WC (β= -12.10; 95% CI = -24.21; 0.00) was decreased during the daily SB who sat for more than 6h/day but who also reported >17.5 MET-h per week^{-1} of activity. **CONCLUSION:** The present study indicates a tentative association between SB and the risk factors of MS, which appears to hold true even after adjusting for the influence of CRF. Our findings suggest that individuals with elevated levels of CRF and TPA may effectively mitigate the heightened risk of metabolic syndrome. Consequently, these results highlight the significance of regular PA participation and, notably, improvements in CRF, particularly through high TPA and elevated CRF levels, in relation to the relative risk factors associated with metabolic syndrome among adults.

P6-16 运动介导 HIF-1 改善心梗心脏中的作用及其机制探讨

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研究目的：心肌梗死(MI)是指由于冠状动脉病变，使相应的心肌细胞发生严重而持久的缺血缺氧，心脏功能下降，最终导致心力衰竭甚至死亡。其死亡率逐年升高并呈年轻化趋势。而心脏康复作为 MI 治疗的最后一环，对提高患者生存质量意义重大。研究表明，运动训练能改善心功能，临床上已把运动作为心梗后康复与预防的重要手段之一。低氧诱导因子-1(HIF-1)是一种内源性心脏保护分子，参与调节多种生理功能，包括细胞存活、上皮细胞稳态、血管张力和代谢稳态。本文将针对运动介导 HIF-1α 在心梗心脏中的作用及机制的研究进展进行综述，为心梗心脏运动康复的机制研究提供理论基础和指导意义。

研究方法：本文通过搜索知网、Pubmed、Web of Science 等数据库对 HIF-1 在运动中改善心梗心脏的作用进行梳理和总结，为本文的研究提供思路和方法。

研究结果：运动介导 HIF-1α 干预心梗心脏主要从常氧运动和低氧运动两个方面进行讨论：(1)目前常氧运动中 HIF-1α 是否产生变化存在争议，因为 HIF-1α 在常氧下极不稳定半衰期很短极易迅速降解，但强度较大运动中 HIF-1α 有上升趋势；(2)HIF-1 是机体应答低氧反应的关键元件，而 HIF-1α 表达取决于低氧的程度和持续时间。众多研究表明，低氧训练可以刺激 HIF-1α 的活性，使骨骼肌 HIF-1α 蛋白含量增加，提高肌肉的无氧能力，但确切的

低氧时间与程度还需进一步研究探讨。

研究结论：本文综述了运动介导的 HIF-1 在心梗心脏表达调控中的重要作用，表明常氧下大强度的运动以及低氧运动可上调 HIF-1α 表达，调动机体的自我保护机制，使心肌细胞产生了一定的缺氧耐受，从而抵抗更严重的缺血缺氧刺激。而 HIF-1 作为低氧状态下的适应性调节因子，通过调节血管新生、炎症反应、氧化应激及心肌能力代谢等多个方面，改善心肌梗死的程度，保护心功能，是目前预防和治疗梗死损伤的有效靶点。尽管取得了这些进展，但还需要进一步的深入研究来阐明 HIF-1α 与其他关键转录因子在调节蛋白表达从而导致心脏保护方面可能的协调或相互作用。

关键词：运动；HIF-1；心梗；

P6-17EMR 环境下运动调节电磁-生物信号转导机制及神经保护作用研究进展

Research progress on the mechanism of exercise-regulated electromagnetic-biological signal transduction and neuroprotective effect in EMR environment

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现今通信设备普及，无线设备、移动基站，尤其是 WiFi 在日常工作生活中爆炸式增长，有必要多学科角度认识和评估 WiFi 信号产生的电磁辐射（electromagnetic radiation，EMR）对人体的影响。大脑和肠道均是感应 EMR 的敏感器官。EMR 导致神经元铁死亡，其特征是依赖铁的脂质过氧化物积累致细胞死亡。其次，EMR 还导致肠道菌群重构及其代谢衍生物发生变化。本文综述了运动在 EMR 环境中的神经保护和辐射防护作用，并讨论了运动神经保护和辐射防护作用潜在的分子机制。提出 EMR 通过神经元铁死亡信号或肠道菌群重构进行电磁-生物信号转换，导致神经精神疾病，运动可能通过多种未知机制保护神经元，从而发挥抗辐射、神经保护作用。梳理铁死亡及肠道菌群在生物体中感应 EMR 并产生相应电磁-生物学效应及运动的辐射防护机制，将为运动抗辐射提供新的科学认识和干预方法。

关键词：电磁辐射；抑郁症；铁死亡；肠道菌群；运动

Nowadays, with the popularity of communication equipment, wireless equipment, mobile base stations, especially WiFi are exploding in daily work and life. It is necessary to understand and evaluate the impact of electromagnetic radiation (electromagnetic radiation, EMR) generated by WiFi signals on the human body from a multidisciplinary perspective. Both the brain and gut are sensitive organs for sensing EMR.EMR causes neuronal ferroptosis, characterized by iron-dependent accumulation of lipid peroxides for cell death. Second, EMR also leads to changes in gut microbiota remodeling and its metabolic derivatives. This review reviews the

neuroprotective and radioprotective effects of exercise in the EMR environment and discusses the molecular mechanisms underlying the effects of motor neuroprotective and radiation protection. It is proposed that EMR performs electromagnetic-biological signal conversion through neuronal ferroptosis signal or gut microbiota remodeling, leading to neuropsychiatric diseases, and exercise may protect neurons through multiple unknown mechanisms, thus playing a radiation-resistant and neuroprotective role. Combing the radiation protection mechanism of ferroptosis and gut microbiota sensing EMR in organisms and producing corresponding electromagnetic-biological effects and exercise will provide new scientific understanding and intervention methods for radiation resistance in exercise.

Key words： electromagnetic radiation; depression; ferroptosis; gut microbiota; exercise

P6-18 Th1/Th2 平衡在运动性免疫抑制大鼠中的作用研究

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目的：探讨运动性免疫抑制大鼠的外周血免疫细胞的时相变化特征及其相关机制，明确“免疫开窗期”的关键点，及 Th1/Th2 平衡在运动性免疫抑制中的作用机理和靶点分子，为制定最佳运动处方指导全民健身和获取竞技运动员最优训练方案提供科学依据。**方法**：8 周龄 SPF 级雄性 Sprague Dawley 大鼠 56 只，随机分为对照组(C 组，n=8)、运动组(E 组，n=48)，E 组通过一次力竭运动建立运动性免疫抑制大鼠模型，根据运动后不同时相，分为 E0 组、E2 组、E4 组、E6 组、E8 组、E24 组 6 个亚组，麻醉后取血、胸腺标本，血常规检测血细胞分类计数，分离外周血单个核细胞，流式细胞术检测外周血 T 细胞亚群分布，ELISA 检测血浆中 Th1、Th2 细胞效应因子，RNA-Seq 转录测序分析胸腺基因表达情况，筛选 DEGs，通过 GO 功能注释和 KEGG 富集分析鉴定 T 细胞分化相关靶向基因及其作用途径。**结果**：与 C 组相比，E4、E6、E8 组白细胞、淋巴细胞计数显著升高($P < 0.05$)，E4 达最高峰；E2、E4、E6、E8 组中性粒细胞数目显著升高($P < 0.05$)，E4 达最高峰；E2、E4、E6、E8、E24 组 CD3+T 细胞显著降低($P < 0.05$)，E4 至最低谷；E4、E6 组 CD3+CD4+T 细胞显著降低($P < 0.05$)，E4 至最低谷；E4、E6、E8 组 CD3+CD8+T 细胞显著升高($P < 0.05$)，E4 达最高峰；E4、E6、E8 组 CD3+CD4+/CD3+CD8+T 细胞显著降低($P < 0.05$)，E4 至最低谷；E0、E2、E6、E8、E24 组 CD4+CD25+ T 细胞和 CD4+CD25+FOXP3+T 细胞显著降低($P < 0.05$)，E4 组显著升高($P < 0.05$)；E4、E6 组 CD3+CD4+CXCR3+T 细胞（Th1 细胞）显著降低($P < 0.05$)，E4 至最低谷；E4、E6 组 CD3+CD4+CCR4+ T 细胞(Th2 细胞) 显著升高($P < 0.05$)，E4 达最高峰。E2、E4、E6、E8 组 INF-γ、TNF-α 显著下降($P < 0.05$)；E2、E4、E6 组 IL-4、IL-6 显著升高($P < 0.05$)。

E0 组 971 个上调 DEGs，353 个下调 DEGs；E4 组 146 个上调 DEGs，847 个下调 DEGs。GO 功能注释和 KEGG 通路富集分析发现，DEGs 显著富集在 IL-17 信号调控通路、Th1/Th2 细胞分化调控通路，促进 Th1 细胞分化、抑制 Th2 细胞发育的关键分子 *IL12Rβ2* 基因表达量在 E4 组显著上调。**结论：**一次性力竭运动造成的运动性免疫抑制在运动后 4h 出现“免疫开窗期”，T 细胞分化异常是其重要特征，Thl/Th2 平衡向 Th2 细胞方向漂移，*IL12Rβ2* 基因可能是 T 细胞分化的调控靶点，Th1/Th2 细胞分化调控通路可能是其作用途径。

关键词：运动性免疫抑制，Th1/Th2 平衡，转录组，力竭运动

P6-19 8 周不同顺序同期训练对普通大学生有氧耐力和力量素质的影响

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研究目的：同期有氧和力量训练是指耐力和力量素质安排在相同训练时期的一种训练方法。本研究旨在探讨 8 周不同顺序同期训练对普通男性大学生耐力素质和力量素质的影响及相关机制。**研究对象：**15 名北京体育大学在校男性大学生，要求受试者无正规训练经历，无受伤史。受试者年龄 20.8 岁，身高 177.0cm，体重 69.5kg。将受试者随机分为力量-耐力组（RE, n=8），耐力-力量组（ER, n=7），进行每周 3 次，共 8 周的训练干预。具体干预方案：RE 组先进行力量再进行耐力训练，ER 组先进行耐力再进行力量训练，耐力训练以 60%-70%最大摄氧量速度进行 30 分钟跑台运动；力量训练主要针对下肢进行负重深蹲、负重提踵和腿屈伸练习，每组 6 次，共 4 组，时间为 30 分钟。力量训练和耐力训练安排在同一节课内进行，中间休息间隔 15 分钟。训练干预前后进行力量和耐力素质相关指标的测试。利用单因素方差分析，比较干预前后相关指标的变化率差异。**研究结果：**8 周同期训练干预前后相比，两组受试者在力量相关指标（深蹲 1RM、半蹲 1RM、反向纵跳高度）和耐力相关指标（3000 米跑计时成绩、最大摄氧量、跑步经济性等指标）均有不同程度的提高（P＜0.05）。与 RE 组相比，ER 组在深蹲 1RM (ER：26.81±7.13%；RE：18.66±9.33%)；半蹲 1RM (ER：24.02±4.58%；RE：18.22±3.69%)；反向纵跳高度（ER：7.99±5.01%；RE：3.560±4.34%)等力量素质指标前后变化率方面显著高于 RE 组（P＜0.05)。但两组在 3000 米跑（ER：19.20±10.13%；RE：22.27±11.33%)、最大摄氧量（ER：29.97±6.89%；RE：27.07±8.77%)和跑步经济性（ER：11.60±8.56%；RE：9.09±4.06%）等耐力素质指标前后变化率方面没有显著性差异（P＞0.05）。**研究结论：**8 周不同顺序同期训练均可以有效提高无训练经历大学生的力量和耐力素质。先耐力后力量的训练模式比相反顺序的训练模式更有利于提高普通男性大学生的力量素质，但不同顺序的同期训练在提高耐力素质方面并没有明显差异。

关键词：同期训练；不同顺序；力量素质；耐力素质

P6-20 纹状体不同类型神经元调节小鼠主动运动的电生理学研究

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目的：通过观察小鼠进行主动运动过程纹状体(Striatum, Str)神经元动作电位（Spike Potential, Spikes）和局部场电位(Local field potential, LFPs)电活动变化，探讨 Str 在自主运动不足动机驱动调控中的机制。**方法：**选用 C57/BL6 雄性小鼠，连续采集 3 天跑盘运动 24h 监测数据，聚类分析相关运动参数划分出不同活动水平群体；采用 Cerebus 在体多通道系统记录 Str 神经元 Spikes-LFPs 变化；采用快速扫描循环伏安法记录小鼠 Str 多巴胺(Dopamine, DA)释放水平。**结果：**(1)通过聚类算法将运动参数聚类为 2 个类别，分别为高意愿(High voluntary runner, HVR)日活动量为 5-10Km/day 和低意愿 (Low voluntary runner, LVR) 日活动量为 0-3Km/day；去趋势化分析发现 HVR/LVR 在不同时间段呈现出相同的昼夜节律，活动高峰期为 19:00-8:00(α1=1.09，α2=1.14)，静止期集中在下午 10:00-17:00，且在高活动时间内 HVR 运动圈数、距离、速度，总运动时间，运动频次和频次下的运动时间显著高于 LVR($p<0.001$)；(2)与 LVR 相比，HVR 纹状体背侧 α 和 β 频段显著降低($p<0.01$)，腹侧显著升高($p<0.01$)；与 LVR 相比，投射神经元自发放电频率(Spontaneous firing rate, SFR)无显著变化，中间神经元 SFR 增高 ($P<0.01$)；LVR Spike 均随机分布，与 LFP 不存在明显的相位锁定关系；HVR α 振荡在 240-270°附近锁相明显，β 振荡在 80~90°附近锁相明显。(3)与 LVR 相比，HVR 纹状体背侧 DA 刺激释放无明显变化，腹侧 DA 刺激释放显著高于 LVR。

结论：通过 K-means 聚类方式对不同主动运动水平小鼠身体活动量及运动参数进行区分和刻画，Str 中间神经元兴奋性变化，导致 α 和 β 频段 PSD 值异常升高，小鼠 DA 刺激释放量随着主动运动水平差异而表现出不同的释放效应，具体表现 HVR 腹侧 DA 刺激释放量显著高于 LVR，推测可能是不同主动运动水平小鼠 DA 刺激释放量差异，导致 DA 与 Str 神经元不同受体结合后，反馈性的引起 Str 神经元突触后细胞膜兴奋性变化效应不同，从而改变了 Str 神经元对运动的调控作用，导致小鼠出现主动运动行为差异的变化。（NSFC：31971095）

关键词：纹状体；主动运动；局部场电位；多巴胺；循环伏安法

P6-21 Effects of deep cervical flexor training combined with kinesio taping on chronic non-specific neck pain

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OBJECTIVE: To explore the effects of deep neck flexor training combined with kinesio taping on pain, function, cervical range of motion, and surface electromyography in patients with CNNP.

METHODS: A total of 64 patients with CNNP were randomly divided into four groups through random number table: control group (n=16), deep cervical flexor training group (DCFT group, n=16), kinesio taping group (KT group, n=16), and kinesio taping with deep cervical flexor training group (combined group, n=16), and treated for 6 weeks. control group only received health education without other intervention; In DCFT group, the deep cervical flexor muscle was trained with pressure biofeedback instrument 3 times a week; In KT group, the bilateral trapezius muscles were taped with Y-type 3 times a week for 48 h each time; In combined group, the patients were pasted with Y-type on the basis of training. Visual analog scale (VAS), Neck Disability Index (NDI), cervical flexion and extension range of motion, and surface electromyography of neck muscles were evaluated pre-treatment and post-treatment.

RESULTS: (1) After 6 weeks of treatment, VAS scores in DCFT and KT group were significantly lower than control group ($P<0.05$), VAS scores in combined group was significantly lower than other groups ($P<0.05$); (2) After 6 weeks of treatment, NDI scores in DCFT and KT group was significantly lower than control group ($P<0.05$), NDI scores in combined group was significantly higher than other groups ($P<0.05$); (3) After 6 weeks of treatment, there was no significant difference in cervical flexion and extension range of motion among the four groups ($P>0.05$); (4) After 6 weeks of treatment, the median frequency (MF) values of the bilateral superior fasciculus trapezius and the splenius capitis muscle in KT and combined group were significantly higher than control group ($P<0.05$), and root mean square (RMS) values were significantly lower than those in control group in the prone position test; (5) After 6 weeks of treatment, the RMS values of bilateral sternocleidomastoid muscle in DCFT and combined group were significantly lower than control group ($P<0.05$), and MF values were significantly higher than control group in supine position test.

CONCLUSION: Both DCFT and KT can effectively relieve pain in patients with CNNP, improve function and surface electromyography. Moreover, the effects of KT combined with DCFT were better than KT or DCFT alone.

Key words: chronic non-specific neck pain; deep cervical flexor training; pressure biofeedback training; kinesio taping; surface electromyography

P6-22 有氧运动通过 ALCAT1 抑制氧化应激诱导的细胞凋亡发挥心梗大鼠心脏保护作用

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目的：Acyl-CoA:溶心磷脂酰基转移酶 1 (ALCAT1)已被报道在心脏病的病因学中发挥关键作用，但在大鼠心肌梗死(MI)模型中，其确切表达还有待进一步研究。有氧运动可以在心肌梗塞后提供直接的保护。然而，运动诱导心肌损伤后心肌保护机制有待进一步研究。因此，本文旨在探讨有氧运动训练对心肌梗死大鼠 ALCAT1 表达的影响及其在心肌纤维化、抗氧化能力和心肌细胞凋亡中的作用。

方法：将第一组 SD 大鼠随机分为正常对照组(CTL)、假手术组(S)、心肌梗死后 1 小时(MI-1 h)、心肌梗死后 6 小时(MI-6 h)、心肌梗死后 12 小时(MI-12 h)、心肌梗死后 24 小时(MI-24 h)、心肌梗死后 5 天(MI-5d)；第二组随机分为正常对照组(CTL)、假手术组(S)、心肌梗死组(MI)、对照组+运动组(EX)、心肌梗死+运动组(MI+EX) 5 组。EX 组和 MI+EX 组大鼠进行 4 周的训练(1 h/天，5 d/周在跑步机上)。结扎左冠状动脉前降支建立心肌梗死模型。我们评估了心肌梗死对心肌损伤、纤维化和心肌功能的影响，以及有氧运动对心肌梗死模型大鼠目的蛋白 ALCAT1 表达、心肌损伤、氧化损伤和心肌细胞凋亡的影响。

结果：与 S 相比，手术大鼠心肌梗死 5 天后出现心肌损伤，表现为 ALCAT1 等心肌酶表达增强;心肌梗死后心肌梗死面积增加，心脏收缩/舒张功能减弱。有趣的是，心肌梗死后有氧运动使 ALCAT1 表达下调，心肌梗死引起明显的心功能障碍和心肌纤维化。心肌梗死后，运动组心肌收缩/舒张功能恢复速度加快，心肌梗死面积、抗氧化酶活性、心肌细胞凋亡明显改善。

结论：以上研究揭示了一个之前未知的内源性心脏损伤因子 ALCAT1，并表明 ALCAT1 在 MI 中损伤心脏，运动训练降低了 MI 诱导的心脏损伤后 ALCAT1 的表达、氧化应激和心肌细胞凋亡。

关键词：心梗大鼠；ALCAT1；氧化应激；细胞凋亡

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P6-23 运动调控 PI3K/Akt 信号通路改善糖尿病糖脂代谢及炎症的研究进展

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摘要：糖尿病作为一种发病机制极为复杂的慢性疾病，近年来2型糖尿病（Type 2 diabetes mellitus，T2DM）的发病率在世界范围内逐年升高。本研究从运动防治 2 型糖尿病模型骨骼肌中 PI3K/Akt 信号通路表达的影响为切入点，探讨运动通过 PI3K/Akt 信号通路的调控改善糖脂代谢及炎症的调节效果，分析运动是如何通过 PI3K/Akt 信号通路对糖尿病进行干预及运动通过调控 PI3K/Akt 信号通路改善 2 型糖尿病的可能机制。本文以“运动/exercise”、“PI3K/Akt”、“2 型糖尿病/T2DM”、“糖脂代谢/Hepatic Glucose and Lipid Metabolism Disorder”、“炎症/Inflammation”等中英文为检索词，通过中国知网（CNKI）、万方、维普、Web of Science、PubMed 及 WHO 官网等相关网站与数据库进行检索。对近年来不同运动方式通过调控 PI3K/Akt 信号通路干预 2 型糖尿病糖脂代谢及炎症的研究进行科学系统的归纳，将动物与人体实验全面整合，分析运动与 2 型糖尿病疗效指标的关系。研究结果：1、运动通过提高胰岛素水平从而激活 PI3K/Akt 通路有助于改善 2 型糖尿病糖脂代谢及炎症。2、运动通过对 PI3K/Akt 信号通路的调控，可以减少视网膜新生血管生成、减轻炎性反应、控制胰岛素抵抗、对抗视网膜神经损伤和氧化应激，从而对 2 型糖尿病视网膜病变起到积极的防治效果。3、不同运动方式均能有效改善 2 型糖尿病患者血糖、血脂、胰岛素抵抗指数等指标，且能有效改善 2 型糖尿病糖脂代谢及炎症，其中有氧运动联合抗阻训练通过调控 PI3K/Akt 信号通路改善 2 型糖尿病糖脂代谢及炎症的效果最好。研究结论：1、运动对于糖尿病患者健康具有很好促进作用，均能降低血糖、血脂，稳定心率等作用。2、运动可以导致体内的 PI3K/Akt 相关信号通路，从而在控制 IR、脂毒性、氧化应激和炎症发生等方面控制 2 型糖尿病的发生与发展，PI3K/Akt 信号通路在防治 2 型糖尿病糖脂代谢及炎症方面具有重要意义。3、运动在改善糖尿病糖脂代谢及炎症过程中通过调控 PI3K/Akt 信号通路的作用具有显著效果。

关键词：运动；PI3K/Akt 信号通路；2 型糖尿病；糖脂代谢；炎症

P6-24 力竭运动对超直接通路各核团 NR2B、GABA-Aα1 蛋白表达的影响

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目的：通过观察运动大鼠力竭前后超直接通路各核团谷氨酸离子型 2B 受体（NR2B）及 γ-氨基丁酸 A 受体 α1 亚基（GABA-Aα1）的蛋白表达水平，探讨超直接通路在运动疲劳

发生过程中的神经调控作用。**方法：**采用免疫组织化学技术对大鼠力竭运动前后及恢复90min时超直接通路各核团NR2B和GABA-Aα1的蛋白表达水平进行检测。**结果：**神经递质受体蛋白NR2B、GABA-Aα1免疫组化染色结果表明，染色具有特异性，阴性对照均未见阳性染色。力竭运动前后及恢复90min大鼠右额下皮质均可观察到神经递质受体蛋白NR2B、GABA-Aα1的阳性染色。对R值及AOD进行统计分析，结果发现，EG组大鼠右额下皮质NR2B阳性细胞R值（0.1003±0.092），阳性细胞AOD值（0.0088±0.0042）以及RG组大鼠R值（0.1067±0.0086），阳性细胞AOD值（0.0112±0.0055）均显著高于CG组（R: 0.0679±0.0074，AOD: 0.0065±0.0013）（P<0.05）。GABA-Aα1阳性细胞R值（0.0726±0.0069），阳性细胞AOD值（0.0078±0.0034）以及RG组大鼠R值（0.0695±0.0065），阳性细胞AOD值（0.0083±0.0032）与CG组（R: 0.0704±0.0077，AOD: 0.0070±0.0024）相比，无统计学差异（P>0.05）。**结论：**在力竭时，右额下皮质NR2B蛋白表达升高，神经元兴奋性增强，向丘脑底核释放的Glu量增多，丘脑底核NR2B蛋白的表达增多，丘脑底核神经元电活动增强，对皮层辅助运动区产生去兴奋作用，皮层辅助运动区NR2B蛋白表达下降也是抑制皮层辅助运动神经元电活动的原因之一。

关键词：超直接通路；NR2B；GABA-Aα1；运动疲劳；大鼠

致谢：国家自然科学基金资助项目（超直接通路对运动疲劳调控作用的机制研究；No. 31900843）

P6-25 有氧运动激活FGF21/PI3K/AKT/VEGF信号通路促心梗心脏血管生成

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目的：本研究旨在探索FGF21在调节心肌微环境以保护和改善心肌梗死心脏功能中的作用及机制。**方法：**采用雄性野生型C57小鼠和FGF21敲除小鼠分为假手术组(S)、心梗组(MI)、心梗运动组(ME)，敲除心梗运动组(KME)。采用左前降支结扎法制备心梗模型，运动组进行5周的正式训练。心动超声仪测量心功能，Masson染色检测心肌梗死面积。Western Blotting实验检测心肌和HUVECs的相关蛋白指标表达。心脏石蜡切片进行PCNA和CD31免疫荧光染色，观察梗死边缘区新生血管数量。人脐静脉内皮细胞探讨可能的作用机制。**结果：**动物实验发现，有氧运动显著上调FGF21表达激活PI3K/AKT信号通路，促进心肌血管新生，而敲除FGF21后运动的保护效应被削弱。细胞实验发现AICAR干预通过上调FGF21表达激活FGFR1/PI3K/AKT/VEGF通路促进HUVECs增殖和迁移，同时H_2O_2干预下rhFGF21通过激活FGFR1/ PI3K/AKT途径促进HUVEC细胞增殖和迁移。**结论：**本研究发现FGF21/FGFR1/ PI3K/AKT/VEGF信号通路参与运动介导的梗死心脏恢复，表明

FGF21 在运动改善梗死心脏微循环中发挥重要作用。

关键词：心肌梗死;成纤维生长因子 21;血管新生;有氧运动

致谢：国家自然科学基金资助项目 (NO. 32171128)

P6-26 不同运动对肥胖小鼠肝脏自噬相关蛋白表达的影响

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目的：观察不同运动对肥胖小鼠肝脏自噬活性的影响，探讨不同运动在防治肥胖过程中肝细胞自噬的变化，以期为运动减肥提供更多理论支持。

方法：四周龄 C57BL/6 雄性小鼠 100 只，进行八周高脂饲料喂养，得到 32 只肥胖小鼠，将肥胖小鼠随机分为：高脂喂养对照组(HHC)，普通饲料对照组(HNC)、普通饲料+有氧运动组(HNE)、普通饲料+抗阻运动组(HNR)，每组 8 只。HNE 组和 HNR 组分别进行八周跑台和爬梯训练。实验动物处死前禁食不禁水 24h，眼框取血。ELISA 法测血糖及肝脏中 TC 和 TG 含量，WB 法测小鼠肝脏自噬相关蛋白表达量。所得实验数据采用 SPSS20.0 进行方差分析，数据呈现采用 M±SD，设定 α=0.05。

结果：(1) 高脂膳食对肝脏自噬相关蛋白表达的影响。八周高脂膳食干预后，小鼠肝脏自噬相关蛋白 Beclin-1 表达量和 LC3Ⅱ/Ⅰ比值都显著降低 (p<0.05)，p62 蛋白的表达量显著升高(p<0.05)，提示高脂膳食可以降低小鼠肝脏自噬活性。(2)不同运动对自噬相关蛋白表达的影响。八周抗阻和耐力运动可以降低肥胖小鼠血清和肝脏中 TG 和 TC 的含量(p<0.05)。小鼠肝脏自噬相关蛋白 Beclin-1 的表达量(p<0.05)和 LC3Ⅱ/Ⅰ比值(p<0.05)都明显升高，p62 蛋白的表达量显著降低(p<0.05)，表明抗阻和耐力运动可以增加肝脏自噬水平，但在不同运动之间，三种自噬相关蛋白均未发现显著差异。

结论：高脂膳食可使肝脏自噬水平降低，增加体内脂质的积累；而抗阻和耐力运动都可以促进肥胖小鼠肝脏自噬水平提高，促进肝脏脂质代谢，且两种运动间无差异。

关键词：自噬；肝脏；抗阻运动；耐力运动

P6-27 有氧运动通过 Irisin 抑制内质网应激和细胞凋亡改善心梗诱导骨骼肌减少

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目的：骨骼肌萎缩对心血管疾病患者的生活质量具有重要影响。心肌梗死（Myocardial

infarction，MI）可诱发远隔器官供血不足，骨骼肌表现为萎缩、收缩能力下降，严重影响患者健康。运动诱导的肌肉因子 Irisin 具有调控肌质量平衡的作用。但 Irisin 在运动改善 MI 诱导骨骼肌减少中的益处仍未完全阐明。本研究旨在探讨有氧运动通过 Irisin 抑制 MI 诱导骨骼肌内质网应激（Endoplasmic reticulum stress，ERS）和细胞凋亡的机制。该结果将强化运动锻炼作为 MI 后心脏功能和骨骼肌质量改善的非药物治疗途径及康复策略的选择，从而为临床药物干预目标的筛选提供依据。

方法：3 月龄 C57BL/6 和 Fndc5 敲除（$Fndc5^{-/-}$）小鼠建立 MI 模型，进行 6 周中等强度运动干预。实验分组：假手术组（S）、心梗组(MI)、心梗+运动组（ME）；$Fndc5^{-/-}$+假手术组（KS）、$Fndc5^{-/-}$+心梗组(KMI)、$Fndc5^{-/-}$+心梗+运动组（KME）。超声仪评定心功能；Laminin 和 TUNEL 检测肌纤维形态学和凋亡水平，Western blotting 和 RT-qPCR 技术检测骨骼肌 ERS、自噬、增殖和凋亡蛋白表达及骨骼肌 Irisin 表达。采用双因素方差分析，$P<0.05$ 具有显著性。

结果：在 WT 小鼠中，与 S 组相比，MI 组 LVIDd 和 LVIDs 显著降低（$P<0.01$）、LVEF 和 FS 显著升高（$P<0.01$）；与 MI 组比较，ME 组 LVIDd 和 LVIDs 显著降低（$P<0.01$，$P<0.05$）、LVEF 显著升高（$P<0.01$）；但 $Fndc5^{-/-}$小鼠心脏收缩功能显著更差；有氧运动促进 Irisin 表达（$P<0.01$），改善骨骼肌细胞横截面积和肌纤维数量（$P<0.05$，$P<0.01$），抑制 ERS、自噬和凋亡蛋白 ATF6、Cas-12、chop、P62、Bax/Bcl-2（$P<0.05$，$P<0.01$）表达，*$Fndc5^{-/-}$*消弱运动对骨骼肌的有益效应。

结论：1.有氧运动促进 Irisin 蛋白表达并改善 MI 小鼠心功能；2.有氧运动通过 Irisin 抑制骨骼肌 ERS 和细胞凋亡并改善 MI 诱导骨骼肌减少。

关键词：心肌梗死、运动、Irisin、骨骼肌减少

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P6-28 运动性骨骼肌损伤中时钟基因 BMAL1 与 BDNF 的作用

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研究目的：运动性骨骼肌损伤（exercise-induced muscle damage, EIMD）多应运动不当诱发，表现为肌肉迟发性酸痛、僵硬、肿胀以及多种功能缺陷。因其复杂的发病机制与模糊的治疗靶点而成为运动医学领域的研究热点。新近研究发现，骨骼肌在调控人体外周生物节律中发挥重要作用，而广泛存在于骨骼肌中的时钟基因也可调控肌肉生理功能，进而影响骨骼肌损伤修复进程。BDNF（Brain-Derived Neurotrophic Factor, BDNF）属于神经营养因子家族成员之一，参与骨骼肌的增殖、分化以及维持神经肌肉接头的结构与功能。最新研究发现，

时钟基因 BMAL1（brain and muscle arnt-like protein 1）可经 BDNF 发挥生理功能，同时 BDNF 又广泛分布于骨骼肌组织中。据此，本研究以运动诱发骨骼肌损伤后核心时钟基因 BMAL1 与神经营养因子 BDNF 的节律表达及其相互关系为切入点，通过一次大负荷运动诱发骨骼肌损伤，观察不同时相下骨骼肌时钟基因 BMAL1、BDNF 与肌卫星细胞标志物 Pax7 表达变化，以期明确 BMAL1 与 BDNF 在运动诱导骨骼肌损伤修复中的生物节律机制，以期为其发病机制与治疗靶点提供新思路。

研究方法：（1）研究对象与分组：选用 24 只 8 周龄 SD 大鼠，随机分为安静对照组（C 组，n=4）和运动模型组（M 组，n=20），根据取材时相的不同，将 M 组大鼠随机分入运动后即刻（0h）及 12、24、48、72h 5 个亚组。（2）运动造模方案：M 组参考 Armstong 离心运动方案并结合光照节律采用一次大负荷运动建立骨骼肌损伤模型，正式干预前进行为期 3 天的适应性训练，第四天正式训练开始于光照时间前运动，坡度-16°，速度 16m/min，运动时间 90min，跑完即刻与 0 时相相同。（3）样本采集与指标测试：分别于运动结束后个时相取比目鱼肌，通过透射电镜观察骨骼肌肌纤维超微结构变化；实时荧光定量 PCR 实验检测 BMAL1、BDNF 的 mRNA 表达量；免疫荧光共定位观测 BMAL1 与 BDNF、BMAL1 与 Pax7 的共定位情况。

研究结果：（1）透射电镜显示：M 组运动后大鼠比目鱼肌部分位置肌节变宽，Z 线模糊不清呈水波状，其中 12h 损伤最为严重，72h 后基本恢复；（2）实施荧光定量 PCR 检测显示：M 组 BMAL1 的 mRNA 表达在 0,12h 升高，与 C 组比较具有显著性差异（$P<0.05$），在 12h 后表达降低与 C 组相比差异不显著（$P>0.05$）；BDNF 的 mRNA 表达呈现先下降、后升高的趋势，与 C 组相比 M 组 0h BDNF 的 mRNA 表达显著下降（$P<0.05$），12h 表达显著增加（$P<0.05$）；（3）免疫荧光观测：C 组未见 BMAL1 与 Pax7，BMAL1 与 BDNF 共表达情况，在 M 组 5 个运动时相中，BMAL1 与 BDNF 共定位标记出现于 0h，于 12-24h 仍有少量共定位标记，48h 和 72h 中共表达信号基本消失，BMAL1 与 Pax7 共定位标记于 12h 开始出现，至 48h 仍有少量标记，72h 中 BMAL1 与 Pax7 共表达信号基本消失。

研究结论：（1）运动诱发骨骼肌损伤后，核心时钟基因 BMAL1、神经营养因子 BDNF 出现节律变化。（2）核心时钟基因可能通过调节 BDNF 的节律表达，进而影响肌卫星细增殖分化，以达到修复损伤骨骼肌的目的。

关键词：运动性骨骼肌损伤；生物节律；时钟基因；BMAL1；神经营养因子；BDNF

P6-29 Physical exercise modulates the microglial complement pathway in mice to relieve cortical circuitry deficits induced by mutant human TDP-43

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Summary

The aggregation of TAR DNA binding protein 43 kDa (TDP-43) is related to different neurodegenerative diseases, which leads to microglial activation and neuronal loss. The molecular mechanism driving neuronal death by reactive microglia, however, has not been completely resolved. In this study, we generated a mouse model by overexpressing mutant human TDP-43 (M337V) in the primary motor cortex, leading to prominent motor-learning deficits. *In vivo* 2-photon imaging shows an active approach of microglia toward parvalbumin interneurons, resulting in disrupted cortical excitatory-inhibitory balance. Proteomics studies suggest that activation of the complement pathway induces microglial activity. To develop an early interventional strategy, treadmill exercise successfully prevents the deterioration of motor dysfunction under enhanced adipocytic release of clusterin to block the complement pathway. These results demonstrate a previously unrecognized pathway by which TDP-43 induces cortical deficits and provide additional insights for the mechanism of exercise training in disease intervention.

Keywords: TDP-43; Physical exercise; Motor cortex; Adipokine; Neuroinflammation

Introduction

TAR DNA binding protein 43 kDa (TDP-43) participates in multiple steps of gene expression regulation, and its cytoplasmic inclusion is the molecular hallmark of several neurodegenerative conditions including frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). In addition to progressively deteriorating neuronal apoptosis, TDP-43 mutation also causes the activation of astrocytes and microglial cells, whose reactivity further promotes neuronal toxicity. The reactive microglial population upon TDP-43 mutations drives multiple neuroinflammatory pathways including the inflammasome and complement components, leading to neuronal death and excess synaptic pruning. Few studies, however, have linked microglial activity and *in vivo* synaptic plasticity or circuitry activity under TDP-43. Further investigations to explore the molecular mechanisms of reactive microglia and their effects on synaptic function may thus benefit the early intervention of diseases.

Aerobic exercise is an effective measure to enhance adult neurogenesis and de *novo* spinogenesis, thus improving synaptic plasticity. The molecular mechanism of exercise training in improving brain health mainly focuses on neurotrophic factors. In recent years, the role of peripheral-derived factors including metabolites or myokines has been appreciated as they may penetrate the blood-brain barrier (BBB) to mediate the brain microenvironment. A recent finding identified blood-borne clusterin, an inhibitor of the complement cascade in suppressing

neuroinflammation after chronic exercise. It is thus interesting to determine whether the complement pathway can provide an ‘‘exercise prescription’’ to relieve TDP-43-induced neuropathology.

Results

Firstly, we established a cortical model via bilateral infection of an AAV vector expressing mutant human TDP-43 (M337V) into mouse M1, When the virus was expressed for two weeks, the mice exhibited a motor learning deficit phenotype, consistenting with the early stages of pathology in ALS patients. Next, we dissected the cortical neural network by 2-photon *in vivo* calcium imaging, we found that TDP-43potentiate total calcium activities of excitatory neurons, and cause hypersynchronization and hyperactivation of cortical PNs. This revealed the disruption of excitatory-inhibitory (E/I) balance. Next, we examined the microglial by immunofluorescent co-labeling, PV INs and microglia showed spatial overlap, this probably explaining depopulation of PV INs. Deeply ,we utilized microglia-specific CX3C chemokine receptor 1 (CX3CR1)-GFP transgenic mice whose PV INs were further labeled by an AAV vector expressing tdTomato under a PV-specific promoter , Dual-color *in vivo* imaging illustrated the TDP-43 increase interaction between microglial cells and PV Ins, and possess a higher fraction of engulfing microglial soma and reactive processes. Subsequently, Proteomics profiling and functional enrichment of differentially regulated genes (DEGs) of M1 extracts indicated that the complement pathway was to be prominently regulated.

Aerobic exercise is known to modulate cortical spinogenesis and neuronal activities, we attempted to further explore exercise interventional strategies. A series of experimental results showed that physical exercise restore E/I balance of motor cortex and motor learning. The morphometric study showed that exercise training reshapes microglial cells to prevent their engulfment of PV Ins, and reshapes the kinetics of microglia, probably by inhibiting the complement pathway. How did exercise inhibit the cortical complement pathway? We thus sampled the whole-blood sample for molecular profiling. Among the major inhibitors of the complement pathway, only Clusterin was markedly increased. Consequently, we investigated the peripheral source of circulating Clusterin, we founded that it comes form gonadal fat tissues. These results illustrated the necessary role of adipocyte-derived clusterin in exercise-mediated alleviation of cortical dysfunctions.

Conclusion

Our work revealed a complete picture of how TDP-43 aggregates result in microglial activation and disruption of cortical E/I balance, leading to motor dysfunction. More interestingly, it demonstrated the necessary role of adipocyte derived clusterin upon exercise to prevent cortical dysfunction.

P6-30 组学技术在运动科学领域研究现状及趋势的知识图谱可视化分析

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目的 组学技术的应用已成为运动科学领域的焦点，但该领域并未有文献计量分析，本研究旨在揭示该技术在运动科学研究中的热点和未来趋势。 **方法** 分别从中国知网数据库和 Web of Science Core collection 数据库进行与运动组学相关研究的中、英文文献检索，时间为 2001 年 1 月 1 日至 2023 年 8 月 10 日；采用 Citespace v.6.2.2 软件分别对中、英文文献中发文量、国家/机构、作者/共被引作者及关键词等指标进行分析，根据结果绘制成图，对数据进行可视化分析。**结果** 最终纳入标准的文献共 648 篇，中文文献 86 篇，英文文献 562 篇。分析结果表明，组学技术应用于运动科学的研究，每年发文量中、英文均呈逐年上升趋势，美国、中国和英国是主要的研究中心；湖南师范大学和 Harvard University 分别为中、英文文献中发文最多的机构；英文文献中美国、中国和英国是发文量排前三的国家，美国的总被引频次最高，史绍蓉、苗华、袁海瑞和 Bouchard, Claude、Eynon, Nir、Roth, Stephen M 分别为该领域中、英文文献中的重要研究学者；突现词检测表明中文文献中有氧运动、高脂血症、代谢组学和英文文献中 mass spectrometry、resistance exercise、dysfunction 是该领域长期存在的研究热点，尿液组学、有氧运动和代谢组将是这几年的研究前沿领域。**结论** 本文首次对运动中组学技术的应用相关文献进行文献计量学分析，揭示了该领域的发展趋势和研究热点。这将为进一步的研究者提供关键信息。

关键词：组学；运动；Citespace；可视化分析

P6-31 Wnt 信号通路及 SFRP1 在大负荷运动后骨骼肌修复过程中的作用

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摘要 1.目的：基于生物信息学鉴定大负荷运动后骨骼肌修复过程中基因的时间序列动态变化，分析运动性骨骼肌损伤修复过程中不同时相Wnt信号通路及SFRP1基因与骨骼肌修复的关系。2.方法：将48只SD大鼠随机分为对照组（C组，n=8）和运动组（E组，n=40），E 组进行90 min下坡跑，分别于运动后即刻（E0组，n=8）、12小时（E12组，n=8）、24小时（E24组，n=8）、48小时（E48组，n=8）、72小时（E72组，n=8）取腓肠肌，通过RNA-Seq转录组测序，使用DESeq2 R包分析各组腓肠肌基因表达情况、筛选差异表达基因，使用

clusterProfile R包、GO和KEGG的注释进行功能富集分析，筛选、分析不同时相富集在Wnt信号通路的差异基因。3.结果：此研究得出大负荷运动后腓肠肌基因表达情况，与C组相比，E0组共1031个差异基因（680个上调，351个下调），E12组共458个差异基因（304个上调，154个下调），E24组共1082个差异基因（568个上调，514个下调），E48组共1542个差异基因（769个上调，773个下调），E72组共1166个差异基因（568个上调，598个下调）。分析发现，大负荷运动后0、12、24、48、72h差异表达基因富集在与促进细胞增殖、分化及迁移等作用密切相关的Wnt信号通路。分析该信号通路的差异基因，发现对Wnt信号通路起负调节作用的SFRP1在0-24h表达上调，48h后表达无差异，减弱对Wnt信号通路的限制，促进大负荷运动后腓肠肌细胞的增殖修复。4.结论：Wnt信号通路参与大负荷运动后腓肠肌的修复过程，SFRP1可能是重要调控靶点。

关键词：SFRP1;Wnt 信号通路;差异表达基因;运动

P6-32 NAMPT 在运动性骨骼肌损伤炎症反应中的调控机制研究

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目的：研究 NAMPT 在运动性骨骼肌损伤炎症反应中的调控机制。方法：取 36 只 8 周龄雄性 SD 大鼠，随机分为对照组 C 组（n=6）和大负荷运动组 E 组（n=30），并按取材时相将 E 组分为 0h、12h、24h、48h、72h 五个亚组（n=6）。E 组大鼠按照 Armstrong 经典离心运动方案进行一次大负荷运动，坡度-16°，速度 16m/min，时间 90min。于实验后不同时间点分批取小腿三头肌。通过透射电镜观察骨骼肌超微结构，采用取血样进行酶联免疫吸附试验（ELISA），检测 CK、CK-MM、IL-6、TNF-α 及 NAMPT 的表达水平，使用实时荧光定量 PCR（RT-qPCR）测定 NAMPT mRNA 的表达，利用 RNA-seq 测序技术测定小腿三头肌组织转录组学,通过 GO、KEGG 富集分析差异表达基因,并筛选分析相关通路与基因，采用实时荧光定量 PCR 验证差异表达基因。实验数据使用 SPSS22.0 软件和 GraphPad Prism 9.0 软件进行统计学分析。结果：1.电镜结果显示，C 组大鼠骨骼肌组织完整，细胞形态正常，Z 丝排列整齐且分布均匀，肌膜下线粒体大小均一，膜结构完整；E 组在运动后 24h，肌纤维排列严重紊乱，肌膜下线粒体大量聚集，膜结构模糊，此时线粒体损伤程度最高，运动后 48 至 72h 肌纤维排列、细胞形态及线粒体结构逐步恢复正常。2.E 组大鼠血清中 CK、CK-MM、IL-6、TNF-α 及 NAMPT 水平明显高于 C 组（$P<0.05$），运动后 48h 至 72h 水平略有降低，但仍高于对照组水平，E 组 NAMPT mRNA 表达水平高于对照组（$P<0.05$）。3.转录组测序结果显示，在运动后 24h 差异最大，共鉴定出 1529 个差异基因，其中 793 个基因表达上调，占 51.86%，736 个基因表达下调，占 48.14%。KEGG 通路富集分析结果显示，共富集到 323 条 KEGG 通路，其主要富集在 AMPK 信号通路、PPAR 信号通路、烟酸和烟酰胺代谢通路、

FAK、癌症信号通路。4.荧光定量 PCR 检测结果显示，NAMPT、Nmnat1、Nmnat3 和 Nmrk2 表达水平与转录组学检测结果一致。结论：NAMPT 在运动性骨骼肌损伤中表达上调，主要通过激活烟酸和烟酰胺代谢通路促进炎症反应。

关键词：运动性骨骼肌损伤；NAMPT；炎症反应

P6-33 运动对肌骨共减综合征的影响研究进展

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研究目的：肌少症（sarcopenia，SP）和骨质疏松症（osteoporosis，OP）在肌骨系统疾病高发的老年人群中较为常见。大量研究指出，二者通过分泌性因子、遗传、营养等因素互相影响，协同致病，并发形成肌骨共减综合征（osteosarcopenia，OS）。相较于单独的 SP 或 OP 患者，OS 患者身体功能下降、骨折、残疾等不良后果的风险更高，严重影响老年人的健康和生活质量。研究证实运动能够通过机械、化学等因素直接作用于人体的肌肉和骨骼，但不同形式的运动在 OS 治疗中发挥的作用尚不明确，其内在机制也有待阐明。因此，本研究拟梳理国内外公开发表的相关文献，从肌骨系统整合视角出发，系统梳理运动对 OS 的影响研究进展，为运动改善 OS 患者人群的肌肉骨骼功能提供更科学化的建议。

研究方法：在 PubMed、Web of Science、Google scholar、中国知网、万方数据知识服务平台等数据库以“osteosarcopenia（肌少-骨质疏松症/肌骨共减综合征）”、“osteoporosis（骨质疏松症）”、“Sarcopenia（肌少症）”、“exercise/training/physical activity（运动/训练/身体活动）”等为关键词，对建库至 2023 年 8 月期间所发表的相关文献进行收集整理，梳理其运动干预方案、机制研究等信息。

研究结果：不同类型的适量运动均能够对肌肉骨骼健康带来益处。抗阻运动（resistance exercise，RE）被认为是防治肌肉骨骼退行性疾病的有效方式，临床研究指出高强度 RE 在治疗 OS 中发挥重要作用。研究发现有氧运动（aerobic exercise，AE）也可以通过改善线粒体功能障碍从而改善骨骼肌功能，而 RE 和 AE 相结合则能够融合两者的效果。全身振动训练（whole-body vibration ，WBV)对于肌肉骨骼的影响尚存争议，能否将其作为 OS 的有效防治方法还需进一步探索。实验证明太极拳、普拉提、瑜伽、肌肉电刺激等非常规运动会对 OS 患者肌肉和骨骼功能产生影响，但效果不显著。有学者建议将传统 RE、高强度 RE 和平衡等身体功能训练相结合作为 OS 的干预手段，并指出多模式运动可能是整体提升肌肉骨骼功能的最佳方案。同时，运动结合营养补充会带来更好效果，一项研究表明 RE 联合维生素 D、钙和蛋白质的补充对 OS 的效果优于单一的营养干预。运动对肌肉骨骼的协同调控作用，主要是通过调节鸢尾素（irisin）、白细胞介素（interleukin）等肌因子的分泌，进而调控骨质量和骨密度;同时，通过调节骨骼细胞中前列腺素 E2（prostaglandinE2，PGE2）、骨钙素

(osteocalcin，OCN)、转化生长因子 β（trans‐forming growth factor β，TGFβ）等因子的分泌，来提高肌肉质量与功能。

研究结论：目前对于运动干预 OS 的研究处于起步阶段，针对于 OS 患者的临床随机对照实验数量较少,部分研究结果存在争议。较为明确的是运动对骨骼和肌肉的作用具有多效性，结合 RE 的多模式运动干预在 OS 的防治中能带来更大的好处，但背后的机制还有待进一步阐明。未来需要更多的 OS 运动处方研究以对各项运动的时间、强度、频度等做出明确的规定。

关键词：运动；肌骨共减综合征；肌少症；骨质疏松症

P6-34 肾源性 ELA 在有氧运动改善心梗心肌纤维化中的作用及机制研究

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目的：探究有氧运动通过激活肾源性 ELA，靶向受损心肌组织，减轻心梗心肌纤维化的分子机制，从心肾轴层面为改善心梗纤维化提供新的治疗靶点。

方法：动物实验：采用雄性 8 周 C57BL/6J 野生型小鼠，采用左冠状动脉前降支结扎法制备心梗模型。采用 *ela* 高表达和低表达 AAV 病毒肾脏注射进行 ELA 表达干预，采用小动物跑台进行中等强度有氧运动干预，通过心动超声、组织染色、RT-qPCR、Elisa 试剂盒、Western Blotting 等实验，研究 ELA 介导有氧运动对心梗心肌纤维化的影响。细胞实验：采用人胚肾小管上皮细胞（HKC）和乳鼠原代心肌成纤维细胞（CFs），使用 AMPK 激动剂（AICAR）干预 HKC，检测 HKC 细胞 ELA 表达和分泌情况。使用 H_2O_2、ELA 重组蛋白和 TGFβ-Smad2/3 通路抑制剂干预 CFs，通过免疫荧光染色和 Western Blotting 实验，探讨 ELA 抑制心肌纤维化的分子机制。

结果：（1）有氧运动和肾脏 *ela* 内源性干预显著影响心梗心肌 ELA 表达。（2）肾源性 ELA 在有氧运动改善心梗心功能、改善心肌纤维化及抑制心肌细胞凋亡中发挥重要作用。（3）肾源性 ELA 介导有氧运动调控 TGF-β1-Smad2/3 信号通路。（4）AICAR 可刺激 HKC 产生和分泌 ELA，且与 AICAR 浓度呈剂量依赖性。（5）TGFβ1-Smad2/3 通路是 ELA 介导有氧运动抑制心肌纤维化的重要信号通路。

结论：本研究发现有氧运动可促进肾源性 ELA 表达，调节心梗后心肌组织中 ELA 水平，通过抑制 TGFβ1-Smad2/3 通路，改善心梗所致心肌纤维化，另外，通过对肾脏注射 *ela* 高表达或低表达 AAV 病毒，内源性干预肾脏 ELA 的生成和分泌，结合有氧运动干预，进一步验证 ELA 改善心梗心肌纤维化的机制。

关键词：心肌梗死；ELABELA（ELA）；有氧运动；TGFβ1-Smad2/3 通路；心肌纤维化
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P6-35 抗阻运动上调 Irisin 促进 2 型心肾综合征小鼠肾脏血管生成

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目的：探讨抗阻运动上调鸢尾素（Irisin）促进肾脏血管生成和延缓心肌梗死诱导的 2 型心肾综合征（Type 2 CRS)小鼠肾脏损伤的作用和可能机制，为临床心肾综合征患者的运动康复研究提供理论依据。**方法：**8 周龄雄性 C57BL/6J 小鼠和 *Fndc5* 基因敲除（$Fndc5^{KO}$）小鼠，采用左前降支结扎法制备小鼠心梗模型。并进行抗阻运动干预，包括 1 周的适应性爬梯运动和 4 周的递增负荷运动（负荷递增至 75%体重时，保持此负荷至结束，每组爬梯 3 次，每天 8 组，每周 5 天）。运动结束后次日，心动超声检测心功能，分离肾脏置于中性甲醛或-80℃中备用。采用 PAS 染色检测肾小管损伤情况，CD31 染色检测肾间质血管密度，Western blotting 测定肾脏中相关蛋白表达，并采用人脐静脉内皮细胞（HUVECs）进行机制研究。**结果：**（1）动物实验发现，心梗诱导小鼠肾脏发生血管稀疏，氧化应激和细胞凋亡，且肾脏 FNDC5 表达降低。而抗阻运动干预促进肾脏 FNDC5 和 Integrin αV/β5 蛋白表达，激活 AMPK-PI3K-AKT-eNOS 通路，增加肾间质 $CD31^{+}$血管数量和 CAT 活性，增加 VEGFA、SOD1、SOD2 和 Sestrin2 蛋白表达，降低 cleaved-Caspase 3 蛋白表达、Bax/Bcl-2 比值和 MDA 含量，延缓肾脏病理进程。且 *Fndc5* 敲除削弱了抗阻运动的保护效应。（2）细胞实验发现，运动或 rhIrisin 干预抑制 H_2O_2 诱导的细胞氧化应激和细胞凋亡，激活 AMPK-PI3K-Akt-eNOS 通路，且 rhIrisin 主要通过激活该信号通路促进细胞迁移和小管形成。**结论：**抗阻运动上调肾脏 Irisin 和受体 Integrin αV/β5 表达，激活 AMPK-PI3K/Akt-eNOS 信号通路，促进肾脏血管生成，延缓心梗诱导的 Type 2 CRS 小鼠肾损伤。

关键词：Irisin；2 型心肾综合征；血管生成；抗阻运动

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P6-36 乳酸杆菌在规律运动改善与年龄相关肌少症中的作用

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随着全球人口老龄化趋势的加剧，与年龄相关肌少症已严重影响老年人生活质量和健康，对与年龄相关肌少症的防治已成为亟待解决的公共健康问题。衰老导致的骨骼肌质量和功能的下降（称为与年龄相关肌少症），部分由肌肉合成代谢抵抗介导。肠-肌-轴是对抗合成代谢抵抗和降低与年龄相关肌少症风险的生理靶标，乳酸杆菌可通过其细胞壁成分或代谢产物

与肠道免疫系统相互作用，从而调节肠道免疫平衡，同时亦可通过多种方式影响肠道菌群的组成和多样性，从而维持肠道微生态平衡，故探究乳酸杆菌在与年龄相关肌少症中的作用具有重要意义。规律运动可能改善肠道微生物的组成和功能，通过促进乳酸杆菌增殖并发挥其生理作用，从而促进老年人刺激肌肉蛋白质合成（MPS）的能力提高，减弱与年龄相关的肌肉合成代谢抵抗（AR）,从而改善与年龄相关的肌少症。

一方面，乳酸杆菌通过增加全身氨基酸的可用性，可能从不同程度上提高全身性和/或细胞内氨基酸可用性，从而进一步改善与年龄相关的氨基酸可用性下降导致外周氨基酸转运到肌肉组织内减少这一情况，促进老年人刺激肌肉蛋白质合成（MPS）的能力提高，最终介导与年龄相关肌少症。另一方面，乳酸杆菌可能通过介导肠道微环境和肠道微生物相互作用，不仅能维持肠上皮屏障的功能和稳态，而且在肠道粘膜屏障以及免疫方面发挥重要作用。具体表现在乳酸杆菌能够诱导肠上皮细胞和树突状细胞表达 Toll 样受体（TLR）和核因子 κB（*NF-κ*B），*NF-κ*B 的激活和易位导致许多调节炎症反应的基因发生转录，从而激活信号通路。此外，乳酸杆菌还能够诱导肠道内天然淋巴细胞（ILC）和调节性 T 细胞（Treg）的增殖和活化，在肠腔中引发抗炎反应来降低衰老过程中诱导全身的炎症，以减弱与年龄相关的肌肉合成代谢抵抗（AR）,从而改善与年龄相关的肌少症。

关键词：乳酸杆菌；与年龄相关肌少症；运动；肌肉

P6-37 推拿经 JAK—STAT 信号通路改善一次性大负荷运动大鼠 EIMD 的效应机制

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研究目的：观察推拿对一次性大负荷运动大鼠骨骼肌结构、肌肉工作能力及运动性骨骼肌损伤（exercise-induced muscle damage，EIMD）的影响，并探讨 JAK—STAT 信号通路的作用机制，以期为推拿在运动医学实践中的推广应用提供实验依据。

研究方法：将 312 只 8 周龄雄性 SD 大鼠随机分为空白对照组（C）、一次性大负荷运动组（E）、一次性大负荷运动+推拿组（ET）。ET 组根据干预后分为 0h/24h/48h/72h 各 4 个时相。经典离心运动方案进行一次大负荷下坡跑台运动，坡度-16 °速度 16m/min，时间 90min。ET 组采用推拿手法模拟仪按揉手法，在 0h/24h/48h/72h 对大鼠小腿三头肌施以操作。压力 4N，120 次/min，共 5 min。左侧腓肠肌内侧头用于制备透射电镜样品，外侧头用于 RNA_seq，转录组测序筛选出差异表达的 mRNA,并进行 GO 和 KEGG 富集分析。DMT 测定右侧比目鱼肌离体肌张力，ELISA 检测 CK 值。

研究结果：（1）C 组肌肉超微结构正常；ET 组在 ZT24、48、72h 线粒体分布逐渐均匀，Z 线清晰及肌原纤维排列整齐；E 组呈现肌原纤维断裂及线粒体肿胀等变化；（2）ET 组在 ZT24、48、72h 单收缩力和强直收缩力显著高于 C 组、E 组（$P<0.01$）；（3）运动后

ZT24、ZT48 和 ZT72，CK 值：E 组较 C 组显著升高，ET 组较 E 组显著下降；（4）转录组学分析：E 和 T 组之间差异 mRNA 的靶基因 KEGG 显著富集分析在 24h、48h、72h 有 JAK—STAT、TNF、IL-17 等信号通路。在 24、48、72h 显著富集到 Junb、Fosb、Socs3 等差异基因。在24h、48h、72h共同显著富集到Socs3、Fosb介导JAK—STAT信号通路,且Socs3、Fosb 在 24h、48h、72h 表达上调。（P<0.01，[log2FC]>2）经 GO 富集分析，筛选出的 Socs3、Fosb 核心靶基因均富集在损伤修复、炎症反应调节等相关过程。

结论：（1）推拿可促进一次性大负荷运动大鼠骨骼肌超微结构损伤修复，并增加肌肉收缩力。（2）推拿可改善一次性大负荷运动大鼠 EIMD，其机制可能与 JAK—STAT 信号通路有关。（3）Socs3、Fosb 可能为推拿经 JAK—STAT 信号通路改善一次性大负荷运动大鼠 EIMD 的靶点。

关键词：一次性大负荷运动；推拿；JAK—STAT；EIMD

P6-38 HIIT 与 MICT 在改善久坐大学生心肺适能中的内部负荷特征及生理机制研究

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研究目的：本研究比较了高强度间歇运动（HIIT）与不同时间的中强度持续运动（MICT）对久坐大学生心肺适能（CRF）指标（心率（HR）、潮气量（TV）、呼吸频率（RR）、每分通气量（VE）、呼气氧气比例（O2%）、呼气二氧化碳比例（CO2%）、摄氧量（VO2）、二氧化碳生成量（VCO2））、感知觉指标（主观疲劳（RPE）、运动感受（FS）和运动觉醒度（FAS））与主观（s-RPE）/客观（TRIMP）训练负荷表达水平的差异。研究方法：实验过程中招募了 30 名静坐少动的男性大学生，分为 HIIT（30min）组（n=9）、MICT（30min）组（n=12）与 MICT（60min）组（n=9）进行急性运动的干预，并在运动过程中对上述指标进行监测。研究结果：在 CRF 方面，HIIT 引发了最高的 HR 与所有呼吸代谢指标的表达水平（$P<0.01$）。MICT 的随着时间的延长，尽管 RR 并未产生显著差异（$P>0.05$），但容量更大的 60min MICT 比 30min MICT 诱发了更高水平的 TV、VE、CO2%、VO2 和 VCO2（$P<0.05$）。在感知觉反应方面，运动强度与 RPE 和 FAS 呈递增关系，与 FS 呈负相关。尽管该关系在训练容量介导下依然存在，但强度是引发此现象的首要因素，且 FAS 的上升具有一定时效性。内部负荷方面，基于 TRIMP 的结果显示，HIIT 的生理负荷水平最高（$P<0.01$）；但基于 s-RPE 的结果表明，60min MICT 的心理负荷要高于 30min HIIT 与 MICT。研究结论：HIIT 在 CRF 改善效应上的优势可能是由单次较高的 HR 表达、呼吸量度、呼吸代谢量与生理负荷水平介导的。但也产生了更低的运动感受与更大的心理负荷。尽管 MICT

的心理负荷剂量最佳，但存在一定时效性。过高的训练容量依然会导致主观感受的下降。因此，将二者优点相结合，以 30min 内的 MICT 为进入工作状态的热身手段，衔接适当容量的 HIIT，可能会在保证久坐大学生单次锻炼的生理负荷量的同时，尽可能降低心理负荷。

关键词：身体活动；久坐行为；心肺适能；运动负荷

P6-39 多组学联合分析推拿在改善运动性骨骼肌损伤导致延迟性肌肉酸痛中的作用机制

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研究目的：已有研究证实了推拿对运动性骨骼肌损伤(EIMD)的治疗作用和对延迟性肌肉酸痛(DOMS)的镇痛作用。本研究旨在应用转录组学和代谢组学联合分析探究推拿对运动性骨骼肌损伤大鼠（EIMD）的早期干预作用。

研究方法：采用转录组学和代谢组学相结合的方法，以一次性大负荷离心运动后的大鼠为研究对象，以推拿作为干预手段（压力：4-5 N，频率：2 Hz；单侧 5min），鉴定推拿对骨骼肌运动性损伤延迟性肌肉酸痛的差异表达基因和代谢物。

研究结果：从转录组学和代谢组学中发现 24 小时组间差异显著，分析数据发现，与对照组相比，推拿干预组骨骼肌中检测到 1887 个差异表达基因和 987 个差异表达代谢物。转录组学结果显示，差异表达基因富集于癌症信号通路、MAPK 信号通路、吞噬体、生热作用等途径。代谢组学结果显示，差异表达代谢物富集于色氨酸代谢、血清素突触通路、果糖和甘露糖代谢、硫胺素代谢等途径。转录组学和代谢组学数据联合分析结果显示，差异表达基因和差异表达代谢物在药物代谢、磷酸肌醇代谢、半胱氨酸和蛋氨酸代谢、络氨酸代谢等途径显著富集。

研究结论：本研究揭示了推拿是缓解运动性骨骼肌损伤大鼠模型早期延迟性肌肉酸痛症状的潜在治疗方法，并且该作用是通过多条生物学途径实现的。通过本研究可以为推拿改善延迟性肌肉酸痛的作用机制提供依据与支持。

关键词：联合分析；推拿；运动性骨骼肌损伤；延迟性肌肉酸痛

P6-40 体力活动强度划分方法的研究进展

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体力活动不足（physical inactivity）是导致健康风险的重要原因之一,给家庭社会乃至国

家带来了巨大的经济负担，为应对这一风险，众多权威专家学者和组织机构纷纷给出了促进健康的运动处方，体力活动强度的选择对于运动处方的制定至关重要。本文对近几年文献进行系统梳理，并对这些文献的观点结果进行整理分析。研究发现，体力活动强度划分分为绝对强度和相对强度。目前国内外对绝对体力活动强度划分主要有以下方法 。1、根据代谢当量划分，代谢当量(Metabolic Equivalent of Energy)，简写为 METs,是指运动时代谢率相对于安静时代谢率的倍数，用于表示各种活动的相对能量代谢水准，按照运动强度，可将 METs 分为低强度、中等强度、高强度三个等级，即低强度<3METs，中等强度 3-6METs，高强度>6METs；然后依据国际体力活动量表（international physical activity questionnaire，IPAQ）评判标准，将体力活动分为低强度体力活动<600METs/周，中等强度体力活动 600-3000METs/周，高强度体力活动>3000METs/周；2、根据心肺功能状态来划分体力活动强度等级；3、根据主观感觉来判断运动强度的等级；4、用平均和相对心率来划分体力活动强度，以心率综合指标和相对心率综合指标衡量体力活动等级；5、说话测试，一般说话测试（Talk Test，TT）和计数说话测试（Counting Talk Test，CTT）为说话测试的两种主要类型。相对强度是指考虑到个人相对其最大能力的努力程度，目前对于体力活动强度的划分更多的是绝对强度的划分，就目前常用的强度划分的方法进行简要的概括，这将有助于扩大我们的研究视野，为体力活动强度的划分提供有价值的参考，未来希望可以基于加速度计测量的数据获得个性化的相对强度加速度计切点，以便每个人都有属于自己的切点，来更好的划分运动强度等级，达到更安全更有效进行身体活动的目的。

关键词:体力活动；强度划分；强度

P6-41 不同运动方式调控神经肌肉接头对衰老大鼠骨骼肌蛋白代谢影响的研究

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本研究通过对衰老大鼠进行运动训练，探究不同运动方式对神经肌肉接头（NMJ）与骨骼肌相关蛋白代谢的影响及机制。将 38 只 3 月龄 SPF 级 Sprague-Dawley (SD)雄性大鼠，其中 10 只为青年对照组（Y 组），其余养至 21 月龄后随机分为老年对照组（O 组、8 只）、耐力运动组（EN 组、10 只）进行每周 5 天跑台训练、抗阻运动组（R 组、10 只）进行每周 5 天尾部负重爬梯训练。8 周训练结束后，取大鼠腓肠肌，并使用 Western Blot 法检测 NMJ

中 Agrin/Lrp4/MuSK/DOK-7 信号通路与骨骼肌蛋白合成与降解相关蛋白 P-AKT、P-mTOR、P-FOXO1 的蛋白表达量。结果显示（1）与 Y 组比较，O 组大鼠腓肠肌湿重比（SI 值）显著降低，与 O 组比较 EN 组和 R 组大鼠腓肠肌 SI 值均显著升高，且抗阻运动更加明显；（2）与 Y 组比较，O 组大鼠腓肠肌 Agrin、Lrp4、Musk 蛋白表达均明显降低（$P<0.01$），Dok7、P-mTOR、P-Akt 蛋白表达显著降低（$P<0.05$、$P<0.001$，$P<0.001$），P-FoxO1 蛋白表达显著上升（$P<0.001$）；与 O 组比较，EN 组 Agrin、P-mTOR 蛋白表达显著升高（$P<0.01$），Lrp4、P-FoxO1 蛋白表达显著降低（$P<0.01$、$P<0.001$）；与 O 组比较，R 组 Agrin、Lrp4、Musk、Dok7、P-mTOR 蛋白表达显著升高（$P<0.001$、$P<0.01$、$P<0.01$、$P<0.01$、$P<0.001$），P-FoxO1 蛋白表达水平显著下降（$P<0.001$）；（3）R 组与 EN 组相比，Lrp4、Dok7、P-mTOR 蛋白表达显著升高（$P<0.01$），P-FoxO1 蛋白表达显著降低（$P<0.01$）。以上结果表明，21 月龄大鼠腓肠肌出现 NMJ 衰老和骨骼肌质量下降；两种运动训练改善了腓肠肌 NMJ 中 Agrin/Lrp4/Musk/Dok7 信号通路的蛋白表达，增加衰老大鼠骨骼肌蛋白质合成、降低骨骼肌蛋白质分解代谢，且抗阻运动效果更加显著。

关键词：骨骼肌；肌肉萎缩；神经肌肉接头；运动

P6-42 运动上调 FGF21 抑制心肌缺血再灌注小鼠下丘脑室旁核氧化应激和铁死亡

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目的：探讨有氧运动是否上调成纤维细胞生长因子 21（fibroblast growth factor 21，FGF21），抑制心肌缺血/再灌注（ischemia-reperfusion，I/R）小鼠下丘脑室旁核（paraventricular nucleus，PVN）氧化应激和铁死亡。

方法：60 只 3 月龄雄性 C57/BL6 小鼠随机分为假手术组（S）、运动+假手术组（ES）、心肌 I/R 2h 组(C+I/R 2h)，运动+心肌 I/R 2h 组（E+I/R 2h），心肌 I/R 24h 组（C+I/R 24h）、运动+心肌 I/R 24h 组（E+I/R 24h），每组 10 只。预先进行 7 周有氧运动干预，7 周有氧运动结束后次日，采用左冠状动脉前降支活扣结扎法，30min 后移除结扎线，制备心肌缺血再灌注模型。再灌注 2h-24h 后，采用心动超声评定心功能，尼氏染色和免疫荧光染色判定神经元损伤；DHE 染色检测 PVN 区 ROS 含量；Western Blotting 检测 PVN 区 FGF21、FGFR1、氧化应激和铁死亡相关蛋白表达。

结果：与 S 组比较，C+I/R 2h 和 C+I/R 24h 小鼠 PVN 区 ROS 含量显著增加（$P<0.05$），P53 蛋白表达以及 P-PI3K/PI3K、P-AKT/AKT 比值显著升高（$P<0.05$），FGF21、FGFR1、SOD1、SOD2、SESN2、HO-1、Nrf2 蛋白表达代偿性升高（$P<0.05$），XCT 蛋白表达显著降低（$P<0.05$），神经元尼氏体出现消解，神经元标志物 Neun 和 Map2 显著减少（$P<0.05$）；

与C+I/R 2h和C+I/R 24h比较，E+I/R 2h和E+I/R 24h组PVN区ROS含量显著降低（*P<0.05*），P53 蛋白表达以及 P-PI3K/PI3K、P-AKT/AKT 比值显著降低（*P<0.05*），FGF21、FGFR1、SOD1、SOD2、SESN2、HO-1、Nrf2 蛋白表达进一步升高（*P<0.05*），XCT 蛋白表达显著升高（*P<0.05*），神经元尼氏体形态完整，神经元标志物 Neun 和 Map2 显著增加（*P<0.05*）。

结论：心肌缺血再灌注可诱导下丘脑 PVN 区出现氧化应激和铁死亡，造成神经元损伤。前期有氧运动可激活 FGF21/FGFR1 通路，抑制心肌 I/R 小鼠 PVN 区氧化应激和铁死亡，减轻神经元损伤。

关键词：心肌缺血再灌注，下丘脑室旁核，氧化应激，铁死亡，FGF21，有氧运动

P6-43 HIIT 对 T1DM 小鼠自身反应性 $CD8^+$T 细胞代谢重编程及功能的影响

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目的：本研究拟基于 Akt/mTOR 信号通路探讨高强度间歇运动（HIIT）对胰岛自身反应性 T 细胞代谢及功能稳态的调控效果及具体机制，以期为 HIIT 防治 T1DM 提供理论依据。

方法：6 周龄 SPF 级 C57BL/6 小鼠随机分为普通安静组（WT）、运动组（WTE）、DM 安静组（T1DM）、DM 运动组（T1DME），每组 8 只。6 周 HIIT 干预结束后，检测小鼠血糖、血清胰岛素含量；苏木精-伊红染色观察胰岛和脾脏组织形态；流式细胞术检测 $CD8^+$T 细胞的增殖活化；RT-PCR 检测上清液 PFP、GZMB、FasL、PTEN、PD1、Akt、c-Myc、HIF-1α 和 GLUT1 表达量；Western Blot 检测上清液 p-Akt、p-mTOR、p-PTEN 和 c-Myc 表达情况；ELISA 检测上清液 IFN-γ、TNF-α 和 IL-2 水平。

结果：①HIIT 可有效减少内脏脂肪含量，改善脂体比；与 T1DM 组小鼠比较，T1DME 组体重和脂体比均无显著变化，血糖显著降低（$P<0.01$），HIIT 可有效降低 1 型糖尿病小鼠血糖含量。②HIIT 有效延缓了 1 型糖尿病小鼠脾脏的损伤，同时可能延缓其免疫功能下降；HIIT 有效延缓了 1 型糖尿病小鼠胰岛的损伤，同时可延缓 A、B、D 细胞功能损伤。③T1DM 组 $CD3^+$T、$CD4^+$T、$CD8^+$T 及 $CD4^+/CD8^+$细胞含量均低于 WT 组（$P<0.01$）；经过 6 周 HIIT 干预，WTE 组 $CD3^+$T、$CD4^+$T、$CD8^+$T 细胞较 WT 组差异无显著性；与 T1DM 组比较，T1DME 组 $CD3^+$T、$CD4^+$T、$CD8^+$T 及 $CD4^+/CD8^+$细胞均增加（$P<0.01$）。④T1DM 组 PFP、GZMB、FasL、HIF-1α 和 GLUT1 表达量均高于 WT 组（$P<0.01$），PTEN、PD1、Akt 和 c-Myc 表达量均低于 WT 组（$P<0.01$）。经过 6 周 HIIT 干预，WTE 组 GZMB 和 GLUT1 表达量较 WT 组降低（$P<0.01$），PTEN、PD1、Akt 和 c-Myc 表达量均增加（$P<0.01$）；与 T1DM 组比较，T1DME 组 PFP、GZMB、FasL、HIF-1α 和 GLUT1 表达量均降低（$P<0.01$），PTEN、PD1、Akt 和 c-Myc 表达量均增加（$P<0.01$）。⑤T1DM 组 p-Akt、p-mTOR、p-PTEN 和 c-Myc 蛋白表达量均低于 WT 组（$P<0.01$）。经过 6 周 HIIT 干预，WTE 组 p-PTEN

蛋白表达量增加（P＜0.01）；与 T1DM 组比较，T1DME 组 p-Akt、p-mTOR、p-PTEN 和 c-Myc 蛋表达量均增加（P＜0.01）。⑥T1DM 组 IFN-γ、TNF-α 和 IL-2 水平均高于 WT 组（P＜0.01）。经过 6 周 HIIT 干预，WTE 组 IFN-γ、TNF-α 和 IL-2 水平与 WT 组差异无显著性；与 T1DM 组比较，T1DME 组 IFN-γ，TNF-α 和 IL-2 水平均降低（P＜0.01）。

结论：HIIT 可通过影响以 Akt/mTOR 信号通路为核心的多种基因蛋白的表达延缓 1 型糖尿病免疫功能损伤，HIIT 是 $CD8^+$T 细胞代谢重编程的一个驱动因素。

关键词：HIIT；T1DM 小鼠；$CD8^+$T 细胞；Akt；mTOR

P6-44 有氧运动/饮食控制通过 Irisin 受体通路促进肥胖小鼠骨形成

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目的 探讨有氧运动和饮食控制通过 Irisin 受体信号通路调控肥胖小鼠骨形成的作用。**方法** 60 只 C57BL/6 小鼠，10 只标准饲料喂养，50 只高脂饲料喂养。10 周后，将 10 只标准饲料喂养的小鼠设置为正常对照（NC）组，并把 44 只肥胖小鼠分为肥胖对照（OC）组、饮食控制（OR）组、有氧运动（OE）组和饮食控制联合有氧运动（ORE）组。采用酶联免疫法、HE 染色、Micro-CT、三点弯曲试验和 Western blot 评估小鼠各项指标。**结果** 与 NC 组相比，OC 组血清 Irisin、OCN 和 BALP 水平均降低（P＜0.05），骨髓脂肪增多（P＜0.05），BV/TV、Tb.N 和 Conn.Dn 降低（P <0.05），最大载荷、断裂载荷和弯曲强度明显降低（P＜0.05），骨中 Irisin、TGFβ1、Runx2 和 Osterix 的蛋白水平降低（P＜0.05），但 Integrin αVβ5 蛋白水平无显著变化（P＞0.05）。与 OC 组相比，OR 组、OE 组和 ORE 组血清 Irisin、OCN 和 BALP 水平升高（P＜0.05），骨髓脂肪减少（P＜0.05），BV/TV、Tb.N 和 Conn.Dn 明显升高（P＜0.05），最大载荷、断裂载荷和弯曲强度明显升高（P＜0.05），骨中 Irisin 和 TGFβ1、Runx2 和 Osterix 蛋白的水平明增多（P＜0.05），但 Integrin αVβ5 蛋白水平无显著变化（P＞0.05）。**结论** 有氧运动和饮食控制可能通过 Irisin 受体信号通路，减少了骨髓脂肪，促进了肥胖小鼠骨形成。

关键词：饮食控制；有氧运动；肥胖；Irisin；骨形成

Aerobic exercise and caloric restriction promotes bone formation of obese mice by regulating Irisin receptor signaling pathway

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Objective To explore the effects of aerobic exercise and caloric restriction on bone formation and Irisin related pathways in obese mice. **Methods** 60 C57BL/6 mice, of which 10 were fed standard feed and 50 were fed high-fat feed. After 10 weeks, 10 mice fed with standard feed were assigned to the normal control (NC) group, and 44 obese mice were divided into obesity control group (OC), obesity caloric restriction (OR), obesity aerobic exercise (OE) and obesity caloric restriction combined with aerobic exercise (ORE). The indexes of mice were evaluated by enzyme-linked immuno scRbent assay, HE staining, Micro-CT, three-point bending test and Western blot. **Results** Compared with NC group, the levels of serum Irisin, OCN)and BALP in OC group were decreased (P<0.05), bone marrow fat was increased (P<0.05); and BV/TV, Tb.N and Conn.Dn were decreased (P<0.05); simultaneously, maximum load, breaking load and bending strength were decreased significantly (P<0.05); and Irisin, TGFβ1, Runx2 and Osterix protein levels were decreased (P<0.05), but Integrin αV and β5 were not changed (P>0.05). Compared with OC group, the levels of serum Irisin, OCN and BALP in OR, OE and ORE groups were increased (P<0.05), bone marrow fat was decreased (P<0.05); BV/TV, Tb.N and Conn.Dn were increased significantly (P<0.05); and the maximum load, breaking load and bending strength were increased significantly (P<0.05); Irisin, TGFβ1 Runx2 and Osterix protein were increased significantly (P<0.05), but Integrin αV and β5 were not changed (P>0.05). **Conclusion** Aerobic exercise and caloric restriction may reduce bone marrow fat and promote bone formation in obese mice by Irisin receptor signaling pathway.

Key words: caloric restriction; aerobic exercise; obesity; Irisin; bone formation

P6-45 HIIT 对衰老大鼠肝脏代谢的影响及可能机制

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目的：探究高强度间歇运动对衰老大鼠肝脏代谢的影响，探索抵抗肝脏衰老的可能机制。方法：将 24 只 18 月龄雌性大鼠随机分为安静对照组(SED)和高强度间歇运动组(HIIT)，每组 12 只。HIIT 组大鼠以 15m/min 速度运动 4min，随后以 25m/min 速度运动 1min，交替进行 9 个循环，每周训练 5 次，共 8 个月；SED 组不安排运动。实验后检测大鼠的肝重、肝重/体重指数；HE 染色检测各组大鼠肝脏组织形态变化；通过蛋白免疫印迹和 RT-qPCR 检测各组大鼠肝脏线粒体氧化代谢功能、细胞凋亡、抗氧化以及炎症相关蛋白等蛋白和 mRNA 的表达；通过蛋白质组学检测各组大鼠肝脏蛋白表达谱变化，通过靶向氨基酸代谢组学检测各组肝脏内氨基酸水平；利用 microRNA 测序检测肝脏 miRNA 谱表达；采用 DIANA 在线分析工具对差异表达 miRNA 进行通路富集分析。结果：与 SED 组相比，HIIT 组大鼠肝重和肝重/体重指数显著增加，且 HIIT 组大鼠肝脏组织脂滴堆积明显减少。蛋白免疫印迹和 RT-qPCR 结果显示，与 SED 组相比，HIIT 组大鼠肝脏线粒体氧化功能、细胞凋亡、抗氧化以及炎症相关蛋白和 mRNA 表达显著改善，且铁死亡相关的 mRNA 表达显著改善。蛋白质组学检测结果显示与 SED 组相比，HIIT 共发现 56 种差异蛋白表达，且在线 KEGG 分析发现代谢通路和甘氨酸、丝氨酸、苏氨酸代谢等通路被显著富集。靶向氨基酸代谢组学结果显示与 SED 组相比，HIIT 组内甘氨酸和丝氨酸水平明显增加。miRNA 测序发现 miR-1-3p、miR-128-3p、miR-132-5p、miR-133a-3p、miR-211-5p 和 miR-369-5p 表达显著改变，KEGG 分析发现 PI3K/AKT 等代谢通路被明显富集，且 PDGFa 和 PDGFRα 可能分别作为 miR-1-3p 和 miR-128-3p 的靶基因介导对 PI3K/AKT 通路的调控。结论：1、HIIT 能够改善衰老大鼠肝脏内脂肪堆积和形态变化。2、长期 HIIT 可改善衰老肝脏内线粒体氧化功能、抗氧化能力、细胞凋亡以及炎症水平。3、甘氨酸可能介导了 HIIT 对衰老肝脏代谢功能的改善，且 miR-1-3p 和 miR-128-3p 可能靶向调控的 PDGFa/PDGFRα/PI3K/AKT 信号通路可能协同介导了甘氨酸抵抗衰老肝脏代谢功能的衰退。

关键词：衰老；肝脏；HIIT；多组学分析

P6-46 肥胖儿童青少年静息代谢率与体成分指标的关系研究

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目的：本研究通过探讨肥胖儿童青少年静息代谢率（Rest metabolism rate，RMR）与各项体成分指标的相关性，为控制体重和指导健身运动提供科学依据。

方法：本研究选取 2022 年 7 月-2023 年 8 月间参加中国华南地区暑期夏令营的肥胖儿童青少年为研究对象，共招募符合条件的 43 名肥胖儿童青少年，其中男生 24 人，女生 19 人。肥胖的诊断标准参照《学龄儿童青少年超重与肥胖标准》。体成分测试：采用人体成分

分析仪（Inbody370，韩国）测定体重、BMI、体脂量、去脂体重、骨骼肌含量、体脂百分比等。静息能耗测试：采用气体代谢分析仪（Cortex Meta Max 3B，CORTEX，德国）进行静息能耗测试。受试者在餐后 2 小时、室温 25-27℃、安静的环境下进行，要求受试者保持清醒静卧 15min。静息能耗的数据截取 11-15min 的平均值计算 VO_2 和 VCO_2，根据 Weir 公式，求出静息代谢率（kJ/d）=（3.9×VO_2+1.1×VCO_2）×1440×4.184，VO_2 为 O_2 耗量（L/min），VCO_2 为 CO_2 产生量（L/min），1kcal=4.18kJ。数据统计分析采用 SPSS26.0 完成，数据采用平均值±标准差表示，受试者体成分指标与静息代谢率的相关性采用偏相关分析（校正年龄和性别）和回归分析，以 P<0.05 为差异具有统计学意义。

结果：受试者基本情况（年龄：13.26±1.75y；BMI：31.16±3.73kg/m^2）。偏相关分析显示，静息代谢率与体脂量（r＝－0.68，P<0.01)、BMI（r＝－0.65，P<0.01）、体脂百分比（r＝－0.51，P<0.01）呈显著负相关，静息代谢率与去脂体重和骨骼肌含量的相关性没有统计学意义。线性回归分析显示，体脂量可显著预测 RMR（R^2=0.48，β=－0.691，P<0.01）

结论：肥胖儿童青少年体脂量、体脂百分比和 BMI 与静息代谢率之间具有显著负相关，其中体脂量与静息代谢率之间的相关联系最高。表明体脂量是影响 RMR 的重要因素，RMR 会随着体脂量的增加而减少。

关键词：肥胖；儿童青少年；静息代谢率；体成分

P6-47 有氧运动诱导 miR-21 调控 PTEN/PI3K/AKT 通路对小鼠缺血再灌注损伤后心肌梗死面积及心肌组织炎症反应的影响

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研究目的：探讨 12 周有氧运动对小鼠心肌缺血再灌注损伤产生的影响及相关机制，进一步研究对损伤后心肌梗死面积及其炎症因子肿瘤坏死因子-α（TNF-α）、白细胞介素-6(IL-6)、NLRP3 炎症小体表达的影响。

研究方法：通过维通立华生物技术有限公司购买 C57BL/ 6 小鼠 60 只(25-30g，6-8 周龄)，随机分为空白对照组 8 只、I/R 模型组 13 只、I/R 模型+12W 有氧运动(AE)组 13 只、12WAE+I/R 组 13 只、12W 安静+I/R 组 13 只，共 5 组。利用冠状动脉左前降支结扎制备心梗小鼠模型，40min 后再灌注制备小鼠心肌缺血再灌注模型，小鼠术后存活率为 90%。术后小鼠休养 1W，随后进行 1w 适应性运动{第 1d 以（40-50％VO 2 max）10m/min*10min，坡度为 0，每天递增 10min，直到第 6d 能以（60%-70%VO 2 max）8m/min*10min+10m/min*50 的速度训练}，之后再进行正式有氧运动训练(以 8m/min*10min+10m/min*50/d 的速度训练,60min/d,6d/w)。实验过程中采用多普勒超声心动图判断小鼠心功能（1 次/2W），训练结束后间隔 1d 先检测心功能，随后采用脱颈处死小鼠，获取心肌组织。TTC 染色观察小鼠心肌梗死面积变化；

通过 Masson 染色测定运动干预对心肌胶原容积百分比(collagen volume fraction，CVF%)的效果；RT-PCR 检测心肌组织中 miR-21 的表达水平；Western blot 检测心肌 PTEN、PI3K、AKT 蛋白表达；右颈动脉血留取血清标本使用全自动生化分析仪进行炎症因子 TNF-α、IL-6、NLRP3，及抗炎因子 IL-10 含量检测。

研究结果：超声心动图结果显示 I/R+12W(AE)组小鼠其左心室射血分数(LVEF)、左心室缩短率(LVFS)较 I/R 组小鼠有明显升高，心功能得到明显改善（P<0.05）。TTC 结果显示，与 I/R 组相比，I/R+12WAE 组小鼠其心肌梗死面积明显减少（P<0.05），与 12W 安静+I/R 组相比 12WAE+I/R 组的小鼠心肌梗死面积明显减少（P<0.05）。Masson 显示与 I/R 组小鼠相比，I/R+12WAE 组小鼠心肌纤维化程度明显降低，与 12W 安静+I/R 组相比，12WAE+I/R 组的小鼠心肌纤维化程度明显降低。RT-PCR 结果显示 I/R 组小鼠心肌组织 miR-21 表达水平下降，I/R+12WAE 组 miR-21 升高。蛋白检测结果发现 I/R+12WAE 组小鼠其心肌 PTEN 蛋白表达下降，且 PI3K、AKT 蛋白表达要比 I/R 组小鼠显著（P<0.05）；血清检测发现与空白对照组相比，I/R 组血清中的炎症因子 TNF-α、IL-6、NLRP3 明显升高，IL-10 表达明显下降；与 I/R 组小鼠相比，I/R+12WAE 组小鼠 TNF-α、IL-6、NLRP3 表达显著降低，抗炎因子 IL-10 表达呈上升水平。

研究结论：12WAE 运动能诱导小鼠心肌缺血耐受，减轻了心肌梗死面积，改善心功能。运动能激活心肌 miR-21 表达，其机制可能是通过 PTEN/PI3K/AKT 信号通路抑制促炎因子 TNF-α、IL-6、NLRP3 的表达，上调 IL-10，适度减轻了缺血后的炎症反应，从而发挥了心肌的保护作用。

关键词：miR-21；PTEN/PI3K/AKT；缺血再灌注；炎症

P6-48 跑台运动改善 MPTP/p 诱导慢性帕金森病小鼠抑郁样行为的机制研究

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目的：帕金森病作为第二大常见的神经系统退行性疾病，严重影响患者的生活质量。大量研究证实，运动在促进脑功能健康和脑神经调控方面发挥重要作用。因此，本文通过 MPTP/p 构建慢性 PD 小鼠模型，旨在研究跑台运动对慢性 PD 小鼠抑郁样行为的影响及其分子机制。**方法:** 60 只 8 周龄雄性 C57 小鼠，适应性饲养 1 周后随机分为 4 组（n=15）：对照组（Con）、PD 组（PD）、4 周运动组（PD+E4）、8 周运动组（PD+E8）。腹腔注射 MPTP（25 mg kg^{-1} d^{-1}, 2 d/w, 5 w）联合 Probenecid（250 mg kg^{-1} d^{-1},2 d/w,5 w）构建慢性 PD 模型。造模结束进行运动协调能力及抑郁样行为检测。免疫荧光染色观察海马 TH 及 Iba-1 的表达；高尔基染色观察海马神经元轴突和树突棘发育情况；Western Blot 检测海马组织中

内源性大麻素受体 GPR55、Iba-1 及 M1/M2 型极化蛋白、神经炎症相关蛋白的表达；RT-PCR 检测海马组织中神经炎症等相关蛋白的 mRNA 水平；ELISA 检测小鼠血清中 IL-1β 的表达。**结果：**1）跑台运动可显著改善 PD 小鼠的运动协调能力，增加 TH 的表达，减少病理蛋白 α-syn 的表达；2）抑郁样行为学表明：与 Con 组相比，PD 小鼠在强迫游泳实验和悬尾实验中的不动时间明显增加，而运动干预后小鼠的不动时间显著缩短。3）与 Con 组相比，PD 组小鼠神经元树突分支数、树突长度、树突棘密度均显著降低，而运动干预后上述指标均得到显著改善；4）跑台运动降低了 PD 小鼠海马中 Iba-1、IL-1β、IL-6、TNF-α 及其 mRNA 的表达水平。5）跑台运动可促进 PD 小鼠海马中小胶质细胞由 M1 型标记蛋白向 M2 型标记蛋白的转化。6）跑台运动可逆转 PD 小鼠海马中 GPR55 的异常低表达。**结论：**跑台运动可缓解 MPTP/p 诱导慢性 PD 小鼠的抑郁样行为，其机制可能是通过上调海马神经元 GPR55 的表达，促进小胶质细胞 M1 向 M2 型转化所介导的抗炎反应与神经保护作用，逆转 MPTP/p 对海马神经元的毒性作用。

关键词：跑台运动；帕金森病；抑郁样行为；GPR55；M1/M2 型小胶质细胞

P6-49 运动通过 GDF-5 促进血管新生增强肾功能

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目的：探究不同运动方式，时间梯度下增加肾脏 GDF-5 表达，促进肾脏血管生成，从而增强肾脏功能及其分子机制，为运动保护肾脏功能与健康打开新的视角。

方法：动物实验：采用雄性 8 周 C57BL/6J 野生型小鼠，有氧运动分为对照组（con）、7 天组、14 天组、21 天组、28 天组，6 只/组，训练 60min/d，5 次/周。运动强度 14m/min,60min/d。抗阻运动分组相同，采用高度为 1m 的爬梯，训练 60min/d， 5 次/周，5 次/每组。发现抗阻运动效果略高于有氧，因此以肾脏 GDF-5 特异性敲低鼠进行抗阻运动对比。通过血尿液肾功能指标试剂盒，组织 HE、免疫荧光染色、RT-qPCR、Western Blotting 等实验，探究 GDF-5 在运动促进血管新生提高肾功能中的作用。细胞实验：采用人脐静脉内皮细胞（HUVEC），使用运动血清干预 HUVEC，检测细胞 GDF-5 表达。使用人 GDF-5 重组蛋白、P38/MAPK 和 Smad1/5/8 抑制剂对比干预 HUVEC，通过免疫荧光染色和 Western Blotting 实验，探讨 GDF-5 促进血管新生的可能分子机制。

结果：（1）有氧运动和抗阻运动干预都有助于增加肾脏 GDF-5 表达且有时间依赖性。（2）运动通过增加肾脏 GDF-5 表达来促进血管新生。（3）运动可通过 GDF5 介导 P38/MAPK 和 Smad1/5/8 通路促进肾脏血管新生，增强肾功能。

结论：本研究发现有氧和抗阻运动都可促进肾脏 GDF-5 表达，促进血管新生并增强肾

功能。另外，通过肾脏特异性敲低 GDF-5 将减弱运动效应，减少血管新生。通过细胞实验进一步探索 GDF-5 的促血管新生机制。

关键词：运动；GDF-5； P38/MAPK 和 Smad1/5/8 通路；肾脏血管新生

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P6-50 有氧运动通过 Notch 信号通路调节巨噬细胞极化改善心肌缺血再灌注损伤炎症反应

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目的：经过前期临床实验发现，在对 PCI 术后患者进行为期三个月的传统中医养生功法干预后，患者心功能明显改善，同时心肌损伤炎症反应进程也得到减缓。因小鼠无法进行传统功法运动训练，据换算运动强度发现传统中医养生功法可以被视为一种有氧运动形式的一部分，故本研究将通过基础实验，验证有氧运动介导 Notch 信号通路调节巨噬细胞极化改善心肌缺血再灌注损伤炎症反应。

方法：选用 3 月龄雄性 C57BL/6 野生型小鼠 36 只，随机进行分组分为空白对照组 6 只，缺血再灌注模型组（I/R）15 只，缺血再灌注模型+有氧运动组（I/R+AE）15 只，用冠状动脉左前降支结扎制备心梗小鼠模型，40min 后再灌注制备心肌缺血再灌注模型，术中死掉 4 只小鼠，存活率为88%。术后小鼠休养1w，随后进行1w适应性运动（第一天以5m/min*10min，坡度为 0，每天递增 10min，直到第 5d，5d/w），之后开始进行正式训练（5m/min*10min+10m/min*30min 的速度进行训练，5d/w）8w。使用超声心动图检测小鼠心功能；流式细胞仪检测巨噬细胞极化；Western blot 检测心肌细胞 Notch 蛋白表达；ELISA 检查 TNF-α、IL-6、iNOS 等炎症指标。

结果：8w 运动结束后发现，I/R+AE 组小鼠其左心室射血分数(LVEF)、左心室缩短率(LVFS)较 I/R 组小鼠有明显升高，心功能有明显改善，具有统计学意义（P＜0.05)；蛋白检测发现 I/R+AE 组小鼠其 Notch 蛋白表达水平比 I/R 组小鼠有明显升高；流式细胞术检测表明与 I/R 组相比，I/R+AE 组小鼠 M2 型巨噬细胞极化增多，M1 型巨噬细胞极化减少；ELISA 结果显示与空白对照组相比，I/R 组小鼠其 TNF-α、IL-6、iNOS 等炎症指标均明显升高，而与 I/R 组相比，I/R+AE 组小鼠其相关炎症指标均有所改善。

结论：8W 有氧运动可以通过 Notch 信号通路调节巨噬细胞极化，并且在这个过程中可以降低 TNF-α、IL-6 和 iNOS 等炎症因子表达水平，同时这些变化有助于促进 M2 型巨噬细胞的极化，发挥抗炎和修复作用，帮助改善患者心功能。

关键词：基础实验，缺血再灌注损伤，8w 有氧运动，Notch 信号通路，巨噬细胞极化

P6-51 基于代谢组学分析推拿促进运动性骨骼肌损伤修复的作用途径

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目的：观察推拿对运动性骨骼肌损伤的干预效应，利用代谢组学探索其可能作用途径。方法：选取 8 周龄 SPF 级雄性 SD 大鼠 66 只，随机分为对照组（C，n=6）、推拿组（T，n=30）及运动组（E，n=30），根据运动后 72h 内不同时相，各组分为 0h、12h、24h、48h、72h 5 个亚组，C 组常规饲养，E 组、T 组按 Armstrong 运动模型进行一次大负荷下坡跑运动，T 组于 0h、24h、48h、72h 进行推拿干预。采用透射电镜观察骨骼肌纤维超微结构，通过非靶向代谢组学技术研究各组大鼠骨骼肌小分子物质代谢动态变化，挖掘差异代谢通路。结果：（1）骨骼肌超微结构：0h 时，E 组超微结构明显损伤，线粒体形态异常，于 24h 到达损伤高峰，48h 至 72h 逐渐恢复至正常。24h 开始，T 组超微结构较 E 组显著改善。因此，本研究集中观察 24h、48h、72h T 组与 E 组间的代谢组学变化。（2）骨骼肌代谢动态变化：①代谢轮廓动态变化：PCA 结果显示，与 E 组相比，T 组进行推拿干预后各时相的代谢轮廓改变明显，QC 样本紧密密集，验证本次实验数据稳定可靠；PLS-DA 模型验证提示相同结果；为增强分析的解释能力和最大化区分组间差异，采用 OPLS-DA 分析运动后各时相骨骼肌代谢轮廓变化，且不存在过拟合，进一步证明推拿干预 EIMD 大鼠可使骨骼肌代谢发生明显变化。②差异代谢物动态变化：T 组与 E 组于 24h、48h、72h 共同差异代谢物包括 D-甘油醛-3-磷酸、谷氨酰缬氨酸、酪氨酸异亮氨酸、羟基脯氨酰赖氨酸、叔丁氧羰基-D-苯丙氨酸等 40 种，主要富集在磷酸肌醇代谢、戊糖磷酸途径、半乳糖代谢、糖酵解/糖原异生、果糖和甘露糖代谢、戊糖磷酸等 11 条参与糖脂代谢生物过程的相关通路。结论：推拿促进运动性骨骼肌损伤修复于 24 小时后效果显著，其可能作用路径为糖脂代谢相关通路。

关键词：代谢组学；推拿；运动性骨骼肌损伤

P6-52 少林养生功法通过 Notch 信号通路调节巨噬细胞极化降低心肌缺血再灌注损伤炎症反应

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研究目的：目前高达 3.3 亿人数患有心血管病，其中缺血性心脏病占据了主导地位，心血管病防控形势仍然严竣。虽然对缺血心肌进行再灌注可使存活的心肌得以补救并降低死亡率，但再灌注后会产生系列不良的变化，造成心肌缺血再灌注损伤

（MyocardialIschemia-ReperfusionInjury，MIRI），导致术后不良事件的高发生率，因此改善患者的预后康复意义重大。目的：探讨为期三月的少林养生功法对 PCI 术后患者的 MIRI 的影响机制。

研究方法：采用前瞻性随机对照实验研究纳入入住郑州阜外华中医院明确诊断为心肌梗死并治疗后符合纳入标准的 60 名患者，并将患者按采用随机数字表法，随机分为实验组和对照组，每组 30 人。对照组接受了标准的冠心病二级预防药物治疗，并接受了常规患教和必要的心理疏导，实验组在对照组的基础上进行五禽戏与易筋经的运动疗法，治疗期为三个月，利用微信群及微信公众平台，一周练习三次，每次练习以少林养生功法体系为主，练习时长约 30min。随时间节点为导入期、治疗 4 周、治疗 8 周、治疗 12 周。观察运动前后 AMI 患者心脏彩超 LVEF、LVED，NT-BNP 等心脏结构与功能指标：并通过酶联免疫吸附法（ELISA）检测 TNFα、IL-6、iNOS 等炎症指标。

研究结果：在心脏结构和功能方面，试验组与对照组患者 LVEF、NT-BNP 均比治疗前有所改善，具有统计学意义（P＜0.05)。而治疗组与对照组患者 NT-proBNP 改善差异不显著，无统计学意义（P＞0.05）。在炎症指标方面，疗程结束后实验组与对照组均有所改善，其中实验组改善程度较对照组明显。

研究结论：在接受了标准的冠心病二级预防药物治疗、常规患教以及心理疏导的基础上，在 AMI 患者中开展五禽戏与易筋经相结合的中医养生功法，可进一步改善心肌缺血再灌注损伤炎症。

关键词：缺血再灌注损伤；少林养生功；Notch 信号通路；炎症反应

P6-53 基于 Firstbeat 系统的自由式滑雪空中技巧运动员训练负荷及疲劳恢复研究

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研究目的：自由式滑雪空中技巧是我国的传统优势项目，在 2022 年冬奥会上，我国取得了 9 金 4 银 2 铜共计 15 枚奖牌，其中自由式滑雪空中技巧项目贡献了 2 金 1 银。基于心率 (HR) 和心率变异性 (HRV) 的生理指标，被广泛用于教练监控和优化运动员的训练负荷。2018 年以来国家空中技巧队开始使用 firstbeat 系统进行训练量和疲劳恢复监控，在 2018 年和 2022 年奥运会上共取得了 2 金 3 银 1 铜的好成绩。本文以国家队自由式滑雪空中技巧世锦赛、奥运会冠军运动员徐某为研究对象，分析其在 2019-2020 年度世界杯期间（长春）的训练监控及疲劳恢复，进而为我国空中技巧科学训练及疲劳恢复提供个体化冠军模型。

研究方法：研究对象为中国自由式滑雪空中技巧女队队员 1 名，1990 年出生，体重 58kg，身高 165cm,世锦赛自由式滑雪空中技巧赛 27 次冠军，北京冬奥会自由式滑雪空中技巧冠军。测试工具为 Firstbeat 训练强度和疲劳恢复监控系统（芬兰），分为负荷评定板块和疲劳恢复

（Recovery Test）两个板块。早上 6:00，运动员在空腹、安静状态下佩戴心率带,测试 3 分钟心率，利用 Firstbeat 系统中 Recovery Test 板块完成，根据心率变异性换算出恢复值。数据为 2019 年备战长春世锦赛前期数据。测试数据采用 SPSS 19.0 统计软件包进行统计学处理，数据以平均数±标准差（M±SD）表示，采用配对样本 t 检验，P＜0.05 为显著性差异。

研究结果：

1、训练监控特征。在徐某日常训练的 11 月 7 日-12 月 4 日期间，训练冲量（Trimp）与训练效果（TE）呈现相同的变化趋势，在训练冲量（Trimp）较大的日期 9 日、19 日、28 日（Trimp 为 102,115,124）训练效果（TE）分别为 2、1.8、2.5。但是也有一些特殊的日子，如 11 月 11 日 Trimp 为 97，TE 为 2.1，比 11 月 9 日的 Trimp102、TE2.0 还要高，这说明在不同训练日，由于运动员机能状态不同，同一难度动作训练负荷不同，产生的训练效果也不同。在备战世锦赛的 12 月 9 日-19 日期间，较低的 Trimp 产生了较大的 TE，如 12 月 3 日，Trimp 为 88，TE 为 2.3,12 月 4 日，Trimp 为 96，TE 为 2.5。这可能与机体的应激状态下，身体内分泌机能旺盛，对 EPOC 产生了较大的影响。

2、疲劳恢复特征。在日常训练阶段，徐某的平均恢复得分（score ）为 137.12，表现为前日训练量较大，次日恢复比率和恢复得分降低。如 11 月 18 日为休息日，19 日恢复比率为 61%，恢复得分为 156；而 11 月 27 日 Trimp 为 141，28 日恢复比率为 50%，恢复得分为 127。也就是说运动员恢复比率的波动趋势与测试前一日的训练负荷呈负相关。在世锦赛期间，徐某的平均恢复得分为 175.6，这期间的平均冲量 Trimp 为 86.5，恢复得分低而运动冲量低，这与运动强度低时面临比赛身体压力大有着密切的关系。

研究结论与建议：Firstbeat 训练强度和疲劳恢复监控系统能够反映运动员的训练情况和恢复状况，在自由滑雪空中技巧项目科学监控中具有良好的可操作性，为量化训练负荷、实现科学化训练提供了一种新手段。

课题来源：河北省体育局体育科技研究项目（基于 Firstbeat 系统监控的空中技巧滑雪运动员运动适应特征研究，课题编号 20211009）

关键字：Firstbeat 系统；自由式滑雪空中技巧；训练强度监控；运动疲劳恢复

P6-54 The role of OTUD5 in skeletal musclein autophagy after eccentric exercise

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The OTU domain-containing protein 5 (OTUD5) is also known as deubiquitination enzyme A (DUBA), its complex structure basis makes it has a variety of biological functions. In this study, we established an eccentric motion model to observe the effect of OTUD5 on autophagy in

skeletal muscle. 48 8-week-old male SD rats were randomly divided into the control group (C) and the exercise group (E). Group E was performed an eccentric exercise on a treadmill and sampled gastrocnemius at 0h, 12h, 24h, 48h, 72h post-exercise. Ultrastructural morphological changes in skeletal muscle were observed by transmission electron microscopy, and the protein expression of OTUD5, PDCD5, Bcl-2, P62, and LC3-II/LC3-I was detected by Western Blot. The results show that eccentric exercise leads to abnormal changes in the ultrastructure of skeletal muscle; the protein levels of OTUD5 was significantly increased at 0h post-exercise ($P<0.01$); the levels of P62, LC3-II/LC3-I and PDCD5 were increased at 12h post-exercise ($P<0.01$), and the expression of Bcl-2 was significantly decreased ($P<0.01$). In conclusion, we suggest that OTUD5 may play an important role in eccentric exercise-induced autophagy in skeletal muscle by upregulating PDCD5 protein levels and inhibiting Bcl-2 protein expression.

Keywords: eccentric exercise; OTUD5; skeletal muscle; autophagy

P6-55 下肢血流限制力量训练对青年女性代谢和免疫应激水平的影响

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研究目的：近年来青年女性的力量素质愈发低下，急需通过力量训练提高其健康水平。通过比较青年女性在黄体期和卵泡期内分别进行血流限制训练（Blood flow restriction training，BFRT）和高强度抗阻训练（High-intensity resistance training，HIRT）后体内相关激素水平的变化，分析在不同生理周期内进行 BFRT 与 HIRT 的效果和优势，为青年女性更为科学和有效地进行力量训练提供实践参考和数据支撑。

研究方法：共招募 12 名月经周期正常的健康青年女性（年龄=20.20±1.32 岁、生理周期=29.70±2.54 天）。通过体温、排卵、血清雌激素等测试确定卵泡期（开始月经后第 6-8 天）与黄体期（排卵开始后第 4-6 天），随机接受 4 种不同的单次急性训练，包括黄体期进行 BFRT、黄体期进行 HIRT、卵泡期进行 BFRT 和卵泡期进行 HIRT。其中，BFRT 是对大腿进行 50%×动脉闭塞压（Arterial occlusion pressure，AOP）的血流限制，同时以 30%×1RM 的强度进行 4 组杠铃蹲起训练，第 1 组完成 30 次，后 3 组每组 15 次，组间间歇 60s。HIRT 是不进行血流限制，仅以 70%×1RM 的强度同样进行 4 组杠铃蹲起训练，每组 8-12 次，组间间歇 3min。在训练后采集唾液样本，测试合成代谢类、分解代谢类以及免疫应激类相关激素水平。

研究结果：（1）青年女性在黄体期进行 BFRT 后的 GH、DHEA 均显著高于在卵泡期进行 BFRT 后（$P<0.05$，$P<0.01$）和在卵泡期进行 HIRT 后（$P<0.01$，$P<0.01$）。在卵泡期进行 BFRT 后的 IGF-1 显著高于在卵泡期进行 HIRT 后（$P<0.05$）。（2）青年女性在黄体期进行 HIRT 后的 C 显著高于在黄体期进行 BFRT 后（$P<0.01$）和在卵泡期进行 HIRT 后（$P<0.01$）。（3）青年女性在黄体期进行 HIRT 后的 Amya 显著高于在黄体期进行 BFRT 后（$P<0.05$）和在卵泡期进行 HIRT 后（$P<0.05$），在黄体期进行 HIRT 后的 IgA 均显著低于在黄体期进行 BFRT 后（$P<0.01$）和在卵泡期进行 HIRT 后（$P<0.05$）。

研究结论：（1）青年女性进行单次急性BFRT后体内的合成代谢水平高于进行HIRT后，且在黄体期时效果更佳。（2）青年女性在黄体期进行HIRT后的合成代谢反应保持在较高水平，但存在发生免疫抑制的可能，会使运动风险增加。（3）实践建议青年女性在进行力量训练时选择将BFRT作为备选手段，在黄体期时优先选择BFRT。

关键词：青年女性；生理周期；血流限制训练；合成代谢；免疫应激

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P6-56 膜联蛋白 A6 在一次离心运动小鼠骨骼肌质膜损伤修复中的作用

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目的：质膜完整性是维持细胞内环境乃至生物体生存和稳态的前提和基础。急性离心收缩常引发质膜破坏，可能导致皮质细胞骨架解体乃至肌纤维死亡，因此快速修复质膜至关重要。膜联蛋白（Annexins，Anxs）是一类 Ca^{2+}和磷脂结合蛋白，其中 AnxA6 分子量最大且拥有 2 个 C 端核心结构域，稳定与调节细胞骨架的，通过形成“修复帽”与 Dysferlin 等发挥协同作用。本研究以 AnxA6 为切入点，探究其在一次离心运动后小鼠骨骼肌质膜损伤修复中的作用特点和时程特征。

方法：将 8 周龄雄性 C57/6J 小鼠随机分为安静对照组（C）、运动后即刻组（E0）、运动后 2h 组（E2）、运动后 6h 组（E6）、运动后 24h 组（E24）、运动后 48h 组（E48）和运动后 72h 组（E72），每组 12 只。经一次下坡跑，使用 Elisa 法测定小鼠血清 CK 活性和 AnxA6 浓度，使用伊文思蓝（Evans blue dye, EBD）和横纹肌特异性细胞骨架适配蛋白 1（Xin actin binding repeat-containing protein 1,Xirp1）染色观察小鼠股四头肌质膜和细胞骨架损伤及修复程度，使用冰冻切片免疫荧光双标技术检测骨骼肌中 AnxA6 与同家族 AnxA1、AnxA2 的共定位水平，使用 Western blot 法测定骨骼肌中 AnxA6、AnxA1 和 AnxA2 的相对蛋白表达量。采用 SPSS 24 对数据进行单因素方差分析或多独立样本非参数检验，$P<0.05$ 表示结果具有显著性差异。

结果：运动后 2h， CK 活性较安静状态显著性升高并达到峰值（$P<0.01$）； 48h 出现

小幅二次升高（$P<0.05$）。E6 组血清 AnxA6 浓度较 C 组显著升高（$P<0.05$），72h 达到峰值（$P<0.01$）。运动后 6h，镜下可见 EBD、Xirp1 阳性细胞，%Area 最大（$P<0.01$）。AnxA6 与 AnxA1 共定位水平无显著变化，但与 AnxA2 在 6h 和 48h 出现共定位系数双高峰（$P<0.01$）。各组 AnxA6、AnxA1 和 AnxA2 表达量无显著变化（$P>0.05$）。

结论：一次性离心运动后，小鼠血清 CK 和 AnxA6 均出现二次升高现象，但 AnxA6 峰值出现晚于 CK，这可能从功能角度反映 AnxA6 参与质膜修复的进程；AnxA6 主要通过增强与 AnxA2 的协同上膜实现骨骼肌质膜修复。

关键词：AnxA6；离心运动；骨骼肌；质膜修复

P6-57 长期低温下高强度训练对小鼠无氧运动能力的影响

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研究背景：无氧运动能力在竞技体育中起到十分重要的作用，对绝大多数竞技体育活动而言，运动员竞技能力的基础取决于有氧能力，而竞技能力的上限却取决于无氧能力。已有文献报道低温和高强度间歇训练（High-intensity Interval Training；HIIT）均会影响机体的运动能力，但尚未有研究报道长期低温暴露与 HIIT 结合对无氧运动能力的影响。因此，本研究旨在探究长期低温暴露下高强度训练对小鼠无氧运动能力的影响。

研究方法：选取 7 周龄雄性 ICR 小鼠分为 4 组，常温安静组（*w*-SED）、常温 HIIT 组（*w*-HIIT）、低温安静组（*c*-SED）和低温 HIIT 组（*c*-HIIT）。HIIT 组小鼠完成 6 周 HIIT 训练干预。干预结束后，所有小鼠测试最大抓握力和大负荷游泳力竭时间，并在大负荷游泳测试结束后，检测运动停止后即刻、5min、9min 和 15min 的血清乳酸（LD）含量。乳酸测试结束后立即取材，测定小鼠腓肠肌 LD 含量，以及磷酸果糖激酶（PFK）和乳酸脱氢酶（LDH）的活性。

研究结果：（1）经过 6 周 HIIT 训练后，与 *w*-SED 组相比，*w*-HIIT 组小鼠的大负荷游泳力竭时间显著增加（$p = 0.07$）；*c*-HIIT 组小鼠的力竭时间比 *c*-SED 组和 *w*-HIIT 组均显著增加（$p < 0.05$）。（2）与 *w*-SED 组相比，*w*-HIIT 组和 *c*-SED 组在 6 周训练干预后最大抓握力无显著性差异（$p > 0.05$），*c*-HIIT 组自第三周开始至训练结束后的抓握力均显著高于其他各组（$p < 0.05$）。（3）与 *w*-SED 相比，*c*-HIIT 组运动后第 9 分钟和第 15 分钟血清 LD 显著升高（$p < 0.05$）。与 *w*-SED 组相比，*w*-HIIT 组肌肉 LD 显著降低；与 *c*-SED 相比，*c*-HIIT 组肌肉 LD 显著降低（$p < 0.05$）。（4）*c*-HIIT 组小鼠无氧糖酵解关键限速酶 PFK 与 LDH 活性均显著高于 *w*-SED 组（$p < 0.05$），且 *c*-HIIT 组小鼠 LDH 活性也显著高于 *c*-SED 组（$p < 0.05$），但与 *w*-HIIT 组相比，虽然 LDH 活性有所增加，但差异性不显著。

研究结论：长期低温下 HIIT 训练能显著促进小鼠无氧运动能力的提高和无氧糖酵解能力的增强。

关键词：低温；高强度训练；无氧运动能力

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P6-58 功能动作系统在舞蹈损伤预防与康复中的应用研究现状

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目的：运动损伤是舞蹈中普遍存在的现象，舞蹈损伤防治一直是舞蹈运动医学和科学研究的重要课题。近年来，功能动作系统（FMS）在舞蹈损伤预防与康复中的应用研究逐渐展开，本文将针对其研究现状进行分析，以期为后续的研究与应用提供参考和借鉴。

方法：利用CNKI、PubMed、Web of Science 等数据库，以“舞蹈”、“损伤”、“功能动作系统”等关键词进行检索，针对筛选的国内外有关文献进行分析。

结果：目前国内外相关研究仍显薄弱，为数不多的研究主要涉及舞蹈大学生、舞蹈演员和舞蹈艺考生的动作表现评估、损伤风险筛查和纠正性训练几方面。研究提出舞者中FMS总分达到损伤阈值的比例较高，一致认为舞者普遍存在着较高的损伤风险；有研究指出目前的损伤阈值不适合舞者，并应用ROC曲线分析方法得出了舞者损伤风险阈值，但其有效性还需进一步验证；关于舞者的动作表现，研究普遍认为是关节灵活性较好，但关节和核心的稳定性较差，存在一些身体薄弱部位、两侧不对称等，同时还有研究认为不同舞蹈专业间存在一定的差异。基于测试评估结果，一些研究进一步研究设计了个性化的纠正性训练，并通过干预实验说明纠正训练能够有效改善舞者的动作模式，进而可降低舞蹈损伤风险。个别应用选择性功能动作评估（SFMA）的研究结果表明，较之常规康复练习方法，SFMA在缓解和改善舞者肌骨疼痛症状和功能障碍方面相对有效。

结论：现有研究在一定程度上说明了FMS在舞蹈损伤风险评估筛查和纠正训练方面的正向作用，有必要进一步深化和拓展有关研究，建立舞蹈自身的数据库，设立适合舞蹈的损伤评估标准，研究设计个性化的纠正性训练，并进行长期的追踪，不断修正和完善纠正训练方案，以提高其有效性，使FMS成为舞蹈损伤预防与康复治疗体系的有益补充。

关键词：舞蹈运动损伤；功能运动系统；纠正性训练

P6-59 水疗对脑瘫患儿运动功能康复疗效及作用机制的研究进展

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目的：脑瘫（cerebral palsy）通常是由于分娩前、分娩中或分娩后发生的导致婴儿大脑发育受损的非进行性脑损伤。其主要表现是运动不能、手部活动障碍、感觉统合失调、言语迟缓和日常生活功能受限等症状。中国脑瘫患者呈逐年递增趋势，给家庭和社会造成巨大负担。水上康复治疗是近年来出现的一种新的康复治疗方法，它是通过水下设备进行训练，利用水的物理特性进行水上康复锻炼，对疾病达到显著的康复效果。方法:运用文献资料法、专家访谈法、逻辑分析法等研究方法，研究水疗对脑瘫患儿运动功能康复疗效及作用机制，并进行总结分析，剖析其康复疗效。结果：1.患儿水疗参与度：水环境对儿童有天然吸引力且水上活动增加康复疗法趣味性，儿童参与水上运动的积极性、主动性和依从性都很好，儿童在水上运动过程中的情绪状态良好，有利于运动发展。2.水疗改善脑瘫患儿运动功能疗效基础：水疗缓解脑瘫症状的具体机制尚不完全清楚。可能如下:1)水具有阻力，在针对脑瘫患儿进行肌力训练时，适量负荷就能达到比常规肌力训练更好的效果，通过练习不断提高肌肉的耐受性，从而增加肌肉力量。水还具有冲击性，可以利用水对肌肉的冲击，激发肌肉的兴奋性，从而增强肌力。2)水具有独特的浮力，可以减少关节负荷、身体不平衡和姿势控制不良，从而起到降低肌张力、改善关节活动度的作用，使脑瘫儿童在水中易于活动;3)水疗可能矫正阻碍有效呼吸的姿势反射，利用水的压力对肺、呼吸肌和内部器官进行刺激，有利于促进协调呼吸和相关功能;4)水疗通过水的阻力、浮力、压力、温热等多因素作用的结果，可能降低骨、肌肉和结缔组织的运动阻力，刺激肢体触觉感受器和压力感受器，感觉输入增多，促进脑瘫患儿运动功能恢复进程。结论：脑瘫患儿运动功能的康复治疗目标是：恢复或改善脑瘫患儿异常肌张力，增加关节活动，增强肌肉力量，提高平衡与协调的能力。脑瘫患儿应在进行常规康复治疗基础上增加水疗，提升脑瘫患儿运动功能康复效果。水疗在临床康复中具有广阔的应用前景,但是效果是否具有持续性、其机制还有待进一步研究。

关键词：水疗；脑瘫患儿；运动功能

P6-60 基于胰高血糖素样肽 1 探讨低氧与运动对心梗后心脏的保护作用

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研究目的：《中国心血管健康与疾病报告 2022(概要)》推算我国心血管疾病现患人数约 3.3 亿，高居我国城乡居民死亡原因首位，开展心血管病的防治工作迫在眉睫。胰高血糖素样肽 1(GLP-1)是一种由肠道 L 细胞和大脑分泌的肠源性胰岛素激动剂，通过神经通路和激素的共同作用调节心血管功能。GLP-1R 是其独特的七螺旋 G 蛋白偶联受体，目前已经在心肌及心内膜中检测到大量 GLP-1R 的存在，且低氧可以于源头提高 GLP-1 分泌，GLP-1 和相关通路分别可以被有氧运动、阻力运动激活，那么低氧及运动联合 GLP-1 是否会对心梗后心脏产生保护作用是值得研究的方向。

研究方法：文献资料法，通过 CNKI 及 pubmed 等数据库对相关文献进行检索。

研究结果：缺氧诱导因子 HIF 家族是低氧研究的关键因子，心梗后心肌组织缺氧坏死，低氧干预氧气浓度及干预时间的选择至关重要。HIF-1α 在重度缺氧情况下活性更强，持续时间较短；而 HIF-2α 则在中度缺氧下活性较强，持续时间也较长。有研究证明，大鼠饥饿的条件下为肠道创造低氧环境，激活 HIF-2α 通过脂质传感增加 GLP-1 的分泌；消化系统中 GLP-1mRNA 的相对丰度与心脏中相似。临床研究主要集中于其受体激动剂 GLP-1RAs 药物(利拉鲁肽、利塞那肽等)直接作用于其受体 GLP-1R 或间接激活相关传导通路及其他因子受体、调节相关因子有丝分裂、抑制血小板的聚集、防止血栓形成等途径保护心脏，对于 GLP-1 内源性干预机制少有了解。运动干预可激活 GLP-1 相关通路，如运动通过 GLP-1 激活 AMPK/Akt/eNOS 通路对内皮细胞产生直接保护作用；激活 CAMP(环磷酸腺苷)/PKA 通路，抑制 MAPK 信号通路，与 RAGE/Rho/ROCK 通路共同发挥稳定内皮收缩和内皮屏障的作用。不少研究为心梗后通过低氧及运动干预激活 GLP-1 提高心梗后心脏功能及康复提供了理论支持。

研究结论：GLP-1 受体于人体各个器官均有分布，且通过不同通路发挥着重要调控作用；机体氧感知机制的阐明为缺血缺氧性疾病的治疗带来了新机遇；运动作为首选无创性治疗，三者结合是否能为心梗后运动康复提供新的方向是值得研究的问题。

关键词：胰高血糖素样肽 1；低氧干预；运动

P6-61 昼夜节律对慢性疾病的研究进展

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研究目的：昼夜节律可分为 2 个部分：位于下丘脑的视交叉上核 (suprachiasmatic nuclein, SCN) 并接收光信号的中央时钟以及位于全身各个组织中的外围时钟。昼夜节律紊乱与各种年龄引起的慢病发生直接相关，如癌症、心血管相关疾病、生殖功能等。因此，本文讨论了昼夜节律紊乱对慢性疾病产生的不利影响。**研究方法：**本文采用文献资料法通过中国知网、维普、pubmed、web of science 等数据库，检索“circadian rhythm”、“chronic disease”、“昼夜节律”、“慢性病”等关键词获得相关文献，并进行整理与分析。**研究结果：（1）昼夜节律钟的失调引发了异常的细胞过程并影响肿瘤的发生。**下调核心时钟基因 Bmal1 引起的昼夜节律紊乱影响了细胞增殖、凋亡和细胞迁移，且细胞运动能力受损，微转移的形成减少。此外，通过瞬时减少 Bmal1 而增加的应激颗粒动态和形成与应激诱导的细胞死亡的抵抗力增加相吻合。体内肿瘤生长的减少可能是由于宿主时钟的额外影响和/或三维肿瘤结构的影响，提出了有关宿主-肿瘤互动的新问题。**（2）昼夜节律的扰乱也是导致心血管病变的原因之一。**在人类 Bmal1 缺陷的心肌细胞表现出扩张型心肌病的典型表型，包括收缩力减弱、钙离子

失调和肌丝紊乱。同时，线粒体裂变和有丝分裂被抑制，导致线粒体氧化磷酸化明显减弱，心肌细胞功能受到损害。Bmal1 的缺失直接导致有丝分裂和线粒体功能障碍，从而导致心肌细胞功能受损。**（3）扰乱昼夜节律对生殖功能产生不利影响。**昼夜节律紊乱减少男性血液中的睾酮水平，使 Leydig 细胞中时钟基因 Bmal1、Clock 转录增加，线粒体膜电位（Δψi）和 ATP 生成下降，失去了它们特有的振荡模式。此外，线粒体生物生成（Nrf1、Tfam）、融合（Mfn2）和有丝分裂吞噬（Pink1 和 Tfeb）的主要标志物也受到干扰，导致了睾丸激素的下降，损害了雄性激素依赖的功能。**研究结论：**本文通过对昼夜节律与慢性疾病的阐述，对其机制进行探讨。为慢性疾病的防治提供了思路。

关键词：昼夜节律；核心时钟基因；慢性病

P6-62 急性 HIIT 与 MICT 干预对久坐成人血管内皮功能的影响及机制

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研究目的：在全球范围内，体力活动不足与久坐行为是造成心血管疾病、糖尿病、高血压、肥胖和癌症等众多慢性疾病的主要风险因素之一，已成为第四大死亡风险因素。久坐行为是影响非传染性疾病发病率和死亡率的重要风险因素，长期久坐少动的生活方式会导致血管内皮功能受损，而运动训练一定程度上能改善心血管功能特别是血管内皮功能。中等强度持续训练（Moderate intensity continuous training, MICT）以适用范围广、强度适中的特点，成为人们最常接触的有氧运动类型。然而，MICT 需要耗费较长的时间来进行，对于因运动时间不充足的久坐人群来说，似乎并不是特别合适的选择。高强度间歇训练（High intensity interval training, HIIT）近年来凭借短时间、高效率等特点，开始逐渐受到大众关注。研究表明，HIIT 可引起骨骼肌和心脏等器官多方面的良性适应变化，如增加骨骼肌线粒体氧化供能相关蛋白的表达、延缓衰老引起的线粒体数量下降、改善骨骼肌毛细血管系统、心肌细胞的适应性变化、以及提高心脏射血分数和每搏输出量等。一项 Meta 分析结果显示，发现 HIIT 在增强血管功能方面比 MICT 更有效；HIIT 对心肺健康与血管功能相关的生物标志物的积极影响大于 MICT。尽管大量研究表明 HIIT 对心血管功能的改善有显著的优势，在提高心肺适能、调节生理功能上发挥作用，但也有相关研究表明 HIIT 训练并不适合所有人群。相关研究表明 HIIT 可能会促使心肌缺血，心肌梗死等疾病突发概率的增加。因此不建议心血管疾病病人进行较高强度的运动训练。而且，目前研究针对单次短时长 HIIT 与 MICT 对血管内皮功能影响的比较研究较少。所以，尚未明确急性 HIIT 和 MICT 对血管内皮功能方面何种方案更有优势，并且其潜在

的机制缺乏深入研究。因此，本研究拟通过比较急性 HIIT 与 MICT 前后久坐成人血管内皮功能以及外周循环血液因子的差异及其可能的潜在机制，为运动改善血管内皮功能提供较完善依据，同时，为久坐成人选择高效的运动方案提供参照。

研究方法：招募有久坐习惯的成年人，在实验开始前经*****伦理委员会的批准（2021LCLL-26）并进行受试者知情同意书签署。经过询问健康状况、病史、评估筛查后，最终参与完整干预实验的人数为 15 人（男性 10 人，女性 5 人）。所有受试者通过软件将实验干预方式进行随机交叉进行高强度间歇训练干预组（HIIT 组）、中等强度持续训练干预组（MICT 组）和对照组（SIT 组），运动方式均为功率自行车干预。HIIT 组运动强度为 20 min 的高强度间歇训练，运动强度为 40%-80% 最大摄氧量（Maximal oxygen uptake, VO_2max）交替间歇；MICT 组运动强度为 40 min 的中强度运动，运动强度达到 60%VO_2max。每次实验均有一周洗脱期，并在干预时进行实时的心率监测。SIT 组干预方式为静坐 1 h。干预前后对受试者进行相关功能指标的检测以及样本的收集：（1）进行血流介导的血管舒张（Flow mediated dilation, FMD ）检测血管内皮功能。（2）在干预前后进行指尖血的实时采集，采用便携式乳酸检测仪对指尖血进行血乳酸浓度检测；（3）使用酶联免疫检测法，对三组血浆的血乳酸、血管内皮生长因子（Vascular endothelial growth factor, VEGF）、胰岛素样生长因子 1（insulin-like growth factors-1, IGF-1）以及鸢尾素（Irisin）浓度进行定量检测。

研究结果：

（1）血管内皮舒张功能检测结果显示，与 SIT 组相比，HIIT 组与 MICT 组的 FMD 值均呈显著性升高，然而两组之间无显著性差异。

（2）与 SIT 组相比，HIIT 组与 MICT 组血乳酸浓度组间显著上升，其中 HIIT 组较 MICT 组血乳酸组间显著上升。

（3）与 SIT 组相比，HIIT 与 MICT 组 VEGF 浓度组间显著上升，HIIT 组较 MICT 组相比组间显著上升；与 SIT 组相比，HIIT 组与 MICT 组 IGF-1 浓度组间显著上升；Irisin 无组间差异。

（4）相关性分析结果显示，急性运动干预后，血管内皮指标 FMD 变化与 VEGF、血乳酸浓度变化呈显著正相关，血乳酸浓度变化与 VEGF、IGF-1 浓度变化呈显著正相关，VEGF 浓度变化与 IGF-1 浓度变化呈显著正相关。

研究结论：急性 HIIT 与 MICT 运动能够有效改善久坐人群的血管内皮功能，其机制可能与运动引起血乳酸介导的 IGF-1、VEGF 的生成与释放有关。HIIT 作为一种短时间、高效率运动干预方式，可替代 MICT 用于久坐人群血管内皮功能的改善。

关键词：久坐人群；血管内皮功能；高强度间歇训练；中等强度持续训练

P6-63 三种不同方式的急性运动对男大学生认知功能的影响

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研究目的：世界卫生组织的《身体活动和久坐行为指南》指出，成年人应该进行规律的中等至高强度的有氧运动和肌肉力量运动，即进行耐力和抗阻相结合的同期训练(Concurrent training，CT)。CT 不仅能促进青年人群的心肺健康，而且能提高其肌肉适能，但其对脑健康和认知功能的促进作用还不确定，为此本研究探讨了急性高强度间歇训练（(High-intensity interval training，HIIT)、抗阻训练(Resistance training,RT)以及 HIIT 和 RT 联合的同期训练对男大学生认知功能、前额叶皮层神经元活动和神经营养因子水平的影响。**研究方法**：本研究从某大学筛选出 39 名符合实验要求的男大学生受试者，随机分为 HIIT 组(n=13)、RT 组(n=13)和 CT 组(n=13)。分别在干预前和干预后即刻采集肘静脉血 10mL 以检测血清脑源性神经营养因子、鸢尾素和 Clusterin 水平，并在佩戴 fNIRS 设备的同时完成 Stroop 和 N-back 任务，以检测任务执行态中的前额叶皮质血流动力学特征和认知功能。所有测试均在上午 8:00-10:00 进行。HIIT 运动方案为：先以 85%VO_2max 高强度蹬车 1min，再以 35%VO_2max 低强度蹬车 1min，交替循环 10 组。RT 运动方案为：深蹲、卧推、硬拉、划船 4 个动作以 70%1RM 重复 4 组，每组重复 8-12 次。CT 方案为：先完成 50%RT 方案，10min 后完成 50%HIIT 方案。为了平衡三种运动方式的生理负荷，采用 Polor 心率带估算三种运动方式干预期间的能量消耗均为 400-500kcal。**研究结果**：1.一次急性 HIIT、RT 和 CT 干预均能显著缩短男大学生 Stroop 和 N-back 任务的反应时，且组间无显著差异；2. 一次急性 HIIT 和 CT 干预均能显著提升男大学生执行 Stroop 和 N-back 任务时前额叶皮质区的脑氧合水平，而一次急性 RT 则显著降低执行 N-back 任务时前额叶皮质区的脑氧合水平；3.一次急性 HIIT、RT 和 CT 干预均能显著提升男大学生血清脑源性神经营养因子和鸢尾素水平，但对血清 Clusterin 水平无显著影响。**研究结论**：急性 HIIT、RT 和 CT 均能对男大学生的认知功能产生积极效应。

关键词：高强度间歇训练；抗阻训练；同期训练；体适能；认知功能

P6-64 有氧运动刺激心肌 GDF-5 分泌并促进心梗小鼠血管新生及其机制研究

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目的：本研究旨在探讨 GDF-5 介导运动改善心梗小鼠心功能中的作用及潜在机制。**方法**：雄性 C57/BL6 小鼠随机分为假心梗组（Sham）、心梗组（MI）、心梗运动组（ME），

采用左冠状动脉前降支结扎法制备心梗模型，小动物超声成像检测小鼠心功能。ME 组小鼠术后休息一周，第二周适应性训练，速度逐渐增加至 10m/min，第三周以 75%VO2max 强度进行正式有氧训练，坡度为 0 °跑速 10m/min， 60 min/d，5 d/wk×4wk。运动结束后次日，再次评估小鼠心功能。眼球取血，开胸摘取心脏。半数小鼠心脏进行形态学染色，观察心肌形态结构，马松染色比较胶原纤维容积百分比，免疫荧光染色融合共定位新生血管。westerning bloting 进行通路探究。人脐静脉内皮细胞（Human Umbilical Vein Endothelial Cells，HUVECs）进行通路验证。**结果：**1. 心动超声结果显示：与 S 组相比，MI 组 EF 和 FS 显著降低（P<0.01），LVIDd 和 LVIDs 显著升高（P<0.01）。与 MI 组相比，ME 组小鼠 EF 和 FS 显著升高（P<0.01），LVIDd 和 LVIDs 显著降低（P<0.01）。2.免疫荧光染色结果显示：与 S 组相比，MI 组 CD31/PCNA 细胞数量显著增加（P < 0.05），ME 组进一步增加，并互包围形成初级血管结构（P<0.01）。3.Western blotting 结果显示，与 S 组相比，MI 组心脏 GDF5 蛋白表达显著降低（P<0.01），PI3K 磷酸化水平和 VEGF 蛋白表达升高但无显著性差异，AKT 磷酸化水平显著降低（P<0.01）。与 MI 组相比，ME 组心脏 GDF5 蛋白表达显著升高（P<0.01），且 PI3K、AKT 磷酸化水平和 VEGF 蛋白表达显著升高（P<0.01）。**结论：**有氧运动刺激心梗小鼠心肌内源性 GDF-5 分泌，改善心梗小鼠心脏微循环，并通过激活 PI3K/AKT/VEGF 信号通路发挥血管新生心肌保护作用。

关键词：心肌梗死，GDF-5，血管新生，有氧运动

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P6-65 A bioinformatics approach based on the GEO database to analyze the effects of different training modalities on gene expression in human skeletal muscle

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Objective To analyze the effects of different exercise modalities over time on transcriptome expression in human skeletal muscle and their molecular mechanisms of health promotion through bioinformatics approaches. **Methods** The GSE165630 dataset was downloaded from the National Center for Biotechnology Information (NCBI) Public GeneChip Data Platform (GEO), and a transcriptional study using next-generation sequencing of lateral femoral muscle biopsies from older adults with a lifetime of high-level training practice (n = 9) (samples included 5 cases of endurance training and 4 cases of resistance training) and age-matched sedentary subjects (n = 5) was performed. The differentially expressed genes (DEGs) were screened using the R "limma" function package, with a threshold value of logFC ≥ 2 and P < 0.05. The target genes were then

enriched for GO and KEGG signaling pathways using the DAVID database, and the protein interaction network was constructed using the STRING database, and the R scripts were used to analyze the protein interactions between the target genes. network, and R script was applied to visualize the genes in the module as well as to screen the key genes. **Results** A total of 814 DEGs were screened in the resistance training group and sedentary group. GO analysis showed that the biological functions of DEGs were mainly related to fibronectin-binding glycosaminoglycan-binding, sulfur-compound-binding, integrin-binding, heparin-binding, collagen-binding and so on, and KEGG analysis showed that the DEGs were mainly related to the glucagon and AGE-RAGE signaling pathways. A total of 967 DEGs were screened in the endurance training group and sedentary group, and GO analysis showed that the biological functions of DEGs were mainly involved in glycosaminoglycan binding, sulfur compound binding, heparin binding, integrin binding, etc. KEGG analysis showed that DEGs were mainly related to calcium signaling pathway, PPAR signaling pathway, regulation of actin cytoskeleton, and adipocytokine signaling pathway. A total of 40 DEGs were screened in the resistance training group and the endurance training group, and the GO analysis showed that the biological functions of DEGs were mainly related to steroid hormone receptor binding, glucocorticoid receptor binding, oxidoreductase activity, and the KEGG analysis showed that the DEGs were mainly related to the MAPK signaling pathway and estrogen signaling pathway. **Conclusion** Bioinformatics technology can effectively screen and analyze DEGs related to exercise and sedentary individuals, and provide ideas for further exploring the mechanism of action and targets of exercise on the promotion of skeletal muscle performance. The study showed that there was a high degree of overlap in the differential effects of resistance and endurance training on skeletal muscle gene expression, and the same qualities were also shown in the respective PPI core genes, while the differential genes between the two groups were focused to the The KEGG enrichment analysis revealed that MAPK and estrogen signaling pathways appeared in both resistance and endurance training, which suggests that long-term adherence to scientific training is beneficial to skeletal muscle performance, and the specific implementation stage can be selected according to the hormone level (or gender) of the targeted training. The conclusions obtained in this study need to be verified by more studies, and exploring the target genes of the effect of exercise training on skeletal muscle through bioinformatics technology can provide a reference for the next mechanism research.

P6-66 The effects of aerobic exercise on the ANXA1/FPR2 pathway and inflammatory response in elderly mice skeletal muscle

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Objective: During aging, the body exhibits a progressive increase in chronic, systemic pro-inflammatory response, which is characterized by an excessive inflammatory factor reaction and an imbalance in inflammatory homeostasis within the skeletal muscle. This significantly affects the quality and function of the muscles. Annexin A1 (ANXA1) is a glucocorticoid-induced protein that exhibits strong anti-inflammatory and pro-resolving effects by interacting with the N-formyl peptide receptor 2 (FPR2) in the G-protein-coupled receptor family. This study aimed to investigate the effects of aerobic exercise on the inflammatory response in skeletal muscle and the ANXA1/FPR2 pathway in elderly mice.

Methods: Twenty-four male 12-month-old healthy C57BL/6J mice were randomly divided into three groups: young control group (Y group, n=8), elderly control group (C group, n=8), and aerobic exercise group (E group, n=8). The mice were individually housed in specific pathogen-free (SPF) conditions with a light-dark cycle and ad libitum access to food and water. After a 5-day adaptation period, the Y group mice were euthanized for tissue collection. The C and E group mice were fed until they reached 18 months of age, during which their physical signs were observed. Once the C and E group mice exhibited signs of aging, such as dull fur color, significant hair loss, increased body weight, and decreased food intake, indicating the establishment of the C57BL/6J aging model, an 8-week intervention period began. The C group received no intervention, while the E group underwent 8 weeks of aerobic exercise intervention using an adjustable experimental treadmill and the Bedford aerobic exercise model. During the intervention period, the general condition and body weight of the mice were observed daily, and grip strength and pole test were performed weekly. After the final intervention training, the mice were fasted for 12 hours, anesthetized with 1% pentobarbital sodium (40 mg/kg) via intraperitoneal injection, and euthanized by cervical dislocation. The quadriceps femoris muscles on both sides were isolated and preserved. Hematoxylin and eosin (HE) staining was performed to observe skeletal muscle cell pathological changes. RT-PCR was used to measure the transcription levels of ANXA1 and FPR2 genes in the tissues. Western blot was performed to measure the protein levels of ANXA1 and FPR2 in the tissues. ELISA was used to measure the levels of IL-6, IL-1β, and TNF-α in the tissues.

Results: Compared to the Y group, the C group mice showed a significant decrease in skeletal muscle grip strength relative to body weight and pole test duration (P<0.05). The cross-sectional area of muscle fibers significantly decreased, with inconsistent sizes and irregular arrangement of muscle cells. The transcription and protein expression levels of ANXA1 and FPR2 were significantly reduced (P<0.05), while the levels of inflammatory factors IL-6, IL-1β, and TNF-α were significantly increased (P<0.05). Compared to the C group, the E group mice showed a significant increase in skeletal muscle grip strength relative to body weight and pole test duration (P<0.05). The cross-sectional area of muscle fibers significantly increased, with uniform sizes and orderly arrangement of muscle cells. The transcription and protein expression levels of ANXA1 and FPR2 were significantly increased (P<0.05), while the levels of inflammatory factors IL-6, IL-1β, and TNF-α were significantly decreased (P<0.05).

Conclusion: Aerobic exercise significantly promotes the expression of the ANXA1/FPR2 pathway and improves the inflammatory response in aging mouse skeletal muscle.

Keywords: Aerobic exercise; ANXA1/FPR2 pathway; skeletal muscle inflammation

P6-67 探究短期 PM2.5 污染暴露下小鼠运动对其认知、情绪及代谢的影响

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目的：本实验通过建立完整的污染暴露模型，探究短期 PM2.5 空气污染对小鼠的情绪以及认知影响，以及在空气污染暴露下进行运动对单纯污染暴露带来消极影响的作用。

方法：本研究采用液化气溶胶模拟空气污染（PM2.5 浓度：0.5-1.0mg/m^3，每天暴露 8 小时），并使用动物跑台进行运动干预（运动强度：10-13m/min，每天 1 次，每次 1 小时）。48 只雄鼠平均分为 4 组，每组 12 只：①CON 组为空白对照；②AP 组进行 PM2.5 污染暴露；③EX 组单纯强度运动干预；④AP+EX 组在进行污染暴露的同时进行运动干预。1 周干预结束后进行旷场实验、高架十字迷宫实验以及三箱社交实验测试；随后进行血液生化测定，最后对小鼠大脑组织 ELISA 检测。

结果：（1）行为学：高架十字迷宫测试显示 AP 组闭臂内停留时间最长（p<0.05），AP+EX 组相比 AP 组更倾向于探索开放臂空间（p<0.01）；EX 组和 AP+EX 组移动范围大于 CON 组和 AP 组（p<0.01）。三箱社交实验显示 AP 组 AP+EX 组小鼠和 EX 组比更倾向于和新物体进行接触（p<0.05）；AP+EX 组小鼠较 AP 组更倾向于交流（p<0.01）。

（2）血液生化：CO_2 浓度显示与 CON 组对比，AP 组浓度最低，EX 组浓度最高，其

中 AP+EX 组高于 AP 组（p<0.05）。血清脂质类结果显示 AP 组小鼠 TC、TG 值显著高于其他三组（p<0.01）。血糖浓度显示 EX 组显著高于 CON 组，AP 组显著低于 CON 组（p<0.05）。

（3）脑组织 ELISA： TNF-α 显示与 CON 组高于 AP 组和 AP+EX 组（p<0.05）。IL-1β 显示 AP+EX 组显著高于其他三组； AP+EX 组低于 AP 组（p<0.05）。小鼠脑蛋白激酶 A 显示三组均高于 CON 组；且 AP+EX 组低于 AP 组（p<0.05）。NF-kB 显示，AP+EX 组较 AP 组小鼠的脑组织 NF-kB 活性较大（p<0.05）。多巴胺显示，三组均显著高于 CON 组；且 AP+EX 组显著高于 AP 组（p<0.05）。

结论：PM2.5 空气污染能够引起小鼠出现抑郁和焦虑情绪，导致机体出现糖脂代谢紊乱及炎症反应。PM2.5 污染暴露下进行运动可以有效缓解空气污染带来的负面影响。

关键词：PM2.5；空气污染；运动锻炼；认知功能

P6-68 维生素 D 缺乏对小鼠能量代谢的影响

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研究背景：流行病学研究表明，全球范围内有超 50%以上人群处于维生素 D 缺乏状态。维生素 D 缺乏也与肥胖及二型糖尿病、非酒精性脂肪肝病等慢性代谢疾病存在密切联系。然而，在维生素 D 缺乏情况下，机体的气体代谢及能量代谢会产生何种变化，目前尚不清楚。是否可以通过调控循环维生素 D 水平来改善机体能量代谢，进而降低慢病发生率，也需进一步探究。因此本研究尝试通过构建维生素 D 缺乏小鼠模型，测量其气体代谢及能量消耗产生的变化，揭示维生素 D 对机体能量代谢的影响。

研究方法：20 只 6 周龄 C57BL/6 雄鼠，随机分为维生素 D 正常饮食组（control group, C）和维生素 D 缺乏饮食组（vitamin D deficiency group, VDD），每组 10 只，VDD 组和 C 组小鼠分别使用 0IU/kg 和含 1000IU/kg 维生素 D3 的 Ain-93G 饲料饲养。小鼠饲养遵循 12h:12h 昼夜交替，自由摄水摄食，实验过程采用黄光灯照明，避免外部光源照射合成维生素 D。12 周饮食干预后称量小鼠体重及身体成分，尾静脉取血后 ELISA 试剂盒检测小鼠血液循环 25（OH）D 水平，验证 VDD 模型构建成功。使用 TSE systems PhenoMaster 小鼠能量代谢笼测量小鼠摄氧（O2）量（单位：L/h/kg）、二氧化碳（CO2）呼出量（单位：L/h/kg）、呼吸商及能量消耗（Energy expenditure, EE, 单位：kcal/h/kg）。使用 SPSS26.0 统计学软件，比较分析各组小鼠 24h 总代谢及昼夜差异。

研究结果：

12 周饮食干预后两组小鼠体重（g）无显著差异（28.27±1.97 vs 28.38±1.71，P＞0.05）；VDD 组小鼠体脂比（%）显著高于 C 组（8.25±2.55 vs 6.17±2.93， P＜0.05）；VDD 组小鼠血液循环 25（OH）D 浓度显著低于 C 组（26.28±4.96 vs 75.055±6.006，P＜0.05），表明

维生素 D 缺乏模型建模成功。在气体代谢方面：VDD 组小鼠与 C 组相比，24h 摄氧量（1732.17±202.39 vs 2184.87±111.03，P＜0.05）、CO_2 排出量（1350.18±223.46 vs 1857.73±56.06，P＜0.05）及能量消耗（8319.79±1044.81 vs 10665.22±375.55，P＜0.05）均有显著降低，但两组小鼠呼吸商差异并不显著（0.78±0.04 vs 0.84±0.07，P＞0.05）。

将各组小鼠所有代谢指标进行昼夜区分后发现，C 组与 VDD 组小鼠日间摄氧量、二氧化碳呼出量和能量消耗均显著性低于夜间（P＜0.05），而各组小鼠呼吸商日夜间无显著差异（P＞0.05）。在昼夜气体代谢方面，VDD 组小鼠的白天和夜晚的摄氧量、CO_2 排出量和能量消耗均显著低于 C 组小鼠（P＜0.05），呼吸商无显著差异（P＞0.05）。

研究结论：维生素 D 缺乏会降低小鼠昼夜能量消耗，增加超重及肥胖的发生风险，但维生素 D 缺乏并未对小鼠呼吸商产生影响。其具体机制有待进一步探明。

P6-69 高强度间歇训练和中等强度持续训练对增龄大鼠脂肪组织不同训练适应性的 miRNAs 分析

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目的：探析高强度间歇训练（HIIT）及中等强度持续训练（MICT）对增龄大鼠脂肪组织不同训练适应性的 miRNAs 谱。方法：将 18 月龄雌性大鼠分为安静对照组（SED）、MICT 和 HIIT 组，每组 12 只。MICT 组以 17 m/min 速度运动 45 min。HIIT 组起始速度为 15 m/min，持续 4 min 后进行高强度训练，速度为 25 m/min，持续 1 min，依次交替 9 个循环，运动周期为 8 个月。油红 O 染色观测细胞内脂质沉积，蛋白免疫印迹和 RT-qPCR 检测脂肪组织 p53、p21、基质金属蛋白酶 3(MMP-3)和单核细胞趋化蛋白-1（MCP-1）表达。蛋白免疫印迹检测脂肪组织甘油三酯脂肪酶（ATGL）、激素敏感脂肪酶（HSL）、过氧化物酶体增殖物激活受体 γ 共激活剂 1-alpha (PGC-1α)、线粒体棕色脂肪解偶联蛋白 1（UCP-1）、PRDM16、p62、ATG3、ATG5、ATG7、ATG12、ATG16L、Beclin1、LC3Ⅰ和 LC3Ⅱ等蛋白表达水平，蛋白免疫荧光观察 p53、MMP-3、MCP-1、p-NF-κB 和 p-lkBα 蛋白含量。对目标脂肪组织进行 miRNA 测序筛选、Gene ontology (GO)分析及 Kyoto Encyclopedia of Genes and Genomes (KEGG) 通路分析。结果：与 SED 和 MICT 组相比，HIIT 组油红 O 染色阳性脂肪细胞数（P＜0.01）及 p53、MMP-3 和 MCP-1 蛋白和 mRNA 表达显著降低（P＜0.01）；HIIT 组 ATGL、HSL、PPAR-γ、ATG3、ATG5、ATG7、ATG12、ATG16L、Beclin1、LC3Ⅰ和 LC3Ⅱ蛋白表达均高于 SED 及 MICT 组（P＜0.05）。MICT 组与 SED 组差异表达 25 个 miRNA，HIIT 组与 SED 组差异表达 34 个 miRNA。GO 及 KEGG 分析显示，差异表达 miRNA 主要与 MAPK、PI3K-Akt 以及 Rap1 信号通路相关（P＜0.05）。同时，分析差异表达 11 个 miRNA (miR-9a-5p、

miR-492、miR-128-3p、miR-124-3p、miR-129-5p、miR-218a-5p、miR-449a-5p、miR-220c-3p、miR-145-5p、miR-200b-3p 及 miR-429)和一些相关基因 (Shc1、Grb2、Itgb1、Ptpn11、Mapk14、Fyn、Plcg1、Sos1 及 Actg1)可能在衰老脂肪组织代谢过程中发挥关键作用。结论：以上发现与脂代谢异常密切相关，可为运动干预抵抗衰老脂肪组织代谢异常的分子机制提供新的见解。

关键词：衰老，脂肪组织，miRNAs，脂代谢，高强度间歇训练

P6-70 Effects of life-long exercise on aging-related inflammatory cytokines, apoptosis, oxidative stress, ferroptosis markers, and NRF2/KAEP 1/Klotho pathway in rat kidneys

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Objective: To investigate the effects of life-long exercise (LLE) on age-related inflammatory cytokines, apoptosis, oxidative stress, ferroptosis markers, and the NRF2/KAEP 1/Klotho pathway in rats. *Methods*: Eight-month-old female Sprague-Dawley rats were divided into four groups: 1) YLLE: 18-month LLE training starting at 8 months of age, 2) OMICT: 8 months of moderate-intensity continuous training starting at 18 months of age, 3) ASED: 8-month-old adult sedentary control group, and 4) OSED: a 26-month-old sedentary control group. Hematoxylin eosin staining was performed to observe the pathological changes of kidney tissue injury in rats; Masson's staining to observe the deposition of collagen fibers in rat kidney tissues; and western blotting to detect the expression levels of IL-6, IL-1β, p53, p21, TNF-α, GPX4, KAEP 1, NRF2, SLC7A11, Klotho and other proteins in kidney tissues. *Results*: Compared with the ASED group, the OSED group showed significant morphological changes in renal tubules and glomeruli, which were swollen and deformed, with a small number of inflammatory cells infiltrated in the tubules. Compared with the OSED group, the expression levels of inflammation-related proteins such as IL-1β, IL-6, TNF-α, and MMP3 were significantly lower in the YLLE group. Quantitative immunofluorescence analysis and western blotting revealed that compared with the ASED group, KAEP 1 protein fluorescence intensity and protein expression levels were significantly enhanced, while Klotho and NRF2 protein fluorescence intensity and protein expression levels were significantly reduced in the OSED group. Compared with the OSED group, KAEP 1 protein fluorescence intensity and protein expression levels were significantly reduced in the YLLE and OMICT groups. Klotho and KAEP 1 protein expression levels and immunofluorescence intensity were higher in the YLLE group than in the OSED group. The expression levels of GPX4 and SLC7A11, two negative marker proteins associated with ferroptosis, were significantly higher in

the YLLE group than in the OSED group, while the expression of p53 a cellular senescence-associated protein that negatively regulates SLC7A11, and the downstream protein p21 were significantly decreased. *Conclusions:* LLE may ameliorated aging-induced oxidative stress, inflammatory response, apoptosis, and ferroptosis by regulating Klotho and synergistically activating the NRF2/KAEP 1 pathway.

Keywords: Life-long exercise; Moderate intensity continuous training; Aging; Kidney tissue; Ferroptosis

P6-71 基于代谢组学研究肠道菌群调控长期大负荷运动小鼠 MSC 稳态的效应机制

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目的：观察长期大负荷运动后肠道菌群及其代谢物对肌卫星细胞稳态的调节，为开发防止运动性疲劳和相关伤病的治疗策略提供了新靶点和新思路。

方法：将 16 只雄性 C57BL/6J 小鼠随机分为空白对照组（C）、长期大负荷运动组（E）。E 组进行四周离心运动（-16°，60-90min/天，6 天/周）建立长期大负荷运动模型。末次运动后 24h 取大鼠粪便、比目鱼肌组织进行指标测试：（1）生理信号采集系统测试比目鱼肌离体收缩力;（2）透射电镜观察肌纤维超微结构变化；（3）液相色谱-质谱联用法测定小鼠粪便和比目鱼肌的代谢物浓度；（4）免疫荧光双标分析比目鱼肌中静息态 Pax7+/Myo D-和周期中 Pax7+/Myo D+细胞数量变化。

结果：（1）E 组单收缩力和强直收缩力高于 C 组但无显著性差异（$P<0.05$）；（2）C 组比目鱼肌超微结构正常，肌原纤维排列整齐；E 组呈现肌原纤维断裂、降解,内质网及线粒体肿胀等变化;（3）代谢组学结果显示：E 组小鼠比目鱼肌、粪便的丁酸-Mct1 含量相比于 C 组发生显著性降低（$P<0.05$）；（4）E 组 Pax7+/MyoD-和 Pax7+/MyoD+细胞数量明显减少（$P<0.05$ 或 $P<0.01$）。

结论：肠道菌群及其代谢物参与了长期大负荷运动过程中肌卫星细胞稳态的调节，提示肌肉中丁酸水平的下降可能是长期大负荷运动过程中肌卫星细胞流失和功能缺陷的原因之一。

关键词：长期大负荷运动；MSC；肠道菌群；丁酸；代谢组学；

P6-72 推拿经 NAMPT/NAD$^+$调控 EIMD 大鼠骨骼肌能量代谢的作用研究

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目的：观察推拿改善 EIMD 大鼠骨骼肌能量代谢促进损伤修复的作用效应，探讨 NAMPT/MAD^{+}在其中的可能机制。方法：（1）实验动物及分组：选取 8 周龄 SPF 级雄性 SD 大鼠 66 只，随机分为对照组（C，n=6）、运动组（E，n=30）及推拿组（T，n=30），E 组与 T 组根据运动后 0h、12h、24h、48h、72h 不同时相又分为 5 个亚组，共 11 个亚组。C 组常规饲养，E 组与 T 组按 Armstrong 模型进行一次大负荷离心跑运动，T 组于 0h、24h、48h、72h 进行推拿干预。（2）取材及指标测定：各亚组大鼠取双侧小腿三头肌，利用小动物抓力测量仪测定四肢抓力，透射电镜观察骨骼肌纤维超微结构，采用 ELISA 法测定 CK、CK-MM、NAMPT、NAD^{+}、ATP、ADP、COXI、COXII 含量。并采用 SPSS 20.0 统计软件对数据进行单因素方差分析，设定 P＜0.05 具有显著性差异。结果：（1）四肢抓力：0h、12h、24h、48h 时，E 组较 C 组显著下降（P＜0.05），T 组于 24h、48h 较 E 组显著升高（P＜0.05）。（2）骨骼肌超微结构：C 组肌原纤维分布均匀，线粒体排列整齐、形态完整，呈长线形或卵圆形，嵴结构清晰；0h 时，E 与 T 组肌原纤维断裂，肌节紊乱，线粒体排列无序、肿胀；12h 及 24h 时，E 组肌原纤维杂乱，线粒体肿胀、自噬，T 组相对稍轻；48h 时，E 组肌原纤维溶解，肌节排列扭曲，线粒体仍肿胀、排列紊乱，但较 24h 时有减轻，T 组明显好转；72h 时，E 组与 T 组超微结构基本恢复正常，T 组较 E 组肌纤维排列整齐。（3）CK、CK-MM 含量：24h、48h 及 72h 时，T 组较 E 组显著下降（P＜0.05）；ATP、ADP 含量：0h 时，T 组较 E 组显著升高及下降（P＜0.05）；COXI、COXII 含量：0h 及 12h 时，T 组较 E 组显著升高（P＜0.05）；NAMPT、NAD^{+}含量：12h、24h、48h 及 72h 时，T 组较 E 组显著升高（P＜0.05）。结论：推拿可经 NAMPT/NAD^{+}改善 EIMD 大鼠骨骼肌能量代谢紊乱，促进骨骼肌损伤修复。

关键词：推拿；运动性骨骼肌损伤；能量代谢

P6-73 运动干预对阿尔兹海默症患者的记忆和脑功能的影响

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目的: 阿尔兹海默症（AD）是一种退行性脑疾病。衰老和生活方式是 AD 的影响因素，而运动被认为可以减轻老年人 AD 的发病。不同的运动方式对老年人的记忆和脑功能的影响是不同的。本文通过对不同运动方式干预 AD 的进展进行综述，旨在为运动干预缓解 AD 患者的记忆与脑功能的下降提供参考。**方法**: 通过 Pubme、Web of Science、中国知网、万方数据库等网站，搜索关键词：“运动”、“运动方式”、“有氧运动”、 “抗阻运动”、“阿尔兹海默症”、“记忆”、 “脑功能”、 “Exercise”、“Mode of exercise”、 “Aerobic exercise”、“ Resistance exercise”、“Alzheimer's disease”、“Memory”、“Brain function”等分析、整理出国内外关于不

同的运动方式和生活习惯的改变与 AD 患者的记忆和脑功能相关的文献。**结果**：1）运动可以有益的改变与记忆相关的代谢组学特征，改善身体素质水平、记忆和认知功能；2）有氧运动通过调节心肺功能和大脑后扣带皮质（PCC）葡萄糖代谢，减轻了大脑的负担、提高了执行功能；3）有氧运动和联合运动对认知功能都有积极的影响，并且抗阻训练对工作记忆有领域特异性的交互作用；4）有氧运动联合抗阻运动比单一运动更能增强神经运动训练的刺激，从而增强认知能力。此外，在有氧运动结合抗阻运动中添加平衡运动可以提高前庭脑区域的厚度和视觉空间的能力； 5）慢性运动对 AD 患者脑功能的有益影响表现为前额叶、前循环和海马体被激活的程度更大，而衰老对海马体体积的影响减弱；6）太极运动对 AD 患者的工作记忆和情景记忆有所改善，这主要是通过增强患者海马体和其内侧前额叶皮层之间的静息状态功能连接（rs FC）；7）正念对 AD 患者的工作记忆能力具有促进作用，冥想对提高情景记忆方面有潜在好处，而开展不同的社会关系活动对工作记忆和情景记忆都有影响。经常冥想，会增加其默认模式网络（DMN）中的皮层活动，增加更高的大脑效率；8）高强度间歇训练通过增加循环血中的 BDNF，延缓了与年龄相关的认知障碍。**结论**：运动干预通过改善海马体体积、脑前额叶皮质等对 AD 患者的记忆和脑功能具有一定的积极影响。

关键词：运动；阿尔兹海默症；记忆；脑功能

P6-74 冲刺间歇训练对阿尔兹海默症患者的认知功能及运动能力的影响

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目的：神经退行性痴呆，特别是阿尔兹海默症的进展是不可逆的，会导致认知、运动、行为等损害。尽管当前的药物治疗可帮助部分认知能力下降的患者，但大多数治疗是不能避免由疾病带来的运动能力和身体机能的下降。然而，有足够的证据表明，积极的生活方式是辅助预防和治疗痴呆症的一种有效方式。与久坐的人相比，经常体育锻炼的人患痴呆的风险下降 28%，患阿尔兹海默症的风险下降 45%。有研究发现，痴呆症患者积极的生活方式可提高的日常生活能力和整体认知状态。此外，有越来越多的证据表明，早期痴呆症患者的心肺适应性和脑萎缩之间存在相反的关系。英国首席医疗官在老年人身体活动指南中建议，每周进行中至高强度身体活动数天，以保持肌肉功能，身体机能和代谢健康。因此，本文主要探讨冲刺间歇训练对阿尔兹海默症患者的认知功能及运动能力的影响。**方法**：通过中国知网以“冲刺间歇训练”、“认知功能”、“运动能力”、“老年痴呆症”为关键词下载并查阅相关文献，通过 pubMed 以“Sprint interval training”、“Sprint training”、“Alzheimer”、“Ability to exercise”、“Cognitive function”下载并查阅相关文献，运用文献资料发、逻辑分析法等对当前的阿尔兹海默症的治疗与防预进行分析，并提出自己的见解。**结果**：1）冲刺间歇训练作为一种高效

的干预措施，参与身体活动的感知控制能力，可作为改善身体健康的直接手段；2）短时间高频率的冲刺间歇训练预示可以带来更大的认知效果。短时间可以减少运动中的疲劳，对运动能力和动机产生积极的影响；高频率可以减少整体时间，稳定运动诱导的神经生物学因素水平，从而改善神经认知健康；3）与其他运动相比冲刺间歇训练更能提高机体的心肺功能，增加骨骼肌线粒体酶的活性，此外通过运动诱导血乳酸的适应对大脑的运动区域提供更高的刺激以及更好的执行能力；4）每周两次甚至一次的冲刺间歇训练可以显著改善老年人的身体功能和有氧运动能力，但是每周两次的训练可以改善全身葡萄糖代谢，而一周一次的冲刺间歇训练就足够对健康产生益处；5）冲刺间歇训练可以增强胰岛素的敏感性质，虽然是短期效应，但是可以作为降低 II 型糖尿病风险的训练手段。**结论**：冲刺间歇训练能明显改善阿尔兹海默症患者的认知功能和运动功能。

关键词：冲刺间歇训练；阿尔兹海默症；认知功能；运动能力

P6-75 miR-338-5p/JAK2/STAT3 通路轴在运动改善肥胖小鼠认知功能中的作用机制研究

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目的：miR-338-5p/JAK2/STAT3 通路轴在运动改善肥胖小鼠认知功能中的作用机制研究。

方法：采用 8 周龄的雄性 m/m 小鼠作为对照组（C 组），8 周龄的雄性 db/db 小鼠随机分为肥胖组（DM 组）、肥胖运动组（DME 组）。各组均进行一周适应性喂养后，DME 组进行 8 周正式跑台训练，其余各组正常饲养。运动干预后各组采用 Morris 水迷宫检测小鼠空间学习和记忆能力。采用 RT-PCR 检测海马组织内 miRNA 的变化；HE 染色和 NeuN 染色观察神经元病理性形态改变、神经元的数量变化；ELISA 分析血清炎性因子表达水平；Western blot 检测海马组织内突触相关蛋白 PSD93、PSD95、SYN 以及 JAK2/STAT3 通路相关蛋白的表达。

结果：1）水迷宫结果显示，DM 组的逃避潜伏期明显延长（P<0.05），穿越靶象限次数、靶象限时间及靶象限时间百分比均较 C 组明显下降（P<0.05），跑台运动干预后均有所改善（P<0.05）；2）RT-PCR 结果显示，与 C 组相比，DM 组小鼠的海马组织中 miR-338-5p 明显下降（P<0.05），DME 组出现上升（P<0.05）；3）ELISA 结果显示：DM 组小鼠血清中 IL-1β（P<0.05）、IL-6（P<0.05）、TNF-α（P<0.05）较 C 组相比均出现明显升高，跑台运动干预后均有所改善（P<0.05）；4）染色结果显示：HE 染色发现 DM 组海马出现神经元损伤，DME 组则有所改善；NeuN 染色显示 DM 组较 C 组成熟神经元数目显著减少，而运动后则明显增加。5）Western blot 结果显示，较 C 组相比，DM 组小鼠海马内海马组织内突

触相关蛋白 PSD93、PSD95、SYN 均出现明显下降（P<0.05），而跑台运动后明显上升（P<0.05）。此外，DM 组小鼠海马内 JAK2 以及 STAT3 的磷酸化（p-STAT3）较 C 组均出现升高（P<0.05），跑台运动干预后 p-STAT3 表达受到抑制（P<0.05）。

结论：运动可能通过上调 miR-338-5p 抑制 JAK2/STAT3 通路反应，降低海马炎症反应，增加神经突触可塑性进而改善肥胖小鼠认知障碍。

关键词：肥胖；炎症；认知障碍；跑台运动

P6-76 不同运动方式预防 AS 的效果对比与研究

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目的：动脉粥样硬化（AS）是一种古老疾病，但由于其发病原因十分复杂，发生机制仍不十分清楚。运动对 AS 的防治作用毋庸置疑，但运动强度、运动形式不同，效果可能并不相同。中等强度持续运动（MICT）是减少体脂的基本措施之一。高强度间歇运动（HIIT）作为一种省时高效的运动形式，彰显了其防肥减肥的优势。AS 的发病机制复杂，脂联素（APN）在其中发挥重要作用，血清 APN 与腓肠肌 APN 受体 1（AdipoR1）结合激活腺苷酸活化蛋白激酶（AMPK），AMPK 可抑制细胞内脂肪和胆固醇合成，从而预防 AS 的发生发展。通过比较 MICT 和 HIIT 预防 AS 过程中对 APN、AMPK 信号通路的激活程度，探讨两种运动方案预防 AS 的效果差异及可能机制，为选择预防 AS 的较佳运动方案提供理论依据。

方法：8 周龄雄性C57BL/6J小鼠 10 只作为正常对照组（C组，10 只）、$ApoE^{-/-}$小鼠安静组（H组，10 只）、$ApoE^{-/-}$小鼠中等强度持续运动组（MICT组，10 只）、$ApoE^{-/-}$小鼠高强度间歇运动组（HIIT组，10 只），C组饲以普通饲料，其余各组饲以高脂饲料。$ApoE^{-/-}$小鼠高脂膳食期间，分别进行相应的运动干预（MICT或HIIT）。MICT组在强度为 50%～70%VO_{2max}下持续运动 45 分钟；HIIT组在强度为 85%～95%VO_{2max}下运动 1 分钟和在强度为 45%～55%VO_{2max}下运动 2 分钟，运动组数由总距离控制。各组小鼠血清指标测试：血脂指标：全自动生物化学分析仪测定甘油三酯（TG）、游离脂肪酸（FFA）、高密度脂蛋白胆固醇（HDL-C）和低密度脂蛋白胆固醇（LDL-C）。各组小鼠基因、蛋白测试：RT-PCR测试小鼠脂肪组织APN基因表达及血清脂联素测定；Western Blot测试小鼠腓肠肌AdipoR1、AMPK蛋白表达。

结果：（1）小鼠血清指标测试结果显示，H 组小鼠血清 TG、FFA 和 LDL-C 水平均显著高于 C 组，HDL-C 含量降低；MICT 组、HIIT 组小鼠血清 TG、FFA、LDL-C 水平均显著低于 H 组，MICT 组 HDL-C 含量无显著性差异，HIIT 组 HDL-C 含量增加；HIIT 组较 MICT 组小鼠血清 HDL-C 含量显著性增加，其他指标均无显著性差异。（2）在预防 AS 的研究中，C 组小鼠脂肪组织 APN mRNA 与血清水平均显著高于 H 组，H 组均显著低于 MICT 组、HIIT

组小鼠，MICT 组与 HIIT 组之间无统计学差异。（3）Western Blot 结果显示 C 组小鼠腓肠肌 AdipoR1、AMPK 蛋白表达水平均显著高于 H 组，MICT 组、HIIT 组均显著高于 H 组，HIIT 组与 MICT 组之间无统计学差异。

结论：MICT 与 HIIT 两种运动方式都能够有效降低 AS 的发生程度，并且 HIIT 运动方式优于 MICT。与 MICT 比较，HIIT 虽未引起小鼠 APN、AMPK 信号通路表达水平统计学意义上的显著变化，但 APN、AdipoR1 与 AMPK 表达均呈增加趋势，由此推测 HIIT 能够通过增加磷酸化水平改善蛋白活性，进而达到提高信号通路工作效率的作用。

关键词：运动；动脉粥样硬化；APN；AMPK

P6-77 满足身体活动指南和老年人认知功能：基于加速度计的客观测量

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目的：世界卫生组织建议每周 150 分钟的身体活动，以获得多种健康益处，本研究旨在探索满足身体活动指南对中国老年人认知功能的益处，并探究性别的差异。研究设计：这是一项横断面研究。方法：采用多段抽样在南京抽取 308 名老年人。收集了社会人口学特征、身体活动和认知功能的数据。使用 ActiGraph GT3X+加速度计测量身体活动，认知功能采用蒙特利尔认知评估法进行测量。结果：认知功能预测因子回归分析显示，满足身体活动推荐值的老年人认知功能评分比不满足身体活动推荐值的老年人高 3.67 分(β = 3.67, 95%CI: 3.04-4.29,$p < 0.001$)。年龄较大、受教育程度<9 年和超重/肥胖与认知功能下降有关。满足身体活动推荐值与更高的执行功能、命名任务、记忆力、注意力、工作记忆、语言流畅性、视觉空间能力和时间和地点取向得分相关。此外，当对满足身体活动推荐值的老年人进行比较时发现，女性表现出更好的认知功能、执行功能、命名任务和视觉空间能力，而男性表现出更好的记忆力。结论：我们的研究结果表明，达到身体活动推荐值的老年人的认知功能明显优于未达到身体活动推荐值的老年人，并且性别在某些功能的改变中起关键作用。

P6-78 低温抗阻运动对 T2DM 大鼠糖脂代谢影响研究

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中国地区已确诊的糖尿病人群中，90 %以上都是 2 型糖尿病（Type 2 diabetes mellitus，

T2DM）。运动作为针对 T2DM 的一种安全、可靠的干预手段进行积极治疗，越来越受到关注；其中抗阻训练对预防骨骼肌减少有不可取代的影响，骨骼肌对缓解胰岛素抵抗有积极的作用，急性冷暴露增加全身能量消耗，还导致血浆葡萄糖和肝糖原含量的减少，增加骨骼肌和脂肪组织对葡萄糖的摄取。本研究旨在探究低温联合抗阻运动双重因素干预下对 T2DM 大鼠骨骼肌代谢的影响。将 60 只雄性 SD 大鼠随机分为 5 组，其中 12 只正常饲养(空白对照组)，另 48 只采用链脲佐菌素方法建立糖尿病模型，造模后的鼠随机分为 T2DM 常温对照组（NC）12 只，低温对照组（LC）12 只，低温抗阻运动干预组（LR）12 只，常温抗阻运动干预组（NR）12 只。抗阻运动为爬梯运动，低温环境为放置在人工智能气候箱中进行。干预 8 周后，检测大鼠空腹血糖、血脂、高低密度脂蛋白与肝糖原，取大鼠股四头肌进行 HE 染色得出：1.与空白对照组相比，低温抗阻运动干预组（LR）的 T2DM 大鼠肝糖原下降，差异极显著（$p<0.01$）；2.低温抗阻运动干预组（LR）的 T2DM 大鼠肌糖原含量照 T2DM 对照组（NC）相比下降，并且差异极显著（$p<0.01$）；3.血液指标也都具有显著性差异变化，相比 T2DM 对照组（NC），低温抗阻（LR）的高密度脂蛋白、总胆固醇、血脂都显著性下降（$p<0.01$），并且低温联合抗阻的干预效果优于单独一种干预方式；4.HE 染色股四头肌切片显示，T2DM 常温对照组（NC）股四头肌细胞排列较紊乱，细胞间隙增宽，有炎性细胞浸润，低温抗阻运动干预组（LR）的股四头肌细胞排列整齐，体积稍有增大。综合以上结果表明，在本实验中低温、抗阻运动干预下，对 T2DM 大鼠的糖脂代谢都起到了一定程度的改善，其中两种方式的联合干预在 T2DM 大鼠的糖脂代谢改善中效果更好，起到了叠加效应。

关键词：低温；抗阻运动；T2DM；糖脂代谢

P6-79 老龄化背景下运动影响晚发型抑郁相关研究的进展

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研究目的：在疫情和生存压力等多重因素影响下，抑郁症已经成为最常见的精神疾病之一。抑郁症分为早发型抑郁（early-life depression， ELD)和晚发型抑郁（late-life depression ，LLD)，其中有研究发现晚发型抑郁症大多发生在老年人群体中，并且增加了老年人死亡、残疾、认知障碍和焦虑的风险。运动作为一种非药物治疗手段，已被证实具有抗抑郁作用。本文对现有的晚发型抑郁症相关研究进行综述，希望能够更全面的了解老年人晚发型抑郁症发生的病理机制，进而为提高他们的生活质量提出行之有效的方案。

研究方法：本文通过使用关键词“运动 抑郁 老年人”在中国知网，PubMed 数据库中搜索相关研究文献，并进行人工筛选及梳理，最后进行归纳总结。

研究结果：大量文献将晚发型抑郁症与脑小血管疾病联系起来，而微血管功能障碍是两者可能的潜在共有靶向机制。微血管功能障碍包括血脑通透性增加、血液灌注调节受损、神经血管耦合和大脑自动调节紊乱等。血管损伤可能破坏参与情绪调节的大脑区域，导致皮质下区域白质高信号和微血管结构和功能受损，进而促进抑郁的发生和持续存在。单次 20 分钟中等强度运动能够使大脑海马区血流量增加，而适度的运动还可以改善内源性抗氧化防御系统，降低炎症因子表达水平，改善血管功能，降低心脑血管疾病合并抑郁症发生的风险。因此，长期保持中等强度运动可以有效保护大脑可塑性，促进大脑健康。

研究结论：运动具有改善抑郁患者身心状态的积极作用，体育锻炼和抑郁之间存在着持续的正反馈机制。适当的运动对维持海马和白质体积的完整性，促进海马体的再生，激活前额叶皮层的功能，最终提高抑郁症患者的大脑神经处理效率和延缓认知退化具有积极作用。根据老年人的身体状况，制定个体化的运动方案十分必要，而有关于适合老年人的更多种类的抗抑郁运动方式及相应的运动强度研究有待于进一步完善。

关键词：“老年人”，“晚发性抑郁症”，“运动”

P6-80 运动预适应在心肌缺血再灌注模型小鼠心脏中的作用及其对 NLRP3 炎症小体的影响

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目的：探讨运动预适应（Exercise Preconditioning, EP）对小鼠心脏缺血再灌注（Ischemic Reperfusion, IR）过程产生的保护作用及其对核苷酸结合寡聚化结构域(Nucleotide-binding oligomerization domain, NOD)样受体热蛋白结构域相关蛋白 3(NOD-like receptor thermoprotein structural domain-associated protein 3, NLRP3)炎症小体的影响。

方法：将 30 只 6 周龄 C57BL/6N 野生型小鼠随机分为空白对照组（Sham，n=8 只）、心肌缺血再灌注模型组（IR，n=10 只）、运动预适应模型组（E/IR，n=12 只），采用结扎左冠状动脉前降支诱导小鼠心肌梗死，术后 40min 进行再灌注构建小鼠 IR 模型。运动预适应干预采用小动物跑台进行中等强度有氧运动（60%-70%VO2max），6d/w，共持续 8w。模型构建过程采用无创多普勒超声心动图检测小鼠心功能，取右颈动脉血采用全自动生化分析仪检测心肌损伤标志物表达水平，取心肌组织采用 TTC 和 HE 染色观察心肌梗死面积和病理变化，检测心肌组织中肿瘤坏死因子 TNF-α、白细胞介素(Interleukin, IL)-1β、IL-18、半胱氨酸天冬氨酸蛋白酶-1(Cystein-asparate protease-1, Caspase-1)及 NLRP3 表达水平。

结果：与 sham 组比较，IR 组小鼠左心室舒张阶段末期内径、左心室收缩阶段末期内径均显著上调（P<0.05），而左心室射血分数和左心室短轴缩短率均显著下调（P<0.05），小鼠血清中肌酸激酶同工酶和心肌肌钙蛋白 I 水平均明显升高（P<0.05）；与 IR 组比较，E/IR 组小鼠左心室舒张阶段末期内径、左心室收缩阶段末期内径均显著下调（P<0.05），而左心

室射血分数和左心室短轴缩短率均显著上调（P<0.05），小鼠血清中肌酸激酶同工酶和心肌肌钙蛋白 I 水平均明显降低（P<0.05）。TTC 和 HE 结果显示 sham 组小鼠组织结构完整；IR 组小鼠心肌梗死面积较大，组织结构完成性破坏，心肌细胞坏死，炎性细胞浸润；E/IR 组小鼠上述病理情况减轻。IR 组小鼠心肌组织中 TNF-α、IL-1β、IL-18、Caspase-1 和 NLRP3 水平均高于 Sham 组(P<0.05)；E/IR 组小鼠上述指标水平均低于 IR 组(P<0.05)，高于 Sham 组(P<0.05)。

结论：EP 可以减轻小鼠 IR 过程产生的损伤，减少心肌梗死面积，其机制可能与抑制 NLRP3 炎症小体活化通路有关。

关键词：运动预适应，缺血再灌注，NLRP3 炎症小体

P6-81 不同的运动强度及方式对肠道菌群的影响综述

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本文通过对运动与肠道菌群之间关系的文献进行深入研究，对不同运动强度及合理的运动强度及方式对肠道菌群的调节效应做一个系统的总结和评估，为人们提供更科学、有效、可行的运动方式以维护肠道健康。结果发现：1.不同的运动强度：低强度的运动可能会改变肠道菌群，但对于经常进行运动或已经拥有较高程度的健康人群，则需持续进行高质量的训练才可能产生肠道菌群的显著改变。中度至高强度运动可以显著改变肠道菌群的丰度、多样性和种类数量，提高有益菌如双歧杆菌等的生长速度。高强度运动可以造成较剧烈的肠道应激和肠道内的微生物变化，包括降低丙酸和乙酸等短链脂肪酸产生，同时抑制有益菌如双歧杆菌的生长。由于高强度运动损害肠道中的一些有益菌，从而导致肠道生态失衡。肠道内生境环境的不平衡可以引起一些消化系统疾病，例如肠道炎症、易感染性胃肠炎等疾病，从而为人们的身体健康带来了不小的风险。2.不同的运动方式：长时间、低强度的有氧运动可以促进肠道菌群的丰富性提高和多样性增加，从而有利于维护肠道健康。这可能与有氧运动能够增加肠道流量和肠壁血流量有关，从而提高肠道环境对微生物定植的适宜程度。高强度无氧运动和高强度有氧运动可能会抑制某些肠道菌群的生长，进一步引起菌群失衡。这种负面影响可能与高强度运动诱导的肠道滞留时间延长、肠道某些区域肠道运动下降有关，从而影响肠道微生物定植的适宜程度。同时这种影响可能是逆转性的，即短期内的肠道菌群失衡可能会随着运动恢复而消失。此外，瑜伽和普拉提等运动方式可通过调节自主神经活动、改善心理健康等途径来促进肠道健康。

关键词：运动强度；运动方式；肠道菌群

P6- 82 “体医融合”背景下《运动生理学》“SPOC”教学模式研究

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随着我国老龄化加剧、全生命周期健康需求及体医融合战略的快速推进，社会对体育人才的需求发生了变化，对健身指导、健康管理、运动防护、体能训练等人才需求量增大，但我国相应人才储备不足。

体育院校学生能够开展不同人群运动技能的有效指导，但医学相关知识储备不足，预防运动损伤，延缓或防止慢病的发生，能力尚显不足。因此，体育专业学生掌握医学科学知识储备，才能有效实施“体医融合”，推进健康中国计划。《运动生理学》为体育类专业学生核心基础课，对人才培养中发挥重要作用。

随着信息技术的飞速发展，大数据、人工智能的广泛应用，课堂教学方式和教学理念发生巨大改变。近几年 SPOC 在线教学方式呈现出爆发式的发展，学生在 SPOC 同步、异步课堂中能相对自主地进行学习，是对教学模式的重构与创新。但 SPOC 教学方式，缺少面对面交流易导致理解误差，及时性差、效率不高。如何以人才培养为根本目的，完成学生《运动生理学》线上教学与传统课堂教学的融合，实现理论知识与运动实践的高度契合是非常重要的。

沈阳体育学院《运动生理学》课程，根据授课内容，选择贴合的社会热点问题或运动关注问题入手，课前通过 SPOC 翻转课堂形式，提前发布教学目标、热点视频、讨论问题、参考资料、学习网站等内容，让学生利用自己的时间提前预习，增强自主学习的意识，并通过课前小测验了解学生预习效果，掌握学生学习动态。课中通过老师与学生的互动，凝练课程关键问题，通过实例使学生充分理解，并通过课程思政内容的设计，增加学生学习的责任感使命感，同时课上就核心内容组织小组讨论，增加学生的团队合作意识，提高思辨能力、理论联系实践能力和创新能力。课下通过布置作业、老师在线答疑、小组互相讨论、拓展相关知识等方式开展，进一步加深学生对问题的理解，提升授课效果。

关键词：体医融合；运动生理学；SPOC

P6-83 Exercise prevents telomere-related diseases

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Background: Telomeres, which are located at the ends of chromosomes and play a protective

role in the structure and function of chromosomes, shorten with each division of the chromosome and are regarded as a major marker of the biological age of the organism. Telomere shortening can accelerate the aging process as well as promote the onset and progression of many diseases. Studies have shown that physical activity is important for individual health and well-being as it slows the rate of telomere wear and tear, maintains telomere length, and reduces the risk of a number of telomere-related diseases. The article summarizes the prevention of telomere-related diseases through exercise by analyzing the correlation between exercise, telomeres, and diseases, providing an important scientific theoretical basis for telomere-mediated exercise for health.

Methods: Using "exercise, telomere, diseases" as search terms, the article searched Chinese and English databases such as CNKI and PubMed to analyze and summarize the relevant literature in line with the topic of this article.

Results: It has been found that the possible mechanisms of action of exercise in regulating telomere length include decreasing the level of oxidative stress and inflammation, increasing telomerase activity, and enhancing the stability of the telomere protein complex. Physical activity to prevent telomere-related diseases mainly includes:(1)Cardiovascular Disease. Biological aging, such as telomere wear and tear, which occurs during the aging process, is thought to to be one of the risk factors for cardiovascular disease. Shortened telomere length increases the risk of cardiovascular diseases such as hypertension, coronary heart disease and atherosclerosis. Scientific exercise can maintain telomere length and reduce the incidence of cardiovascular disease and mortality by enhancing the body's antioxidant capacity, among other mechanisms, but this process must be carried out under the guidance of a professional. (2)Depression and Anxiety. Telomere length is inextricably linked to psychological conditions. Studies have shown a negative correlation between psychological disorders such as depression and anxiety disorders and telomere length. Shorter telomere length can lead to a higher risk of anxiety and depression in people with poorer psychological status. People who voluntarily participate in sports can reduce oxidative stress and inflammation and increase telomerase activity to delay telomere shortening while reducing symptoms such as depression, psychological distress, and improving quality of life. (3)Diabetes. Shorter telomere length significantly associated with diabetes risk. Diabetes mellitus occurs as a result of hyperglycemia, which increases intracellular reactive oxygen species concentrations, and high levels of lipid peroxidation accelerate the shortening of telomere length in diabetic patients. Aerobic and resistance exercise can control the risk of diabetes by increasing insulin sensitivity and enhancing the body's aerobic endurance to reduce oxidative stress levels and maintain telomere length. (4)Obesity. Obesity is an abnormal process in which telomeres shorten due to elevated levels of oxidative stress and inflammation in the body as a result of excess fat accumulation. Studies have shown that leukocyte telomere length is lower in obese

populations than in normal weight population, and high waist circumference index showed a significant association with shorter telomere length. Obesity usually occurs due to lack of physical activity. Long-term physical activity can play a positive role in reducing obesity and telomere wear by improving cardiorespiratory endurance and health. (5)Cancer. Telomeres are closely related to the onset and progression of cancer. In contrast to the replicative senescence that normal somatic cells have, cancer cells overcome the Hayflick limit to gain the ability to proliferate indefinitely. Most of the tumor cells coexist with high telomerase activity, which maintains a constant telomere length and the ability to continue dividing. Physical activity plays a positive role in reducing pain, improving bone health and other dysfunctions in cancer patients, and inhibiting tumor progression as an adjunct to clinical treatment.

Conclusion: Abnormal telomere length can lead to a variety of chronic diseases such as cardiovascular disease, cancer, diabetes, obesity, and mental illness. Exercise has a positive effect on slowing down telomere length that shortens with age. Long-term adherence to exercise training can prevent and alleviate the occurrence of telomere-related diseases while maintaining telomere length, which further confirms the possibility of telomeres in the exercise treatment of related diseases and the promotion of body health, and the positive correlation between exercise and telomeres provides strong evidence to support this.

Keywords: exercise; telomeres; diseases

P6-84 虫草素通过 VGSC 改善脂多糖诱导的 C2C12 肌管萎缩

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摘要：本研究以 C2C12 细胞（小鼠成肌细胞）为对象，初步探讨了虫草素对炎症性萎缩肌管电压门控钠通道（VGSC）功能特性的变化及其改善肌管萎缩作用，旨在评价虫草素通过 VGSC 对炎症性肌肉萎缩的保护作用及其分子机制。在形态学上采用免疫荧光法观察肌管长度、肌管融合率、胞内钠离子浓度，进一步使用定量聚合酶链式反应(qPCR)和 Western Blot 法检测肌肉萎缩因子相关 mRNA 水平和蛋白表达水平，最后通过细胞膜片钳技术记录肌管的动作电位和 VGSC 内在动力学变化。结果表明，经过虫草素处理的萎缩肌管，在形态学上有了明显的改善作用，肌肉萎缩因子相关 mRNA 水平和蛋白表达水平有所下降。在动作电位和 VGSC 内在动力学上，我们发现虫草素提高了萎缩肌管动作电位频率，促进了

钠通道的激活和失活。因此，这些发现揭示了虫草素通过 VGSC 改善炎症性骨骼肌萎缩，并为预防肌肉萎缩药物的开发提供一定的参考依据。

关键词：C2C12；骨骼肌萎缩；虫草素；VGSC

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Cordycepin ameliorates C2C12 myotube atrophy induced by lipopolysaccharide through VGSC

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In this study, C2C12 cells (mouse myoblasts) were used to investigate the effects of cordycepin on the functional characteristics of voltage-gated sodium channel (VGSC) in myotubes of inflammatory atrophy and its effect on myotube atrophy, in order to evaluate the protective effect of cordycepin on inflammatory muscular atrophy through VGSC and its molecular mechanism. The myotube length, myotube fusion rate and intracellular sodium concentration were observed by immunofluorescence, and the levels of muscular dystrophy factor-related mRNA and protein expression were detected by quantitative polymerase chain reaction (qPCR) and WesternBlot. Finally, the action potential of myotube and the internal dynamics of VGSC were recorded by patch clamp technique. The results showed that the morphology of atrophic myotubes treated with cordycepin was significantly improved, and the levels of mRNA and protein expression related to muscular dystrophy factor were decreased. In terms of action potential and internal kinetics of VGSC, cordycepin increased the frequency of action potential of atrophic muscle tube and promoted the activation and inactivation of sodium channels. Therefore, these findings reveal that cordycepin improves inflammatory skeletal muscle atrophy through VGSC and provides a certain reference basis for the development of drugs to prevent muscle atrophy.

Keywords: C2C12; skeletal muscle atrophy; cordycepin; VGSC

P6-85 Effects of bacoside A on phenytoin-induced cerebellar disfunction model rats

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Objective: To observe the effects of bacoside A (BA) on phenytoin (PHT)-induced cerebellar disfunction model rats. **Methods:** Thirty adult healthy male SD rats with weight 200-220 g were randomly divided into control (CON), model (PHT) and bacoside A-treated groups (PHT+BA) (n=10 each group). The rats in PHT and PHT+BA groups were given 75mg/kg phenytoin (i.p., qd, 7 days, while the first day dose was 200mg/kg) to prepare cerebellar disfunction model rats, while the rats in the CON group were injected with the same volume of normal saline. Then the balance beam test was used to exam the degree of cerebellar functions. After modeling, the rats in PHT+BA group were injected with 10mg/kg bacoside A (i.p., qd, 5 days), while the rats in the CON group and PHT group were injected with the same volume of normal saline. After drug intervention, open field test and balance beam test were performed to evaluate the cerebellar motor coordination function of rats. **Results:** (1) Compared to the CON group, the pole crossing time of balance beam was significantly prolonged in the PHT group and the PHT+BA group (P<0.01). (2) After BA intervention, the total movement distance of open field test decreased in the PHT group (P<0.01), while the pole crossing time shortened in the PHT+BA group (P<0.05). Compared with the CON group, the balance beam scores were increased in the PHT group (P<0.05). **Conclusions:** Bacoside A has some therapeutic effects on phenytoin-induced cerebellar disfunction model rats.

Key words: Phenytoin; bacoside A; Cerebellar disfunction; rats

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P6-86 红景天对低氧运动小鼠骨骼肌保护作用机制研究

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研究目的:探索红景天对低氧运动小鼠骨骼肌细胞损伤的保护作用机制。

研究方法: 方法将 40 只雄性小鼠随机分为常氧运动组、低氧运动组和红景天＋低氧运

动组,每组均为 10 只。红景天＋低氧运动组小鼠给予灌胃红景天口服液(20g kg^{-1} d^{-1}),小鼠连续给药 15d 后进行为期 4 周的低氧运动(氧浓度 11.3%，15m/min,60min/d)。常氧运动组在常氧环境同样进行为期 4 周的运动（(15m/min,60min/d)），和低氧运动组环境同样进行为期 4 周的运动（(15m/min,60min/d)），最后一次训练结束后的 24h 取材。小鼠眼眶取血,分离血清,将样品保存-80℃冰箱; 快速取出骨骼肌组织,在液氮中冷冻,保存在-80 ℃ 冰箱中用于 Elisa、RT-PCR 和 Western blot 实验。检测骨骼肌血清甘肽过氧化物酶(GSH-PX)、超氧化物歧化酶(SOD)、丙二醛(MDA); RT-PCR 法检测骨骼肌 Bcl-2、Bax、HIF-1α 和 VEGF mRNA 水平的表达；Western blot 检测骨骼肌 Bcl-2、Bax、HIF-1α 和 VEGF 蛋白水平的表达。组间比较采用单因素方差(ANOVA)分析。

研究结果:1)与常氧运动组相比,低氧运动组骨骼肌组织 GSH-PX、SOD 均显著性降低(P＜0.05),MDA 含量显著性升高(P＜0.01)。2)与低氧运动组相比,红景天＋低氧运动组 GSH-PX、SOD 活性均显著性升高(P＜0.05), MDA 含量显著性升高(P＜0.05)。3) 与常氧运动组相比,低氧运动组骨骼肌组织 Bcl、HIF-1α 和 VEGF mRNA 表达均显著性升高(P＜0.05),Bax mRNA 表达显著性降低(P＜0.05)。4) 与低氧运动组相比,红景天＋低氧运动组骨骼肌组织 Bcl、HIF-1α 和 VEGF mRNA 表达均显著性降低(P＜0.05),Bax mRNA 表达显著性升高(P＜0.05)。

研究结论:红景天通过减轻低氧运动小鼠氧化应激反应抑制骨骼肌细胞凋亡。

关键词：红景天；低氧运动；骨骼肌

P6-87 一次运动对青少年外周血单核细胞基因表达的生物信息学分析

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一次运动会改变循环中性粒细胞和外周血单核细胞（PBMC）的基因表达，范围从细胞生长到促炎和抗炎过程。探究一次运动对青少年外周单核细胞基因表达影响，以期揭示运动通过 PBMC 对青少年健康的潜在机制。方法：从美国国立生物技术信息中心（NCBI）公共基因芯片数据平台（GEO）下载 GSE14642 和 GSE11761，对人外周血 PBMC 细胞样本进行转录谱分析，GSE14642 样本来源 20 名健康女性青少年（年龄范围 8-17 岁），GSE11761 样来源 20 名健康男性青少年（年龄范围 8-17 岁），运动方式均为 10 次 2 分钟的恒定工作速率的自行车运动，受试者在运动开始前和结束即刻进行血液采集，之后使用 OptiPrep 分离 PBMC。密度梯度介质 (SIGMA)。使用 TRIzol 提取总 RNA。cRNA 杂交到 Affymetrix U133+2 阵列。采用 R 语言“limma”函数包筛选差异表达基因（DEGs），设定阈值为$|logFC|\geq 1$ *且* $P<0.05$*。结果：运动前后男性青少年共筛选出 26 个（其中上调 19 个，下调 7 个）DEGs，运动前后女性青少年共筛选出 62 个（其中上调 60 个，下调 2 个）DEGs，男性与女性青少年共 19 个 DEGs 完全相同。*STRING 构建 PPI 网络，经 Cytoscape 的 CytoHubba 插件鉴定

出与青少年一次性运动后 PBMC 相关的 7 个 Hub 基因，分别为 KIR3DL3、KIR2DL3、S1PR5、KIR3DL1、ADGRG1、FASLG、SH2D1B，*GO 分析显示 DEGs 生物学功能主要涉及先天免疫反应、内皮细胞的凋亡、成纤维细胞的增值、生殖腺发育等，KEGG 分析显示 DEGs 主要与自然杀伤细胞介导的细胞毒性和抗原加工提呈有关。结论：*所得出的 Hub 基因、关键及相关的生物途径和分子通路对于一次运动对青少年 PBMC 的研究提供了一定的依据。

关键词：一次运动；青少年；外周血单核细胞；基因

P6-88 肩胛稳定性训练联合肌肉能量技术对大学生头前伸姿势的干预效果研究

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目的:本研究在肩胛稳定性训练（SSE）纠正头前伸姿势（FHP）的基础上,联合肌肉能量技术(MET),并与单一使用 SSE 做对比,探讨纠正 FHP 的新思路。**方法:**采用头颈角(CVA)评定头颈姿势。选取哈尔滨体育学院头前伸姿势 30 例,CVA≤53°，年龄 18-25 岁,签署知情同意书后随机分成 SSE、SSE+MET 和空白对照三组，6 周,每周 3 次训练。SSE 组：受试者利用弹力带对前锯肌、斜方肌中束、斜方肌下束、菱形肌进行抗阻训练,每个动作 3 组,每组 10 次,总训练时间 30 分钟。SSE+MET 组：在 SSE 之前增加 MET 训练。针对胸大肌、斜方肌上束及肩胛提肌等进行手法放松。受试者在特定的方向和位置上,以抵抗 20%的最大阻力做主动等长收缩 10s，放松 10s，之后将受试者颈部被动活动到最大范围,维持 20s,反复 5-10 次。空白对照组不进行任何康复干预。在干预前后测试 CVA、颈椎前屈、后伸、左右旋转和左右侧屈的颈部关节活动度、头颈部疼痛、用力肺活量、第一秒末用力呼气量等指标。通过 SPSS 26 分析,组内训练前后用配对样本 t 检验;不同组间用单因素方差分析。**结果:**①SSE 组、SSE+MET 组和空白对照组实验前 CVA、CROM、VAS 评分、呼吸功能等无显著性差异(P>0.05)。②6 周干预前后 SSE 组和 SSE+MET 组的 CVA、CROM 和呼吸功能等均有明显改善(P<0.05)，空白对照组无变化。三组的用力肺活量与第一秒末用力呼气量指标干预前后无显著变化。③6 周后，SSE 组和 SSE+MET 组 VAS 改善效果明显好于空白对照组(P<0.05)，其中 SSE+MET 组的头颈部疼痛改善更明显(P<0.05)。**结论:**6 周的 SSE 组、SSE+MET 组都能改善头前伸姿势者的 CVA、CROM、减轻头颈部疼痛、改善呼吸机能，提高颈部功能。与单独使用 SSE 相比,采用 MET 联合 SSE 对改善 FHP 的影响更大，并且 MET 与 SSE 操作简单,无疼痛性刺激,值得推广。

关键词：肩胛稳定性训练；肌肉能量技术；头前伸姿势比

P6-89 运动通过 FGF21 通路调控肝脏脂代谢改善胰岛素抵抗的机制研究

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目的:研究运动对胰岛素抵抗小鼠的作用及 FGF21 通路在运动干预中的具体机制。

方法:以 4 周龄的雄性 C57BL/6 小鼠为实验对象,随机分为正常对照组(CON 组)、高脂饲料组(HFD 组)、高脂运动组(Ex-HFD),每组 10 只。CON 以正常饲料喂养,HFD 和 Ex-HFD 组饲以高脂饲料喂养 12 周,建模成功后;Ex-HFD 组小鼠进行 60min/天、强度为 75%VO2max 的跑台训练。利用小鼠葡萄糖耐量试验(OGTT)和胰岛素抵抗指数(HOMA-IR)检测建模;通过观察各组小鼠肝脏 FGF21、FGFR1、β-klotho、IRS1、SREBP、FAS 的 m RNA 和蛋白表达水平,以及 SOD、GSH-Px 和 MDA 表达的变化,探讨 FGF21/FGFR1/β-klotho 通路在运动干预 IR 中的作用及机制。

结果:1、(1)OGTT 试验结果:与 CON 组相比,HFD 组小鼠的血糖峰值明显升高,且峰值出现的时间点有所延后;在服糖后 15min-30min 血糖值维持高水平;30min 后呈现缓慢下降趋势,在 30-60min 血糖恢复速度明显下降,但在 120min 时血糖仍显著高于基础血糖水平。与 HFD 组相比,Ex-HFD 组服糖后峰值显著下降,并且在 15-120min 血糖的恢复速度明显加快。 (2)各组小鼠 ISI、HOMA-IR 变化:与 CON 组相比,HFD 组小鼠 HOMA-IR 显著增加(P<0.01),ISI 显著降低(P<0.01);与 HFD 组小鼠相比,Ex-HFD 组小鼠 HOMA-IR 显著降低(P<0.05,P<0.01),ISI 显著增加(P<0.01)。综上结果表明,12 周高脂饮食喂养成功建立了小鼠 IR 模型,12 周 60min 跑台运动可有效预防 IR 的形成。2、12 周跑台运动后各组小鼠肝脏 FGF21、FGFR1、β-klotho、IRS1、SREBP、FAS 的变化:与 CON 组小鼠相比,HFD 组小鼠肝脏 FGF21、FGFR1、β-klotho、IRS1m RNA 和蛋白表达水平均显著降低(P<0.01), SREBP 和 FAS mRNA 和蛋白表达表达量显著增加(P<0.05),肝脏 SOD、GSH-Px 水平显著下调(P<0.01), MDA 水平显著增加(P<0.01)。与 HFD 组小鼠相比,Ex-HFD 组小鼠肝脏 FGF21、FGFR1、β-klotho、IRS1 mRNA 和蛋白表达水平均显著上调(P<0.01), SREBP 和 FAS m RNA 和蛋白表达量显著下调(P<0.05),肝脏 SOD、GSH-Px 水平显著升高(P<0.01), MDA 水平显著降低(P<0.01,P<0.05)。

结论:12 周跑台运动通过增强 FGF21/FGFR1/β-klotho 表达水平调控肝脏脂代谢缓解胰岛素抵抗的形成。

关键词：运动；FGF21;脂代谢；胰岛素抵抗

P6-90 Treadmill exercise pretreatment ameliorated vascular dementia-induced structural synaptic plasticity impairments in rat prefrontal cortex and improved recognition memory

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Objective: The aim of our study was to investigate structural synaptic plasticity in prefrontal cortex of rat under treadmill exercise pretreatment or naive conditions in vascular dementia model, followed by recognition memory performance in a novel object recognition task.

Methods: Twenty-four Sprague-Dawley rats were enrolled in this study and randomly divided into following 4 groups: control group (C group, n = 6), vascular dementia group (VD group, n = 6), treadmill exercise and vascular dementia group (Exe+VD group, n = 6), treadmill exercise and black group (Exe group, n = 6). The rats between Exe+VD and VD groups were received 4 weeks of treadmill exercise interventions. Then, the rats in Exe+VD and VD groups were received bilateral common carotids arteries operation to create vascular dementia model. 1 week later, open-field task and novel recognition memory task were adopted to evaluate anxiety-like behavior and recognition memory in each group. Then, immunofluorescence and golgi staining was used to analyze neuronal number and spine density in rat prefrontal cortex. Transmission electron microscope was applied to observe synaptic ultrastructure. the level of dopamine and 5-HT in the prefrontal cortex were detected by microdialysis couple with high-performance liquid chromatography.

Results: Behavior results demonstrated that 4 weeks of treadmill exercise pretreatment significantly ameliorates recognition memory impairment and anxiety-like behavior in AD rats (P<0.01), while non-exercise VD rats exhibited impaired recognition memory and anxiety-like behavior when compare with control group (P<0.001). In addition, NeuN immunostaining results showed a significant decrease of NeuN-marked neuron between the C and VD groups (P<0.01), but significantly increase in this molecular marker in rats in Exe+VD group compared to control group (P<0.01). Golgi staining results demonstrated that the prefrontal cortex neurons in the VD group displayed a significantly lower number of dendritic spines than C group (P<0.01), and there were more spines on the dendrites of prefrontal cortex cells from Exe+VD rats than on those from VD rats (P <0.01). Transmission electron microscope further revealed that the number of synapse in the prefrontal cortex significantly decreased in VD group when compared with C

group(P<0.01), but 4 weeks of physical exercise can rescue this phenomenon (P<0.01). Last, the level of prefrontal cortex dopamine and 5-HT in VD group significantly decreased (P<0.01), and this phenomenon can be rescue by treadmill exercise (P<0.05).

Conclusion: Treadmill exercise pretreatment ameliorated vascular dementia-induced structural synaptic plasticity impairments in rat prefrontal cortex and improved recognition memory.

Key words: treadmill exercise; vascular dementia; synaptic plasticity; recognition memory.

P6-91 心动周期和心电周期之议析——一个生理学名词的建议

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心脏的重要功能是泵血，心室肌细胞、心房肌细胞有节律的收缩、舒张有赖于心肌细胞规律的电位变化过程。心动周期主要指心脏工作细胞的机械收缩舒张过程和经历的时间，而心脏工作细胞的电变化现象是一个客观过程和“独立存在”，也需要一个专有的术语予以概括和定义。根据组织学和电生理学特点，一般将心肌细胞分为工作细胞（包括心房肌、心室肌）和自律细胞（主要包括窦房结细胞、浦肯野细胞等）。本文主要针对心脏的工作细胞的周期性电学变化现象展开讨论，建议以专有名词表述这个“独立存在形象”，用“心电周期（cardiac electro-cycle 或 cardiac ecycle）”描述心房肌、心室肌的电变化过程和规律，用心动周期描述心肌的机械变化过程，两者既有质的区别，又有紧密的必然的联系。

1.心动周期

心脏的一次收缩和舒张所经历的时间称为一个心动周期（cardiac cycle），包括心房的舒缩和心室的舒缩，表达出心室“泵血”的功能。当前“生理学”教材中的“心动周期”其内涵就是机械过程，并不必然包括心脏细胞电位变化的内容。

2.明确“心电周期”概念的建议

对于心脏的工作细胞，心电过程、心脏的机械舒缩过程是相伴随而存在、更是相继而循序发生的生理学过程，心肌细胞电位变化的有序发生过程是先导----“在前”，正常情况下是来自于自律细胞“窦房结”；在时间上紧密继之以心肌细胞的机械收缩舒张过程：兴奋--收缩偶联----“继后”。心房是一个合胞体、心室是另一个合胞体，这样的结构，保障了所有心房肌细胞、所有的心室肌细胞分别依序几乎同时发生去极化电变化，相继地发生各自的“兴奋--收缩偶联”过程，宏观地表现为心房的同时收缩或舒张、心室肌细胞的同时收缩或舒张。

心脏工作细胞的电学现象，是一个客观过程，是一个独立存在，作为以揭示、阐明生命的过程及其机制为主要目标的生理学，应该给这个“独立存在”一个命名。为了和心脏的机械舒缩活动“心动周期”理论相联动，建议以心脏工作细胞的电变化过程来定义和研究“心电周

期”，即从窦房结发放的电兴奋信号到达了右心房、左心房肌细胞的时刻点作为一个心电周期的开始----心房肌细胞开始去极化。心脏工作细胞所经历的一次电位变化过程，称为心电周期，一般指从心房肌细胞去极化开始到相邻的下一次心房肌细胞去极化开始之间的过程和时间，在心电图上的标示为 P 波起点到紧邻的下一个 P 波起点。

关键词：心电现象，心动周期，心电周期，生理过程

P6-92 骨骼肌疲劳对肌肉收缩产生的被动力量及核心蛋白作用的影响

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骨骼肌收缩主要由肌动蛋白，肌球蛋白以及核心蛋白等相互作用从而产生主动力量（Active force）和被动力量（Passive force）。（1）主动力量由肌球蛋白（Myosin）和肌动蛋白（Actin）相互作用所产生，（2）被动力量是指在肌肉拉伸时，主要由核心蛋白（Titin）所产生的力。核心蛋白是一种与 Z-disk 和肌球蛋白相关的蛋白质，是骨骼肌中最大的蛋白质。早期研究表明，核心蛋白的功能仅仅在于当肌肉收缩时，将肌球蛋白保持在肌节中心。最近研究表明，**核心蛋白具有调节主动力量的功能** [1]。

主动力量和被动力量主要区分方式为：力的产生是否由于 Ca^{2+}的刺激，引起肌肉收缩。所以核心蛋白在主动力量产生过程中常常被忽略，因为肌动蛋白所产生的被动力量要比肌动蛋白所产生的主动力量要低的多。但这并不意味着主动力量在收缩过程中显得最为重要。在之前的研究中表明，**被动力量可能可以改变主动力量的收缩** [2]。

研究者前期已研发体内活体-收缩模型。在该模型中，大鼠后肢肌肉通过坐骨神经表面电极受到电刺激，并通过反复收缩，使其在体内产生肌肉疲劳，保持了肌肉的完整性和有效性。前期研究，首次运用不同的收缩模式，对腓肠肌（Gastrocnemius）进行疲劳刺激。在显微镜下，运用物理性去膜分离技术，对肌纤维进行物理性去膜。为了保证数据的有效性，肌纤维将在 15 分钟内完成数据采集。此研究探讨了肌肉疲劳对被动力量所产生的影响。核心蛋白在结构上通常位于不可扩展的 A-band 和可扩展的 I-band。其关键在于，I-band 由近端免疫球蛋白域 PEVK 和 Ig domain，以及远端免疫球蛋白域的变化。**因此，探究骨骼肌疲劳状态下，被动力量的产生以及核心蛋白作用的影响是揭示肌肉疲劳产生机理的探索。为预防一系列骨骼肌病理性疾病，以及基于核心蛋白引起的心肌疾病等症状奠定科学基础。**

关键词：肌肉疲劳，核心蛋白，被动力量

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P6-93 Supramammillary nucleus-hippocampal neural circuit modulates motor skill learning

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Objective Motor skill learning, in healthy or clinical populations, usually requires extensive execution of a motor task to achieve gains and skill improvement in performance, which are important foundations for language, cognition and social functions. Multiple brain regions participate in motor skill learning in different ways at the level of target setting, selection, or execution, such as basal ganglia, hypothalamus, motor cortex and hippocampus. However, circuit-level organization and function of motor skill learning remain poorly understood. Supramammillary nucleus (SuM) is a nucleus located in the hypothalamus. Previous studies found that activation of SuM neurons regulated cognitive and spatial navigation behavior, and SuM can also selectively transfer different types of information to the hippocampus. We hypothesized that the papilla-hippocampal circuit plays an important role in motor skill learning. This study aims to explore the hypothalamic neural circuit mechanism of regulating motor skill learning by the supramammillary nucleus-hippocampus. **Methods** Motor skill learning ability in mice was detected using the balance beam and accelerated rotation tests. During motor skill training, the activity of SuM neurons was monitored by optical fiber calcium recording in vivo, and the activation of SuM neurons was detected by c-Fos immunostaining. Cholera toxin and muscarinic acid were used to inactivate SuM neurons and explore the function of Sum neurons in motor skill learning. Virus tracer was used to trace the SuM-hippocampal circuit. The method based on DREADD was used to manipulate the Sum-hippocampus neural circuit and explore the function of Sum-hippocampus innervation in motor skill learning. **Results** The destruction of SuM neurons could reduce the motor skill learning ability. SuM neurons showed higher level of activity and more synchronous events during motor skill learning. SuM-DG and SuM-CA2 are anatomically independent of each other. Chemical activation or inhibition of Sum-DG innervation can improve or decrease motor skill learning ability in mice, whereas manipulation of the SuM-CA2 circuit did not affect motor skill learning. **Conclusion** SuM-hippocampal DG but not SuM-hippocampal CA2 neural circuit regulates motor skill learning in mice.

Key words: Motor skill learning; Supramammillary nucleus; Hippocampus; Neural circuit

P6-94 Tafazzin 介导的心磷脂合成在 HIIT 抑制衰老骨骼肌铁死亡的作用机制研究

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目的：高强度间歇运动（HIIT）对衰老骨骼肌形态和功能、氧化应激、线粒体氧化磷酸化活性、Tafazzin（TAZ）表达、心磷脂合成和铁死亡的影响；细胞实验采用 H_2O_2、RSL3 激动剂对 TAZ 过表达慢病毒转染进行干预，探讨 TAZ 在衰老细胞和铁死亡发生中延缓骨骼肌萎缩中的作用和分子机制。

方法：动物实验：1）选用 48 只约 8 月龄清洁级 Sprague-Dawley 大鼠，分组：青年安静对照组（ASED 组）、老龄安静对照组（OSED 组）、老龄持续性耐力组（OMICT 组）和老龄高强度间歇训练组（OHIIT 组），共 4 组，每组 12 只；采用呼气分析运动试验对大鼠进行最大吸氧量测定。正式训练前后分别以速度 10m/min（30%～40%VO_{2max}）跑台 1min 进行热身和放松。OHIIT 组起始速度 15m/min（45%～55%VO_{2max}），时间为 4min；之后进行高强度运动，速度为 25m/min（85%～95%VO_{2max}），运动 1min，依次交替进行 9 个循环；OMICT 组以 17m/min（运动强度 75%～80%VO_{2max}）运动，运动组的运动总时间均为 45min，坡度为 0°，训练共计 8 个月；抓力和耐力测试评价骨骼肌功能，蛋白免疫印迹和 RT-PCR 等检测相关蛋白和基因表达，线粒体脂质组学检测骨骼肌脂质代谢情况；**2）**采用 L6 细胞，过表达 TAZ 转染 L6 细胞的模型上，给予 H_2O_2 干预，制备衰老氧化损伤模型，分组：NC 组、NC+ H_2O_2 组、TAZ 组、TAZ + H_2O_2 组、NC+ RSL3 组、TAZ 组、TAZ + RSL3 组。CCK-8 检测细胞活性，流式细胞仪检测细胞周期分布，比色法检测心磷脂生物合成、免疫荧光评价铁死亡相关蛋白表达。

结果：1）与 OSED 组相比，OHIIT 组体脂%（p<0.05）降低，瘦体重%（p<0.05）和股四头肌相对重量（p<0.01）显著增加；与 OSED 组相比，OHIIT 组抓力、张力、力竭时间和最大速度显著提高（p<0.01）； 2）用 Western blot 结果显示，与 OSED 组相比，OHIIT 组的 MuRF1（p<0.05）和 Atrogin-1（p<0.01）显著减少，OHIIT 组 Parkin 和 Pink1 显著增加（p<0.01），OHIIT 组 Bcl-2 显著增加，Caspase-3 显著减少（p<0.01）；此外，OHIIT 组 SLC7a11、FTH1 和 GPX4 显著增加。3）酶联免疫吸附显示，与 OSED 组相比，OMICT 和 OHIIT 组 4-HNE、MDA 和 LPO 显著降低、T-GSH、GSH、GSSG 和 GSH/GSSG 显著增加。4）广泛靶向脂质组学检测，HIIT 能逆转增龄导致的骨骼肌线粒体甘油二脂、溶血磷脂酰胆碱、磷脂酸、磷脂酰胆碱、磷脂酰乙醇胺和磷脂酰丝氨酸显著下，通过 RT-qPCR 技术检测心磷脂合成相关的酶，与 ASED 组相比，OSED 组 CLS、Plscr3 和 TAZ 显著降低，MitoPLD 和 ALCAT1 显著增加；与 OSED 组相比，OHIIT 组 TAZ mRNA 和蛋白表达显著增加（p<0.01）；5）通过 Western blot 和细胞免疫荧光方法验证，TAZ 过表达可缓解 H_2O_2 或铁死亡诱导剂 RSL3

处理导致的 L6 细胞线粒体质量控制相关蛋白（PGC-1α、UCP1、SDH、pink1 和 parkin）表达下降；TAZ 过表达也可抑制 H_2O_2 诱导的 ACSL4 和 ALOX5 水平增加，并促进 SLC7a11、Nrf2 和 GPX4 表达下降；细胞免疫荧光和流式细胞术检测脂质过氧化水平，TAZ 可缓解 H_2O_2 诱导的 C11-BODIPY581/591 水平增加。

结论：1）HIIT 可通过改变骨骼肌形态和功能、降低 E3 泛素化连接酶、自噬、凋亡、铁死亡、氧化应激水平，延缓衰老骨骼肌萎缩；2）HIIT 增加 TAZ 内源性表达和 CL 合成提高，并改善衰老骨骼肌线粒体氧化磷酸化活性和线粒体质量控制；3）TAZ 可通过 CL 合成降低 H_2O_2 和 RSL3 诱导的 L6 细胞衰老指标，降低细胞内降低铁死亡水平。

关键词：HIIT、心磷脂、铁死亡、Tafazzin、肌肉减少症

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P6-95 个体、家庭和物理环境因素对学龄儿童基本动作技能的影响

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目的：本研究旨在探究与学龄儿童 FMSs 有关的个体、家庭和物理环境层面的影响因素，识别潜在的、可改变的危险因素，以期为后期制定有针对的干预方案提供参考。

方法：共 1012 对亲子组合受邀参与本研究。**儿童个体层面**，测量身高、体重、身体成分、FMSs 和体适能，以及身体活动、久坐行为和睡眠时长；采用问卷收集人口统计资料、感知运动能力、运动愉悦感和心理幸福感。**家庭和物理环境层面**的因素包括父母亲的人口统计资料、身体形态数据、父母亲对儿童 PA 行为的支持，以及家庭和社区周围的运动环境，问卷收集。采用分层回归检验儿童个体层面，家庭层面和物理环境层面的因素与 FMSs 之间的关系。

结果：结果发现，①7 个因素（年龄、性别、BMI、LPA、体适能、父母的支持, 家庭和社区周围的运动环境）解释了移动技能 29.3%的方差（$F(22, 988)=18.605$，$P<0.001$）；②8 个因素（年龄、性别、SLP、PMC、体适能、父母的支持, 家庭和社区周围的运动环境）解释了球类技能 41.3%的方差（$F(22, 988)=31.581$，$P<0.001$）；③8 个因素（年龄、性别、BMI、SLP、PMC、体适能、父母的支持, 家庭和社区周围的运动环境）解释了综合技能 46.2%的方差（$F(22, 988)=38.506$，$P<0.001$）。其中，年龄、性别、体适能水平、父母的支持, 家庭和社区周围的运动环境是 FMSs 一致的预测因子。

结论：本研究调查了影响中国学龄儿童 FMSs 发展的社会生态因素，为未来的 FMSs 促进研究奠定了基础。首先，研究结果支持影响儿童 FMSs 发展的因素是多维的、复杂的，且因技能类型的不同而略有差异。其次，儿童个体层面的影响因素似乎是最重要的。未来的研究需要采用严谨的纵向设计，选择更全面的 FMSs 评估工具（包括移动技能、球类技能和稳

定性技能），客观测量父母的 PA 行为，以深入了解社会生态因素与儿童 FMSs 之间的关系强度和方向。此外，未来的干预研究应该重点关注女童和肥胖儿童球类技能的发展。

关键词：学龄儿童，基本动作技能，社会生态影响因素

P7 呼吸生理

P7-1 镁和钙离子之间的相互作用：解码其对肺动脉平滑肌细胞钙化的影响

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目的：探讨钙化（Calcification）对肺动脉平滑肌细胞（Pulmonary vascular smooth muscle cells, PASMCs）的影响，特别是镁离子（Magnesium ion, Mg^{2+}）和钙离子（Calcium ion, Ca^{2+}）信号和能量代谢的变化，为血管平滑肌细胞钙化的机制研究与预防治疗提供新的理论基础及依据。

方法：（1）使用 10 mM β-甘油磷酸（β-GP）制备高磷培养液干预大鼠 PASMCs 7 d 建立钙化模型，运用茜素红染色鉴定钙沉积，运用 RT-qPCR、Western blot 检测钙化相关因子表达。（2）运用 RT-qPCR、Western blot 检测 Mg^{2+}转运蛋白和经典瞬时感受器电位（Canonical transient receptor potential, TRPC）表达，并用实时细胞动态荧光检测胞内和线粒体内 Mg^{2+}、Ca^{2+}浓度，探究 Mg^{2+}转运蛋白通道特性和 Ca^{2+}内流特性。（3）检测葡萄糖摄取能力、乳酸产出和线粒体呼吸功能，评估 PASMCs 能量代谢。

结果：相较 CON-PASMCs，（1）经高磷培养液干预 7 d 的 PASMCs 钙沉积明显。成骨标记物 Runx2、Msx2、SOX9 和促钙化 BMP2 的 mRNA 及蛋白表达明显增高，钙化抑制因子 MGP 的 mRNA 及蛋白表达明显降低，提示钙化 PASMCs 模型建立成功。（2）钙化 PASMCs 中 SLC41A1、SLC41A3 和 TRPM7 等镁转运体呈现高表达。静息胞浆游离浓度 Mg^{2+}（$[Mg^{2+}]_i$）升高，线粒体游离 Mg^{2+}浓度（$[Mg^{2+}]_m$）降低，SLC41A1 和 TRPM7 功能增强。（3）钙化 PASMCs 中 TRPC1、PRPC4 和 TRPC6 等呈现高表达。静息$[Ca^{2+}]_i$升高，受体操纵性钙内流（ROCE）和钙池操纵性钙内流（SOCE）峰值增强，线粒体游离 Ca^{2+}浓度（$[Ca^{2+}]_m$）升高。（4）钙化 PASMCs 中，葡萄糖摄取能力减弱，24h 乳酸产出降低，提示钙化 PASMCs 糖酵解能力下降。（5）钙化 PASMCs 中，基础呼吸、ATP 产量、最大呼吸和储备呼吸能力均明显升高，提示钙化 PASMCs 氧化磷酸化增强。

结论：高磷诱导 PASMCs 钙化，使 SLC41A1、SLC41A3 和 TRPM7 等镁转运体数量与

功能增强，导致$[Mg^{2+}]_i$升高，$[Mg^{2+}]_m$降低；同时 ROCE 和 SOCE 作用增强，导致$[Ca^{2+}]_i$升高，并促进$[Ca^{2+}]_m$升高；钙化 PASMCs 供能方式转变，线粒体氧化磷酸化功能增强，糖酵解水平减弱。

关键词：肺动脉高压，血管钙化，镁转运体，TRPC，能量代谢

P7-2 高镁对慢性低氧肺动脉高压大鼠冠状动脉重构和 TRPCs 介导 ET-1 高反应性的影响

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肺动脉高压（pulmonary hypertension, PH）是肺动脉压力持续升高，引起右心室重构的疾病，可导致右心衰竭。瞬时受体电位通道（transient receptor potential channels，TRPCs）与心肌肥厚、心力衰竭密切相关。

PH 大鼠中，冠状动脉（coronary artery，CA）平滑肌细胞和内皮细胞功能障碍引起血管重构，内皮素-1（endothelin-1，ET-1）等活性增强，使血管收缩反应性增高。Mg^{2+}是 Ca^{2+}通道拮抗剂，参与心血管功能调节。

目的：明确 PH 大鼠中，由 TRPCs 介导的 ET-1 引起 CA 收缩和重构以及高镁的衰减作用。为进一步研究 PH 的发病机制提供新的线索，并提示高镁可能作为潜在的治疗策略。

方法：（1）慢性低氧 PH（CHPH）大鼠模型测定右心室收缩压（RVSP）、右心室质量指数（ RVMI）、HE 染色观察肺动脉及 CA 形态；（2）通过 DMT 微血管张力检测技术，记录 ET-1 引起去内皮 CA 张力的变化；（3）通过 RT-PCR、Western Blot 实验筛选出差异表达的 TRPCs 的 mRNA 和蛋白；（4）根据筛选结果，使用可分别特异性激活钙池操纵性钙通道（SOCC）和受体操纵性钙通道（ROCC）的激动剂 CPA 和 OAG，验证上调的 TRPCs 对 CA 收缩能力的影响；（5）通过细胞增殖、迁移实验验证 PH 大鼠 CA 重构。

结果：较 CON 组，（1）CH 组 RVSP、RVMI 显著增加，形态学观察可见 CH 组肺动脉及 CA 平滑肌层明显增厚，管腔减小；（2）正常镁时，CH 组左、右 CA 对 ET-1 收缩反应增强，反应最大值（E_{max}）增强，高镁可抑制 ET-1 引起 CON 组和 CH 组左、右 CA 的收缩反应，E_{max}降低；（3）CH 组 CASMCs 的 TRPC3、TRPC4 的 mRNA 和蛋白表达增加；（4）正常镁时，CH 组左、右 CA 对 CPA、OAG 收缩反应增强，高镁可抑制由 CPA、OAG 引起 CON 组和 CH 组左、右 CA 的收缩反应；（5）正常镁时，CH 组 CASMCs 增殖、迁移能力显著增强，高镁可减缓 CON 组和 CH 组 CASMCs 的增殖及迁移。

结论：慢性低氧促进 CA 重构，以及 TRPC3/TRPC4 表达上调所介导的 CA 对 ET-1 的高反应，高镁可衰减 PH 大鼠 CA 重构和对 ET-1 的高反应性。

关键词：肺动脉高压；冠状动脉；TRPCs；高镁；血管重构

P7-3 OGG1 通过 miR-145/KLF4 通路影响肺纤维化的机制研究

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目的：肺与外界环境相通的结构特点使其易受内外源性的氧化刺激，与肺纤维化（PF）的发生密切相关。多数研究氧化刺激下，蛋白质或脂类代谢异常对纤维化的调控，而氧化修饰的 DNA 调控 PF 的机制尚不清楚。DNA 氧化产物 8-羟基鸟嘌呤（8-oxoG）具有致突变性，由 8-羟基鸟嘌呤核糖水解酶 1（OGG1）启动碱基切除修复(BER)途径去除。课题组前期利用 OGG1 敲除小鼠建立博莱霉素(BLM)诱导的 PF 模型，发现敲除 OGG1 可以缓解 PF。除此之外，OGG1 还是氧化应激下的转录调节酶。在 PF 病理过程中，miRNAs 表达失调。我们推测 OGG1 可能通过调节 miRNA 表达影响 PF。我们运用 GEO 数据库及 qPCR 筛选出 OGG1 调控的差异基因 miR-145，通过 TargetScan 和 miRanda 筛选出 miR-145 靶向 KLF4，但 OGG1 是否通过调控 miR-145/KLF4 通路影响 PF 需进一步研究。

方法：8 周龄雄性 C57BL/6 小鼠随机分四组,每组 6 只：对照组 WT 和 $OGG1^{-/-}$小鼠气管注射 NaCl;实验组 WT 和 $OGG1^{-/-}$小鼠气管注射 BLM，第 21 天取材，免疫荧光、WB、qPCR 检测 KLF4、ZO-1、E-caherin、spc、colI 及 miR-145 的表达。转染 OGG1-siRNA 沉默 MLE-12 中 OGG1 表达，用 BLM 刺激 24h，检测 KLF4、ZO-1、E-caherin、spc 与 miR-145 的表达。MLE-12 瞬转 miR-145 mimic/inhibitor，48h 后观察 KLL4 表达。MLE-12 细胞转染 KLF4-siRNA，BLM 刺激 24h 后观察 ZO-1、E-caherin 等表达。MLE-12 转染 FLAG-OGG1 48 小时后用 BLM 刺激，利用 FLAG 抗体富集得到与 OGG1 结合的 DNA 片段，并设计 miR-145 启动子区引物进行 CHIP 实验。

结果： BLM 刺激后，小鼠肺组织炎症细胞浸润，细胞外基质沉积；OGG1 敲除可减轻 PF 表现。qPCR 显示，小鼠气管注射 BLM 后，miR-145 表达降低，OGG1 敲除可增加其表达。免疫荧光结果发现，KLF4 与 spc 共定位于上皮区域，纤维化区未见表达，选用 MLE-12 细胞进行后续研究。MLE-12 经 BLM 刺激后，KLF4 表达明显增加，OGG1 沉默后 KLF4 表达降低。miR-145 表达在 OGG1 沉默后明显增加，BLM 刺激后降低，在 OGG1 沉默 BLM 组表达回升。瞬转 miR-145mimic 后，MLE-12 中 KLF4 表达明显抑制，加入 inhibitor 后恢复。MLE-12 转染 KLF4-siRNA 并给予 BLM 刺激，发现 KLF4 沉默减轻 BLM 刺激后上皮细胞的破坏。CHIP 结果：miR-145 启动子区含有 OGG1 的结合位点，BLM 刺激后，OGG1 与其结合增加。

结论：OGG1 的敲除可以减轻小鼠 PF 并增加 miR-145 表达，进一步抑制 KLF4。OGG1/miR-145/KLF4 通路可能参与 PF 发生发展。

P7-4 Preliminary observation of eugenol effects on urethane-induced lung cancer model mice

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Objective: To investigate the effects of eugenol on the lung cancer model mice induced by urethane. **Method:** Forty-five female Kunming mice were randomly divided into modeling group (*n*=30) and control group (*n*=15). The modeling group was given intraperitoneal injection of 800mg/kg urethane for 5 consecutive weeks to prepare the lung cancer model mice. Thirty mice after modeling were randomly divided into model group and eugenol group (*n*=15). Eugenol (100mg/kg, qd) was administered in the eugenol group mice by gavage for 3 consecutive weeks. The body weight, food intake, and water intake of mice were measured every week, and open field teat at the end of modeling and drug administration was conducted to detect behavioral changes such as autonomous activity in mice. Then the mice were sacrificed, and the lung tissue was taken to calculate lung index, and observe histopathological changes after sections and HE staining. **Result:** (1) During the modeling period, compared with the control group, the modeling group mice lost body weight, and decreased their weekly food and water intake ($P<0.05$). In the open field test, the autonomous activity number and the crossed number of the central area of the model group mice was less than that of the control group ($P<0.05$). (2) During the administration of eugenol, the body weight, food intake, and water intake of the eugenol group mice showed an increasing trend compared to the model group. After the administration, the open field test showed an increasing trend of autonomous activity number in eugenol group mice compared to the model group, and the similar crossed number of the central area like that of the control group. (3) The pulmonary index of model group mice was higher than that of control group ($P<0.05$), while that of the eugenol group mice was lower than that of the model group ($P<0.05$). (4) The incidence of lung adenocarcinoma in the model group was 37.5%, while that in the eugenol group was 14.3%. The lung tissue morphology in the control group was normal, but the lung tissue cells of the model group mice showed densely proliferation, and the adenocarcinoma cells arranged in a disordered manner with glandular tubes or solid nests, deeply stained nuclei and pathological nuclear division. Compared with the model group, the lung tissue structure of the eugenol group mice was basically

clear, with fewer glandular tubular adenocarcinoma cells and fewer pathological mitotic phenomena. **Conclusion:** Eugenol may have certain inhibitory effects on the lung cancer model mice induced by urethane.

Keywords: Eugenol; Lung cancer; Behavioral measurement; Histopathology

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P7-5 BAX 激动剂 BTSA1 抗肺纤维化的保护作用及机制研究

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目的 肺纤维化（pulmonary fibrosis，PF）是一种进行性、与年龄相关的间质性肺部疾病，其诊断中位年龄为 66 岁，生存期仅为 3-4 年，目前并无有效的治疗策略。BAX 是一种促凋亡蛋白，其与 BCL-2 家族中的抗凋亡蛋白的相互作用对调控细胞凋亡具有重要作用。研究报道，特发性肺纤维化病人肺组织中存在衰老肌成纤维细胞；而肌成纤维细胞的凋亡抵抗现象是纤维化疾病发生发展的重要机制。基于此，我们采用 BAX 激动剂 BTSA1 直接活化 BAX，进而促进衰老肌成纤维细胞的凋亡，有望为治疗肺纤维化提供新的治疗策略。

材料与方法：在体内水平，采用 8 周龄和 20 月龄小鼠，气管注射 BLM 或口咽滴注 BLM 分别构建消退型及非消退型肺纤维化模型，探讨在肺纤维化组织中衰老肌成纤维细胞的凋亡抵抗特性发生的机制，造模后第 10 天腹腔注射 BAX 激动剂 BTSA1，检测衰老肌成纤维细胞数量并观察其对肺纤维化的影响。体外水平，采用 X 射线辐照和 H_2O_2 构建衰老肌成纤维细胞模型，外源性给予 BAX 激动剂 BTSA1，检测成纤维细胞活化情况以及衰老肌成纤维细胞衰老相关的分泌表型（senescence-associated secretory phenotype, SASP）相关因子分泌情况，检测 BAX 活化情况，检测衰老肌成纤维细胞凋亡情况，探索 BAX 影响肺纤维化发生发展的潜在调控机制。

结果：BLM 诱导的肺纤维化小鼠肺组织中存在衰老肌成纤维细胞，且其数量与肺纤维化严重程度呈正相关，且衰老肌成纤维细胞中存在 BAX 与 BCL-XL 的高表达，BTSA1 可减少肺内衰老肌成纤维细胞数量并减轻肺纤维化。在体外，BTSA1 可通过活化 BAX 显著减少 SASP 相关因子分泌，促进衰老肌成纤维细胞凋亡，清除衰老肌成纤维细胞。

结论：BTSA1 直接活化 BAX 促进衰老肌成纤维细胞凋亡，从而减轻肺纤维化。

关键词：衰老肌成纤维细胞，BAX，BTSA1，肺纤维化

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P7-6 Tregs 通过 NLRC3 抑制左心疾病相关性肺动脉高压的内皮间质转化

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目的：调节性 T 细胞（Tregs）是肺动脉血管重构的关键调节因素之一。然而，Tregs 是否调节肺静脉内皮细胞稳态以及在左心疾病相关性肺动脉高压（PH-LHD）中的作用及机制尚不清楚。因此，本研究旨在揭示 Treg 通过 NLRC3 调控 PH-LHD 血管重构的具体分子机制，为今后 PH-LHD 的治疗提供新的依据和靶点。

方法：采用主动脉缩窄术(TAC)进行压力负荷构建左心疾病相关性肺动脉高压（PH-LHD）的动物模型，右心导管和心超检测肺动脉压力和右心室压力等血流动力学变化。流式细胞术和免疫荧光实验检测小鼠外周血和肺脏中 Treg 细胞募集情况和分布。谱系示踪荧光小鼠（$CDH5Cre^{+/-}$-$mT/mG^{+/-}$）以及 Treg 细胞与原代肺血管内皮细胞共培养揭示 Treg 细胞对内皮间质转化的作用。NLR 家族在 TAC 小鼠 Tregs 细胞中的基因谱筛选 Treg 中作用于 PH-LHD 的关键基因 NLRC3。通过免疫重建和 NLRC3 敲除的谱系示踪（$CDH5Cre^{+/-}$-$mT/mG^{+/-}NLRC3^{-/-}$）小鼠验证 Treg 中 NLRC3 对 PH-LHD 的内皮间质转化的调控作用。高通量测序、分泌因子测定、Treg 细胞和效应 T 细胞共培养以及 Treg 细胞和内皮细胞共培养等技术用来揭示分子机制。

结果：左心疾病相关性肺动脉高压的肺血管周出现显著的 Treg 细胞募集增多，外周血中 Treg 细胞数量显著下调。进一步发现 Treg 募集的肺血管发生内皮间质转化，并明确 Treg 调控肺静脉内皮间质转化的作用。接着，我们筛选出 Treg 中调控 PH-LHD 的重要基因模式识别受体 NLRC3，NLRC3 基因缺失的 Treg 对内皮间质转化的抑制作用显著减弱。机制上，NLRC3 缺失显著抑制 Treg 细胞的增殖招募、免疫抑制作用以及细胞因子白介素 18（IL-18）的分泌。Treg 通过 NLRC3 调节 IL-18 的分泌影响内皮细胞中受体络氨酸激酶信号通路，继而调控内皮细胞的损伤和内皮间质转化，最终影响 PH-LHD 的肺血管重构。

结论：Tregs 中模式识别受体 NLRC3 缺失抑制 Treg 的增殖招募、免疫抑制作用以及促进 IL-18 的分泌增多，导致肺静脉、动脉内皮间质转化，最终加重肺血管重构和右心功能。

关键词：肺动脉高压；调节性 T 细胞；左心疾病；NLRC3

P7-7 组蛋白甲基转移酶 SETDB1 通过 NUAK1 调控肺动脉平滑肌细胞糖代谢重编程

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肺动脉高压（Pulmonary arterial hypertension，PAH）是一种恶性程度高、死亡率高的心

肺血管疾病，其特征是复杂的肺血管重构和肺血管阻力增加，继发右心室肥厚，导致右心衰竭甚至死亡。在肺动脉高压（PAH）进程中，肺动脉平滑肌细胞（PASMCs）被报道发生代谢重编程，并加速细胞增殖，但机制不祥。组蛋白甲基转移酶（histone methyltransferases, HMTs）是一种重要的表观遗传调控分子，因其在疾病中经常发生功能失调，且酶活性调控可用于治疗而受到广泛关注。本研究发现原发性 PAH 患者肺动脉平滑肌细胞（Pulmonary arterial smooth muscle cells, PASMCs）组蛋白甲基转移酶 SETDB1 表达水平降低，H3K9 三甲基化（H3K9me3）水平降低；正常人 PASMCs 和小鼠 PASMCs，缺氧处理 24 小时，检测正常组和缺氧处理组 SETDB1 蛋白表达水平和 H3K9 三甲基化水平，结果表明缺氧可导致 SETDB1 蛋白表达水平和 H3K9 三甲基化水平降低；对正常和 SuHx-PAH 模型小鼠肺组织进行了靶向定量代谢组检测，与正常组相比，SuHx-PAH 模型小鼠肺组织代谢产物有明显差异；利用 GEO 数据库 GEO accession：GSE144274 中 4 例正常人和 4 例原发性 PAH 患者 PASMCs 的 RNA-seq 结果，筛选并分析了糖酵解途径催化酶。结果显示，相比正常人 PASMCs，原发性 PAH 患者 PASMCs 糖酵解途径限速酶己糖激酶 1（HK1）、磷酸果糖激酶（PFKM）、丙酮酸激酶（PKM）均升高；在敲减 SETDB1 的人和小鼠 PASMCs 较正常 PASMCs，糖酵解速率的几个关键点，包括葡萄糖转运体 1（GULT1）、HK1、糖酵解关键酶 PFKFB3 的表达以及乳酸的分泌增加；对敲低 SETDB1 的正常人 PASMCs 进行蛋白质组和转录组检测，经蛋白质组和转录组关联分析发现，包括 AMPK 相关激酶家族 NUAK1 在内的 4 个靶点的蛋白和 mRNA 表达上调；在人和小鼠 PASMCs 敲减 SETDB1，NUAK1 蛋白和 mRNA 表达均上调。上述结果提示 SETDB1 可能通过 NUAK1 导致 PASMCs 发生糖代谢重编程。

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P7-8 吡格列酮对 PM2.5 暴露致慢性咳嗽豚鼠的神经源性慢性气道炎症的影响及其机制

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目的：探究过氧化物酶体增殖物激活受体 γ(PPARγ)激动剂对 PM2.5 暴露所致豚鼠慢性咳嗽神经病理作用的影响。**材料和方法：**1.将实验豚鼠随机分为空白组（A 组）、模型组（M 组）、吡格列酮组（P 组）和 PPARγ 拮抗剂组（T 组）进行实验造模。1-28 天，给予 M、P、T 组气管滴注雾霾悬浊液(2.5mg/kg, 0.1g/ml)，1 天 2 次。第 22-28 天，P 组腹腔注射 0.4%吡格列酮[10mg／(kg d)]，T 组腹腔注射 0.06%T0070907[1.5mg／(kg d)]，A 组、M 组均腹腔注

射相同容积 0.5%DMSO 的 PBS，每天 1 次。2.造模结束后用 4%柠檬酸雾化引咳，RM6240C 型生物信号采集处理系统记录咳嗽潜伏期，观察咳嗽敏感性。3.取肺泡灌洗液进行白细胞计数。4.用柠檬酸雾化 5-10min 诱发咳嗽，实验结束后，用免疫组织化学方法观察肺组织神经源性炎性介质 P 物质表达。5.免疫荧光法观察各组豚鼠脑组织 Iba-1/iNOS、Iba-1/Arg-1 表达。6.Western blot 法检测脑组织内 Arg-1、iNOS、PPAR-γ、NF-κB p65 表达。**结果：**1.与 A 组比较，M 组、T 组豚鼠可见咳嗽咳痰。2.M 组（（13±4.28）s）、T 组（（15.04±2.31）s）咳嗽潜伏期较 A 组（（64.51±5.27）s）缩短，咳嗽敏感性升高，P 组（（124.50±6.34）s）咳嗽潜伏期延长，咳嗽敏感性降低（均 P<0.05）。3.与 A 组比较，M 组、T 组肺泡灌洗液白细胞总数与巨噬细胞比例较 A 组上升，气道炎症细胞浸润增加；P 组气道炎症细胞浸润减少。4.M 组肺组织神经源性炎性介质 P 物质表达较 A 组升高，P 组肺组织 P 物质表达较 M 组下降。5.免疫荧光：M 组较 A 组 $iNOS^+$ $Iba\text{-}1^+$细胞数量增加，$Arg\text{-}1^+$ $Iba\text{-}1^+$细胞数量减少；P 组较 M 组 $iNOS^+$ $Iba\text{-}1^+$细胞数量降低，$Arg\text{-}1^+$ $Iba\text{-}1^+$细胞数量增加。6.Western blot 法检测：M 组 iNOS、NF-kB p65 表达较 A 组增高，Arg-1 表达降低；T 组 PPAR-γ 表达低于 M 组、P 组；与 M 组相比，P 组 Arg-1、PPAR-γ 表达显著增高，iNOS、NF-κB p65 表达降低（均 P<0.05）。**结论：**1. M 组豚鼠有慢性气道炎症的外周和中枢表现，表明慢性咳嗽模型造模成功。2.吡格列酮能促进小胶质细胞 M2 极化，减轻 PM2.5 暴露所致豚鼠神经源性慢性气道炎症和慢性咳嗽。3.吡格列酮可能是通过激活 PPAR-γ/NF-κB 通路，抑制气道神经源性炎症，减轻慢性咳嗽症状。

关键词：慢性咳嗽，神经源性慢性气道炎症，PM2.5

P7-9 细菌溶解产物 OM-85 对早期肺腺癌免疫微环境的调控机制研究

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目的 临床上早期肺癌多以肺结节的形式表现，中国肺结节发病率约 10%-20%，其中发生恶性病变的几率约 5%。OM-85 Broncho-Vaxom (BV)是一种细菌溶解产物，已被证明具有免疫调节作用，本研究为探讨 OM-85 对早期肺腺癌的免疫调节作用及可能机制，进而提供一种有效的早期治疗策略。

方法 我们建立了与人临床早期肺腺癌拟合度较高的基因工程小鼠 KT 模型（$Kras^{LSL\text{-}G12D}$ $Tgfbr2^{loxp/loxp}$）以及与人良性肺结节拟合的基因小鼠 K 模型（$Kras^{LSL\text{-}G12D}$）。6-8 周龄小鼠 48 只，随机分为 4 组。a 组，良性结节对照组；b 组，良性结节治疗组；c 组，早期肺腺癌对照组；d 组，早期肺腺癌治疗组；对照组予以 PBS 缓冲液。自 5 周从 MicroCT 上可观察到肺结节出现开始用药，通过动态观察小鼠肿瘤生长情况，组织病理、流式细胞中免疫细胞的分布情况，利用单细胞测序（scRNA-seq）和空间转录组技术进行肿瘤微环境分析。同时收集临床列队中 OM-85 治疗组、抗生素组和对照组样本，肿瘤免疫微环境标志物，包括 CD8、CD56、CD16、CD68、HLA-DR、CD3 和颗粒酶 B 等，使用多重免疫荧光（multiple Immunofluorescence, mIF）测定进行评估，通过比较这些标志物及其组合来分析肿瘤细胞与不同免疫细胞之间的空间关系。

结果 OM-85 BV 治疗组的肿瘤生长和免疫细胞及因子水平与良性结节对照组相似，但激活的免疫细胞高于早期肺腺癌对照组，OM-85 BV 可能通过调节 T 细胞、NK 细胞和巨噬细胞的数量和活性来抑制早期肺腺癌的进展。

结论 总之，OM-85 BV 是一种低成本的替代候选药物，可以通过简单的给药来抑制早期肺腺癌的进展。

关键词：早期肺腺癌；细菌溶解产物；免疫微环境；NK 细胞；巨噬细胞

P7-10 探究 P2Y12 受体在 PM2.5 暴露致慢性咳嗽豚鼠小胶质细胞极化的作用

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目的：探究通过使用米诺环素抑制 P2Y12 受体，影响 Ras 同源基因家族成员 A(RhoA)/Rock2 及 p38 丝裂原活化蛋白激酶（p38MAPK）信号通路表达，从而调控 PM2.5 染毒致慢性咳嗽豚鼠小胶质细胞极化变化的机制。

方法：利用颗粒物采样器 TH-150C 采集环境 PM2.5，制备 PM2.5 悬浮液（0.1g/ml）。将健康雄性 Hartley 白化豚鼠随机分为生理盐水对照组、PM2.5 暴露模型组、PM2.5 暴露+米诺环素干预组，每组 8 只。生理盐水对照组鼻滴生理盐水，PM2.5 暴露组鼻滴 PM2.5 悬浊液（0.1g/ml），200μL/次/只，bid，共 28d，米诺环素干预组自造模第 7 天后给予腹腔注射米诺环素（20mg/kg， 0.9% 盐水)，bid，共 14d。用 RM6240E 型生物信号处理系统检测豚鼠咳嗽敏感性；取肺泡灌洗液（BALF）、气道 HE 染色观察气道内炎性细胞的浸润；免疫组化法、Western Blot 检测各组豚鼠气道与肺内神经源性炎症介质 P 物质（SP）及咳嗽反射中枢面神经核（P7）、三叉神经脊束核（Sp5）及咳嗽高级调控中枢前额叶（PF）内 P2Y12R、RhoA、Rock2、p38MAPK 的表达；免疫荧光法、Western Blot 检测各组豚鼠上述延髓小胶

质细胞极化情况：小胶质细胞标志物（Iba-1）/ iNOS 阳性细胞（M1 促炎型小胶质细胞）、Iba-1/精氨酸酶-1(Arg-1)阳性细胞（抗炎型小胶质细胞）的表达。

结果：PM2.5 暴露组与空白对照组相比，咳嗽潜伏期缩短（p<0.05），3min 和 5min 内咳嗽次数增加（p<0.05），咳嗽潜伏期缩短，表明咳嗽敏感性明显增高；BALF 中白细胞总数增多且淋巴细胞比例增高（P<0.05），气道与肺内 SP 表达增加（P<0.01），表明产生外周气道炎症，PM2.5 暴露致慢性咳嗽模型构建成功。PM2.5 暴露组豚鼠脑内 P7、Sp5 与 PF 处 P2Y12R、RhoA、Rock2、p38MAPK 表达上调（p<0.01），Iba-1/iNOS 阳性细胞的表达上调（p<0.01），Iba-1/ Arg-1 阳性细胞的表达下调（p<0.01）。与 PM2.5 暴露组比较，米诺环素干预组豚鼠 3min 和 5min 内咳嗽次数减少，咳嗽潜伏期延长，BALF 中白细胞总数减少且淋巴细胞比例减少（P<0.05），气道与肺内 SP 表达降低，上述脑区内 P2Y12R、RhoA、Rock2、p38MAPK 的表达也有所降低（p<0.01），Iba-1/ iNOS 阳性细胞的表达下降（p<0.01），Iba-1/ Arg-1 阳性细胞的上升（p<0.01）。这表明米诺环素可抑制咳嗽反射中枢及咳嗽高级调控中枢内小胶质细胞 P2Y12R 表达，使小胶质细胞从 M1 型转向 M2 型，从而抑制 RhoA/Rock2 及 p38MAPK 表达调控慢性咳嗽豚鼠的中枢致敏。

结论：咳嗽反射中枢与咳嗽高级调控中枢内小胶质细胞向 M1 型极化参与 PM2.5 暴露所致的慢性咳嗽，其发病机制与豚鼠脑内的气道的神经炎症活动有关；而米诺环素可通过抑制 P2Y12R 表达，使小胶质细胞从 M1 型转向 M2 型，阻断 RhoA/Rock2 及 p38MAPK 信号通路使慢性咳嗽豚鼠使中枢致敏缓解；气道炎症减轻；咳嗽敏感性降低。

P7-11 Circ-calm4 通过调控 COMP 介导肺动脉平滑肌铁死亡

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背景及目的：肺动脉高压一种是严重威胁人类健康的肺血管疾病。血管重构是肺动脉高压的主要病理改变，血管平滑肌表型转化在肺血管重构中发挥重要作用。铁死亡是新近发现的新的细胞死亡表型，有研究发现铁死亡参与肺动脉高压过程，但机制尚未阐明。非编码 RNA 参与铁死亡调控和肺动脉高压的多种病理过程。本研究旨在探讨细胞核内的 circRNA —— circ-calm4 调控肺动脉平滑肌细胞铁死亡的作用和分子机制，为肺动脉高压提供新的诊断和治疗靶点。

方法：通过 western blot、免疫荧光、MDA、iron assay 检测，明确 circ-calm4 在肺动脉平滑肌细胞铁死亡中的作用；构建肺动脉高压小鼠模型，鼻饲法滴入 AAV9-sh-circ-calm4 病毒，通过心动超声以及血流动力学指标检测，明确 circ-calm4 在肺动脉高压中的作用；提取肺组织，通过 western blot、免疫荧光、MDA、iron assay 等检测、应用生物信息学分析，阐明 circ-calm4 通过调控 COMP 介导肺动脉平滑肌铁死亡；应用生物信息学分析，通过 Dot

blot、DRIP 等实验，阐明 circ-calm4 通过与 COMP 基因启动子形成 R-loop 调控 COMP 表达的分子机制；构建 circ-calm4 ASO，通过 western blot、免疫荧光、MDA、iron assay 等检测，明确 circ-calm4 与 COMP 启动子形成的 R-loop 在肺动脉平滑肌铁死亡中的作用。

结果：（1）circ-calm4 介导缺氧诱导的肺动脉平滑肌细胞铁死亡；（2）circ-calm4 负性调控 COMP 表达；（3）COMP 是调控肺动脉平滑肌铁死亡的关键分子；（4）缺氧条件下，circ-calm4/COMP 通路调控肺动脉平滑肌细胞铁死亡；（5）circ-calm4 通过与 COMP 基因启动子形成 R-loop 调控 COMP 表达。

结论：本研究明确了 circ-calm4 通过 COMP 调控缺氧诱导肺动脉平滑肌铁死亡；circ-calm4 与 COMP 启动子形成 R-loop 调控 COMP 表达介导肺动脉平滑肌铁死亡，参与肺动脉高压病理过程。

关键词：肺动脉平滑肌细胞；铁死亡；circ-calm4；R-loop；肺动脉高压。

P7-12 1,25(OH)$_2$D$_3$ inhibits Lewis lung cancer cells migration via NHE1-sensitive metabolic reprograming

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High prevalence and metastasis rates are characteristic of lung cancer. The glycolysis provides energy for the development and metastasis of cancer cells. The 1,25-dihydroxy vitamin D3 (1,25(OH)$_2$D$_3$) has been linked to reducing cancer risk and regulates various physiological functions. We hypothesized that 1,25(OH)$_2$D$_3$ could be associated with the expression and activity of NHE1 of Lewis lung cancer cells, thus regulating glycolysis as well as migration by actin reorganization. Followed by online public data analysis, VDR, the receptor of 1,25(OH)$_2$D$_3$ has been proved to be abundant in lung cancers. We demonstrated that 1,25(OH)$_2$D$_3$ treatment suppressed transcript levels, protein levels, and activity of NHE1 in LLC cells. Furthermore, 1,25(OH)$_2$D$_3$ treatment resets the metabolic balance between glycolysis and OXPHOS, mainly including reducing glycolytic enzymes expression and lactate production. In vivo experiments showed the inhibition effects on tumor growth as well. Therefore, we concluded that 1,25(OH)$_2$D$_3$ could amend the NHE1 function which leads to metabolic reprogramming and cytoskeleton reconstruction, finally inhibits the cell migration.

Keywords: Lewis lung cancer cells, 1,25$(OH)_2D_3$, NHE1, glycolysis, migration

P7-13 TGM2 通过影响内皮功能参与主动脉夹层发生发展的机制研究

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目的：主动脉夹层（aortic dissection）是指主动脉内膜撕裂后，腔内的血液通过内膜破口进入动脉壁中层形成夹层血肿，并沿血管长轴方向扩展，形成动脉真、假腔病理改变的严重主动脉疾病。内皮细胞（endothelial cells，ECs）是心血管系统中与血液最直接接触的细胞，是调节循环稳态的关键细胞。越来越多的研究证据表明，内皮功能失调（endothelial dysfunction，ED）是多种心血管系统疾病形成的早期病理事件，而 ED 在主动脉夹层的发生发展中的分子机制尚不清楚，且研究较少。谷氨酰胺转移酶 2 (transglutaminase 2，TGM2) 参与细胞凋亡与细胞黏附，对内皮功能有潜在影响。本研究从 ECs 着手，深入研究 TGM2 参与主动脉夹层的发病机制，为主动脉夹层的预防及治疗提供新策略。

方法：收集主动脉夹层患者和正常组织进行高通量蛋白组学测序和单细胞测序，筛选与 ED 相关因子。从临床样本，主动脉夹层动物模型构建，离体细胞实验三个方面进行研究，通过蛋白质印迹法、免疫组化法、免疫荧光、实时荧光定量 PCR 等检测相关分子。通过苏木精-伊红染色、弹性纤维染色法、Masson 三色染色法、透射电镜等观察主动脉壁和内膜层结构和形态。

结果：在人组织夹层样本，观察到内膜层的 ECs 数量明显减少，且内皮结构紊乱，以及 TGM2 在主动脉夹层样本高表达。在离体细胞实验、人主动脉内皮细胞的主动脉夹层模型中 TGM2 显著升高，且 NF-κB 信号通路激活，能够降解弹力纤维的基质金属蛋白酶 2、基质金属蛋白酶 9 显著升高，炎症相关黏附分子血管细胞黏附分子-1 显著升高，ECs 间连接分子 VE-钙黏蛋白的显著下调、表明 ECs 之间的连接遭到破坏，这些因子表达的改变共同体现了内皮功能的失调。而对 TGM2 的敲低则减轻了这些变化。

结论：ED 与主动脉夹层密切相关，TGM2 通过 NF-κB 信号通路促进 ED，从而参与主动脉夹层的发生发展。TGM2 很有可能成为预防或治疗靶点。内皮功能相关的靶点很有可能为预防、诊断和治疗主动脉夹层提供新策略。

关键词：主动脉夹层；内皮功能失调；谷氨酰胺转移酶；炎症；黏附因子

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P7-14 HMGA1 调控成纤维细胞炎症促进主动脉夹层的发生

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主动脉夹层（Aortic dissection，AD）是一种高致死的心血管疾病，通常认为发病基础是主动脉壁中层结构的异常，当中层平滑肌细胞发生退变、弹性纤维减少和发生囊性坏死时，中层结构受到破坏，其顺应性降低，从而减弱了主动脉壁对血流切应力的抵抗力，易发生夹层。目前对夹层的研究主要集中在中膜的相关结构改变以及相关调控机制上，但近些年来，有研究发现主动脉外膜对主动脉夹层的发生、发展起着重要的作用。主动脉外膜是位于主动脉最外层的组成结构，主要包括外弹力层、滋养血管及周围疏松结缔组织（含成纤维细胞和组织巨噬细胞）。在血管损伤后炎症反应最早是起源于血管外膜，而其主要成分成纤维细胞分泌多种促炎性因子如 IL-6、单核细胞趋化因子，高迁移率族蛋白 A1 (HMGA1)参与介导许多炎症通路，前期研究结果显示在主动脉患者的外膜中表达明显升高。

目的：探索主动脉外膜炎症对主动脉夹层的影响，高迁移率族蛋白 A1 (HMGA1)调控成纤维细胞炎症对主动脉夹层疾病进展的影响和潜在的作用机制。

方法：本研究主要涉及临床样本、细胞和动物模型三个层面。1.在临床样本的检测当中研究标本取自经手术证实的胸主动脉夹层分离患者主动脉壁，通过免疫组化（IHC）、免疫荧光（IF）、Real-time PCR、Western Blot 等技术分析 HMGA1 主动脉外膜中表达的差异。2.构建了 HMGA1 过表达和沉默载体,通过 Western blot 实验检测成纤维细胞炎症相蛋白水平,明确 HMGA1 对成纤维细胞炎症的影响。通过细胞划痕实验和 Transwell 实验进一步验证 HMGA1 对成纤维细胞增值和迁移的影响。3.通过 Ang II 诱导的主动脉夹层大鼠模型证实,HMGA1 调控成纤维细胞炎症促进了胸主动脉夹层的进展。

关键字：HMGA1；成纤维细胞；炎症；主动脉夹层

P7-15 FOSL1 介导血管外膜病变促进主动脉夹层发生的机制研究

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主动脉夹层（Aortic dissection, AD）的发生发展具有原因多、机制复杂、进展快、死亡

率高等特点，已经成为损害我国居民健康安全的常见疾病。有研究表明，AD 的发病方式可能为外膜滋养血管破裂，血管内的血液溢入中膜，导致夹层的发生。目前，AD 的病因和机制研究已经取得了一些成果，但其具体发病机制尚无定论。主动脉壁由高度动态的细胞群和细胞外基质（Extracellular matrix, ECM）组成，它们执行复杂的生物力学功能，以提供适当的顺应性和足够的强度来响应血流动力学变化。一些报道提出，主动脉外膜成纤维细胞是细胞外基质分泌的主要细胞，病理条件下易分泌过多的胶原蛋白引起血管纤维化，从而导致 AD 的发生。

目的：观察 FOSL1 在 AD 患者、AD 动物模型和 AD 细胞模型中的改变对主动脉血管外膜胶原沉积的影响，并探讨其分子机制，以更好的阐述 AD 的发病机制。进一步了解 FOSL1 通过主动脉外膜成纤维细胞对 ECM 的调节作用，探讨其诱导血管重构的分子机制，寻找可能的 AD 潜在治疗靶点。

方法：（1）收集主动脉组织样本，AD 组取自经手术证实的胸主动脉夹层患者主动脉壁，正常对照组主动脉组织取自未患有主动脉及血管相关疾病的捐献者主动脉壁，进行临床标本组织测序；（2）收集 AD 患者和正常组织主动脉样本进行临床样本 HE 染色、Masson 染色，免疫组化染色等；（3）使用 3 周龄雄性 SD 大鼠 BAPN 联合 Ang II 给药进行动物模型的构建；（4）用 Ang Ⅱ给药处理大鼠主动脉外膜离体成纤维细胞，建立 AD 细胞模型。

结果：（1）临床标本组织测序结果表明 FOSL1 在 AD 患者主动脉外膜成纤维细胞中明显升高；（2）临床样本 Masson 染色结果显示 AD 患者主动脉外膜中胶原沉积明显增加，免疫组化染色结果表明与正常组相比，AD 组外膜中 FOSL1 表达明显升高；（3）免疫组化染色结果表明 BAPN 联合 Ang II 建立的大鼠模型主动脉外膜组织中，FOSL1 表达明显升高；（4）细胞模型中，Western Blot、细胞荧光染色等结果表示 FOSL1 通过 TGF-β1 促进成纤维细胞表型转化(α-SMA 表达升高)和胶原沉积(COL1A1、COL3A1、MMP9、MMP2 表达升高)。

结论：FOSL1 诱导血管重构，通过 TGF-β1 介导外膜胶原沉积促进 AD 的发生和发展，揭示了 FOSL1 通过主动脉外膜成纤维细胞对 ECM 的调节作用，使 FOSL1 很有可能成为 AD 的潜在治疗靶点。

关键词： 主动脉夹层； 细胞外基质； 成纤维细胞； FOSL1；

P7-16 HMGA1 调控 Wnt/β-Catenin 信号在肺动脉高压大鼠内皮间质转化中的作用

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目的：内皮间质转化（Endothelial to mesenchymal transition, EndoMT）是内皮细胞失去细胞间的紧密连接而获得间充质细胞的迁移能力，使它们到达周围组织，进而导致血管腔阻塞，血管内压力增高，引起肺动脉高压（pulmonary arterial hypertension, PAH）。EndoMT

在 PAH 的发展进程中起关键作用。本研究探讨在 PAH 发生过程，HMGA1 是否调控 Wnt/β-Catenin 信号通路参与 EndoMT 参与 PAH 肺微血管内皮细胞（Pulmonary microvascular endothelial cells, PMVECs） EndoMT 的发生。

方法：①构建 PAH 大鼠模型，利用免疫组化、western blot、细胞划痕、Transwell 迁移实验检测 PAH 大鼠 PMVECs 中存在 EndoMT；②利用 western blot 检测 HMGA1、β-Catenin 及 Wnt 受体 FZD5、LGR5、FZD7 蛋白在 PAH 大鼠 PMVECs 中的表达变化；③利用 Transwell 迁移实验检测 HMGA1 对 PMVECs 迁移能力的影响；④干扰 HMGA1 及在 PMVECs 中加入 Wnt 抑制剂后验证 HMGA1 对 Wnt/β-Catenin 通路的调控作用。

结果：①PAH 肺微血管中存在 EndoMT，PAH 模型组 PMVECs 迁移能力显著增强，同时伴随内皮细胞特异性蛋白 CD31 表达下调，间充质细胞特异性蛋白 α-SMA、Vimentin 表达上调；②HMGA1、β-Catenin、FZD7、FZD5、LGR5 在 PAH 模型组 PMVECs 中表达显著升高；③干扰 HMGA1 表达，PMVECs 的迁移能力显著降低，且 α-SMA、Vimentin、β-Catenin、FZD7、FZD5、LGR5 的表达显著减少，而 CD31 的表达显著升高；④ PMVECs 加入抑制剂后进行 HMGA1 过表达，可部分逆转 EndoMT，同时伴随 β-Catenin、FZD5、LGR5 表达下调。

结论：大鼠 PMVECs 可能通过 HMGA1 表达升高，激活 Wnt/β-Catenin 信号，导致 EndoMT 参与 PAH 的发生。

关键词：肺动脉高压，内皮间质转化，HMGA1，Wnt/β-Catenin

P7-17 慢性高原缺氧及高原返回后对小鼠肺功能的影响

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中长期暴露于高原低压低氧环境会导致肺组织结构发生改变，目前的研究主要关注于慢性缺氧因肺小血管重构而导致的肺动脉高压，对于肺组织整体结构于呼吸功能的影响的研究并不多。我们课题组在前期缺氧性肺动脉高压的研究中意外发现，慢性缺氧会使大鼠的肺组织重量与大小明显增加，但高原缺氧对呼吸功能的影响尚不明确。

目的：观察慢性高原缺氧及返回平原后，小鼠肺功能指标的变化情况。

方法：以 c57 小鼠为研究对象，使用小动物低压舱建立模拟 5500 米低压缺氧五周模型，缺氧后返回地面再饲养五周。将小鼠随机分为三组，每组 13 只，对照组（CON）、低氧组（H）、低氧返回组（HR）。造模结束后，使用全身描记系统 WBP 测定小鼠的基础肺功能

指标，随后牺牲小鼠取肺组织称重。

结果：与 CON 组小鼠相比，H 组小鼠肺组织占体重的比值明显增加（0.428±0.020 vs 0.744±0.053）%，肺功能指标发生的变化主要有，呼吸频率（f）、分钟通气量(MV)、呼吸间歇收缩指数(Penh)、最大吸入流速（PIFb）、最大呼出流速（PEFb）、50%量呼气流速（EF50）、呼吸转换占比（TP）明显升高，潮气量（TV）及收缩指数(PAU)有升高趋势。吸气时间（Ti）、呼气时间(Te)、放松时间(Tr)明显降低，呼气末暂停时间(EEP)有降低趋势。

对于上述变化，在 HR 组小鼠中，肺组织重量占体重之比较 H 组明显减轻（0.566±0.037）%，但仍未恢复至对照水平。呼吸频率、潮气量、分钟通气量、最大呼出流速、呼气时间、50%量呼气流速、呼气末暂停时间、放松时间与 H 组相比明显逆转至对照水平。但呼吸间歇收缩指数、收缩指数、吸气末暂停时间较 H 组反而有进一步升高。最大吸入流速、吸气时间较 H 组没有明显恢复。

上述实验结果提示我们，缺氧五周可以使小鼠肺组织明显增重，大多数肺功能指标也发生明显变化，缺氧后恢复五周可部分逆转肺组织增重，但仍无法恢复至对照水平，部分肺功能指标可以完全恢复，部分无法恢复，甚至可能比缺氧后进一步升高。

结论： 慢性缺氧可导致小鼠肺组织增重并使肺功能发生明显变化，解除缺氧刺激后经过同样时间恢复，无法完全恢复至未缺氧的水平。

关键词：高原缺氧，脱习服，肺功能

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P8 循环生理

P8-1 Asynchronous changes of hydrogen sulfide and its generating enzymes in most tissues with the aging process

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Aging is an inevitable and irreversible biological process, which gradually increases the risks

for various disease and death. As a newly discovered endogenous gasotransmitter, hydrogen sulfide (H_2S) has been found to provide multiple beneficial effects on the regulation of aging and age-related pathologies, this study was aimed to systematically investigate the relationship and enzymatic mechanism between asynchronous aging processes and H_2S concentrations in various tissues in aging mice. The samples of plasma and thirteen tissues were collected from four cross-sectional age groups (3, 6, 12, and 18 months of age) spanning the lifespan of male C57BL/6J mice. The H_2S concentration and the activities of three H_2S-generating enzymes, i.e., cystathionine gamma-lyase (CSE), cystathionine beta-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MST) in thirteen tissues were measured by a reported liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with monobromobimane (MBB) derivatization. In addition, the expressions of CSE, CBS and 3-MST in those tissues were analyzed by western blotting. We found that the H_2S concentrations were decreased asynchronously with the aging process in plasma, heart, liver, kidney, spleen, subcutaneous fat and brown fat, and were increased in brain and lung. At least one of the three H_2S-generating enzymes expression was compensatively upregulated with the aging process in most tissues, among which the up-regulation of CSE was the most obvious while the activities of three H_2S-generating enzymes did not change significantly with the aging process in the most tissues.

Key words: Hydrogen sulfide, Aging, H_2S-generating enzymes.

P8-2 Senescence of vascular smooth muscle cells contributed pathogenesis of aortic medial calcification and regulated by α_1-adrenergic receptors in rats

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OBJECTIVE: Aortic medial calcification (AMC) is a common vascular pathology manifestation of aging and its associated diseases such as atherosclerosis, diabetes, hypertension, and end-stage renal disease. Recently, a large number of studies have found that the accumulation of senescent cells in tissues may lead to biological dysfunction and aging-related diseases. The role and the regulation of senescent vascular smooth muscle cells (VSMCs) in AMC is still not well studied. α_1-adrenergic receptor (α_1-AR) plays an important role in both cellular senescence and AMC. Therefore, we aimed to confirm the contribution of senescent VSMCs on the pathogenesis of AMC, which might be regulated by α_1-AR.

METHODS: AMC was induced by intramuscular injection of vitamin D_3 (600000 U/kg/day)

in 180-200 g male SD rats. Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and heart rate (HR) were recorded. Aortic sections were stained with alizarin red. Western blot was performed to detect the levels of relevant proteins, including the osteoblastic markers, bone morphogenetic protein-2 (BMP2) and Runt-related transcription factor-2 (RUNX2), the senescent markers, p53, p21, p16 and SA-β-gal, each isoform of α_1-AR and its downstream signaling molecule, phospholipase C beta 1 (PLC-β1).

RESULTS: Compared with the control group, SBP and PP were significantly elevated in rats with AMC. Alizarin red staining showed significant calcium salt deposition in the aortic tunica media of rats with vitamin D_3 injection. The protein levels of osteoblastic markers, BMP2 and RUNX2, senescent markers, p53, p21 and p16, α_1-AR and its downstream signaling molecule PLC-β1 were all elevated in the calcified aorta. Subcutaneous injection of D-galactose (D-gal, 500 mg/kg), the agent inducing cellular senescence, caused aortic calcium salt deposition, elevated SBP and PP, as well as increased protein levels of BMP2, RUNX2, p53, p21, p16, α_1-AR and PLC-β1. Conversely, administration of the anti-aging drug Senolytics (dasatinib 5 mg/kg and quercetin 50 mg/kg, administered continuously three times a week for 4 weeks) in rats with vitamin D_3 injection can significantly ameliorate aortic calcium deposition, SBP, PP, osteogenic phenotype and senescent phenotype. Activation of α_1-AR by intraperitoneal injection of norepinephrine (0.2 mg/kg for 4 weeks) in rats with vitamin D_3, significantly exacerbated calcium salt deposition, SBP and PP, the transformation of VSMCs from a contractile to an osteogenic phenotype, as well as upregulated the protein levels of p53, p21, p16 and SA-β-gal. In contrast, administration of prazosin (5 mg/kg for 4 weeks) blocked α_1-AR significantly improved the above indices in rats with AMC.

CONCLUSIONS: The senescence of VSMCs might play crucial role in the pathogenesis of AMC, and regulated by α_1-AR activation. Inhibition of VSMCs senescence shed new light on the prevention and treatment of AMC, and α_1-AR might be an effective targe.

Keywords: aortic medial calcification, vascular smooth muscle cells, senescence, α_1-adrenergic receptors

P8-3 Acetate attenuates microglia-mediated neuroinflammation in spontaneously hypertensive rats

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Hypertension is a common cardiovascular disease characterized by sympathetic

overactivation. The rostral ventrolateral medulla (RVLM) is an important nucleus for sympathetic neuromodulation, and its elevated excitability is closely related to enhanced sympathetic nerve activity. Microglia-mediated neuroinflammation is involved in sympathetic hyperactivation in hypertension. Acetate, one of the short-chain fatty acids metabolized by gut microbes, inhibits lipopolysaccharide-induced neuroinflammation. The aim of this study was to investigate whether acetate exerts its antihypertensive effect by inhibiting neuroinflammation in RVLM. In the present study, we found that blood acetate concentrations were significantly lower in spontaneously hypertensive rats (SHRs) than in Wistar Kyoto (WKY) rats. Addition of acetate to drinking water significantly reduces arterial blood pressure in SHRs. The magnitude of blood pressure reduction induced by intraperitoneal injection of hexamethonium bromide was significantly lower in acetate-treated SHRs than in control SHRs. Immunofluorescence results showed that the number of $cFos^+$ neurons in the RVLM was increased in SHRs compared with WKY rats and decreased in acetate-treated SHRs compared with control SHRs. The mRNA expression levels of IL-1β, IL-6 and TNF-α in the RVLM were significantly higher in SHRs than in WKY rats, while were lower in acetate-treated SHRs compared with the control SHRs. The number of $IBA1^+$ microglia in RVLM in SHRs was significantly lower than that in WKY rats, while the number of microglia in acetate-treated SHRs was significantly higher than that in control SHRs. The maximum branch length and mean branch length of microglia in SHRs were significantly shorter compared to WKY rats, and were significantly increased in acetate-treated SHRs compared to control SHRs. Sholl analysis showed that the complexity of microglia in SHRs was significantly less than that in WKY rats, and the complexity of microglial was significantly greater in acetate-treated SHRs compared with control SHRs. Our results revealed the anti-hypertensive effect of acetate may be related to the fact that acetate regulates morphology and function of microglia in RVLM, thereby inhibiting neuroinflammation in hypertension.

Keywords: Hypertension; Rostral ventrolateral medulla; Short-chain fatty acids; Microglia; Neuroinflammation

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P8-4 The role of m^6A demethylase FTO regulation of BMP4 expression in myocardial hypertrophy

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Objective: Studies indicate that N6-methyladenosine (m^6A) RNA methylation regulates mRNA stability and changes in protein expression and regulates cardiac homeostasis and various cardiovascular diseases. However, research has yet to be conducted on the function of the m^6A modification in Bone morphogenetic protein 4 (BMP4), which plays a crucial role in myocardial hypertrophy. We aimed to investigate the changes in m^6A methyltransferase expression during the dynamic development of myocardial hypertrophy, along with the involvement of fat mass and obesity-associated (FTO) in regulating BMP4 expression in myocardial hypertrophy.

Methods: Transverse aortic constriction (TAC) was carried out on C57BL/6 mice to construct a pressure overload myocardial hypertrophy model. M-mode Ultrasound testing, HE, WGA, and Masson staining techniques were applied to detect the heart structure and function two, four, and eight weeks after TAC. The expression levels of m^6A modifying enzymes and fibrosis-related symbols (COL1, COL3, and α-SMA) were determined using WB and qRT-PCR. The m^6A methylation of total RNA in cardiac tissue was identified using the EpiQuik m^6A RNA Methylation Quantification Kit. Four weeks after TAC, mice were subjected to m^6A RNA immunoprecipitation (MeRIP) sequencing and RNA sequencing to attempt to screen the dynamic map of m^6A methylation and genome expression in myocardial hypertrophy, particularly BMP4 and to investigate the impact of m^6A modification on BMP4 expression in myocardial hypertrophy. The RIP experiment detects whether there is an interaction between FTO and BMP4. After AAV9-mediated FTO overexpression plasmid injection into the tail vein of TAC mice, cardiac structure and function, m^6A modification, and BMP4 expression were examined.

Results: Compared to the sham group, mice two weeks after TAC demonstrated a trend of myocardial hypertrophy, increased left ventricular end-diastolic internal dimension (LVIDd), decreased ejection fraction (EF), and fractional shortening (FS). Mice developed myocardial hypertrophy four weeks after TAC and cardiac failure eight weeks after TAC. Further evidence via HE and Masson staining revealed that the degree of fibrosis changed dynamically with time after TAC. Compared to Sham, the FTO protein and RNA levels increased two weeks after TAC and decreased four and eight weeks after TAC, respectively. Four weeks following TAC, colorimetric quantitative analysis revealed an elevation in m^6A methylation levels. MeRIP sequencing analysis showed that 1179 peaks of m^6A modifications were upregulated and 733 peaks of m^6A modifications were downregulated. The results of the MeRIP sequencing analysis revealed a significant change in the level of m^6A methylation modification of BMP4 mRNA following myocardial hypertrophy. The MeRIP-qPCR and qRT-PCR results verify the m^6A modification and BMP4 mRNA expression levels after four weeks of TAC and are consistent with sequencing analysis. A combined MeRIP sequencing and RNA sequencing analysis indicated that hyper-methylation genes were more likely to have higher transcriptional expression. After TAC,

BMP4's protein level considerably increased at four weeks, then dropped at eight weeks. The upregulation of BMP4's two m^6A modification sites at the eight-week mark also vanished. In the development of myocardial hypertrophy in mice, m^6A modification may modulate the expression of BMP4 protein by affecting the stability of BMP4 mRNA, based on the results. The Insulin-like growth factor 2 mRNA binding protein (IGF2BP) family belongs to the m^6A binding protein, which plays a role in stabilizing by recognizing the m^6A modified site.

Moreover, we demonstrated that IGF2BP2 recognize and bind the m^6A sites of BMP4 and promotes the stability of its mRNA. RNA sequencing, GEO database, western blot, and qRT-PCR analyses indicated a significant increase in IGF2BP2 expression after myocardial hypertrophy. Verification of the RIP experiment demonstrates that the IGF2BP2 protein interacts with BMP4 mRNA in the mouse heart and that this interaction increases substantially after hypertrophy. After TAC, the overexpression of FTO, as compared to the TAC control group, the total m^6A modification level in the heart reduced, LVIDd reduced, EF increased, and the protein and mRNA expression levels of fibrosis-related symbols (COL1, COL3, and α-SMA), myocardial hypertrophy indicator BNP and BMP4 decreased significantly.

Conclusion: Myocardial hypertrophy is a dynamic process in which the methylation modification of m^6A changes as well. The demethyltransferase FTO upregulates the expression of BMP4 by regulating m^6A modification and participates in the structural remodeling and functional changes of cardiac hypertrophy. Furthermore, we demonstrated that IGF2BP2 recognizes and binds the m^6A site of BMP4 and promotes its mRNA stability.

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P8-5 Rev-erbα regulate diurnal pumping rhythm through repressing Sln transcription and protects cardiomyocytes from pressure overload injury

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Introduction: Persistent cardiac hypertrophy often progresses to maladaptive myocardial remodeling and ultimately to heart failure and sudden death. Therefore, maladaptive myocardial remodeling is considered an important therapeutic target for many cardiac diseases. Rev-erbα is a clock protein which closely associated with pressure overload-induced cardiac hypertrophy and ischemia-reperfusion injury. However, activation or repression of REV-ERBα both show beneficial effects to the heart. The related mechanism is unclear. We aimed to investigate the

molecular mechanisms by which Rev-erbα regulates cardiac remodeling and to explore preventive and curative strategies to protects cardiomyocytes using REV-ERBα agonists and antagonists.

Methods: (1) Establishment of pathological cardiac hypertrophy model: Aortic Constriction (TAC) surgery was performed on wild type mice and Rev-erbα knock out mice; (2) Mice cardiac pumping function were detected with ultrasonic technology before and after TAC surgery; (3) Quantitative Real-time PCR (qRT-PCR) and Western blot (WB) techniques were used to detect the expression of Rev-erbα and related proteins at the mRNA and protein levels; (4) Masson trichrome staining and HE staining were used to evaluate the extent of myocardial injury and fibrosis; (5) Wheat germ agglutinin (WGA) staining was used to measure the volume cardiomyocytes; (6) Immunofluorescence staining used to measure cardiomyocyte proliferation, damage and protein levels; (7) Transmission electron microscopy and confocal techniques were used to observe the extent of myocardial cell damage in mice, including structural changes in myocardial fibers and mitochondria; (8) The model of Rev-erbα knockdown and overexpress in H9C2 cell was utilized by transfection techniques; (9) Chip-seq technique to analyze the target genes regulated by Rev-erbα protein; (10) Calcium transient technique used to visualize changes in Ca^{2+} level in the sarcoplasmic reticulum of resting and angiotensin II-induced cardiomyocytes; (11) The Seahorse technique assesses cellular mitochondrial function by measuring the rate of cellular consumption of oxygen (OCR).

Results: (1) Cardiac pumping function were significantly impaired in WT+TAC group, while the pumping function of Rev-erbα KO+TAC group were not significantly decreased; (2) Compared to the WT group, the expression of Rev-erbα in the heart tissue of mice in Rev-erbα KO group was decreased at both mRNA and protein levels, whereas the expression of Rev-erbα in WT+TAC group was first decrease and then increase at both mRNA and protein levels; (3) Compared with WT group, myocardial fibers in Rev-erbα KO group were neatly arranged, with normal myocyte size and insignificant fibrosis, whereas myocardial interstitium, myocardial fiber breakage and fibrosis were significantly increased in WT+TAC group. On the contrary, myocardial fiber breakage and myocardial fibrosis were reduced in Rev-erbα KO+TAC group; (4) Cardiomyocyte injury was severe in WT+TAC group, and this severity was attenuated in KO+TAC group; (5) There was significant difference in cardiomyocyte cross-sectional area between WT and Rev-erbα KO groups, and the cardiomyocyte cross-sectional area in WT+TAC group was 1.5 times higher than that in Rev-erbα KO+TAC group; (6) Transcriptome sequencing results showed significantly elevated expression of Sarcolipin (Sln) in cardiac tissues of KO group mice; (7) Chip-seq results provide further evidence that Rev-erbα can transcriptionally inhibit the expression of Sln; (8) Inhibiting or promoting the expression of Rev-erbα can enhance or weaken the calcium transient of cardiomyocytes; (9) Inhibition of Rev-erbα expression in myocardial cell

promotes myocardial proliferation and mitochondrial fission without mitochondrial autophagy through transcriptional inhibition of Sln; (10) Promoting Rev-erbα expression in myocardial cell reduces myocardial fibrosis and promote mitochondrial fusion through transcriptional inhibition of Sln.

Conclusion: Inhibition of Rev-erbα expression in myocardial cell promotes myocardial proliferation and mitochondrial fision through transcriptional inhibition of Sln which prolong myocardial pumping function under pressure overload. Promoting Rev-erbα expression in myocardial cell reduces myocardial fibrosis and promote mitochondrial fusion through transcriptional inhibition of Sln which facilitate cardiomyocyte survival under pressure overload and protects cardiomyocytes from pressure overload injury.

Key words: Rev-erbα, Sln, myocardial hypertrophy, pumping function, mitochondrial division

P8-6 预热适应对高温所致血管内皮细胞损伤的保护作用及其机制

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目的：观察 40℃，2 h/d，持续 3 d 的预热适应对血管内皮细胞热应激的保护作用，并探讨可能的机制。

方法：选取人脐静脉内皮细胞（HUVEC）、小鼠脑微血管内皮细胞（bEnd.3）、人主动脉内皮细胞(HAEC)，随机分为非预热适应组和预热适应组。预热适应组细胞先接受 40℃，2 h/d，持续 3 d 的预热适应，然后置于 43℃高温环境中进行 2h 的热应激。非预热适应组正常培养后置于 43℃高温环境中进行 2h 的热应激。热应激后，利用 CCK8 法检测细胞活力，流式细胞术检测细胞周期及凋亡，免疫荧光检测细胞骨架，qPCR 检测 VEGF、ICAM-1、EPO 的表达，Western Blot 检测热休克蛋白 HSP70 及 HSP90 的表达。

结果：（1）热应激后，与非预热适应组细胞相比，预热适应组细胞活力明显增加，S 期细胞占比降低，细胞凋亡减少，细胞骨架皱缩减少。（2）预热适应组细胞 VEGF、ICAM-1、EPO 的表达明显增加。（3）预热适应组细胞 HSP70 及 HSP90 的表达显著升高。

结论：预热适应可以增加热应激后血管内皮细胞的活力，部分恢复血管内皮细胞的功能，且这种保护作用可能与 HSP70 及 HSP90 的表达上调有关。

关键词：热适应，血管内皮细胞，细胞凋亡，热休克蛋白

P8-7 The regulatory mechanism of transcription factor TBX20 in human congenital heart disease

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Background: Congenital Heart Disease (CHD) is a prevalent congenital malformation, with an incidence of 1% to 2% among newborns and it is responsible for the majority of non-infectious neonatal deaths. TBX20, a member of the T-box family of transcription factors, plays a crucial role in cardiac development as a transcription factor. TBX20 is considered an important candidate gene for congenital heart disease, as mutations in TBX20 are associated with CHDs, including abnormalities in atrial septum, atrial growth, and valvulogenesis. However, the precise mechanism by which TBX20 contributes to the CHD remains uncertain.

Materials and Methods: Firstly, TBX20 mutated amino acids were identified in clinical diseases through the process of DNA extraction and sequencing of blood samples obtained from patients with congenital heart disease (CHD) who were admitted to clinics. Secondly, the influence of TBX20 mutation on CHD was investigated by determination of crystal structure of TBX20. Additionally, the biochemical experiments and cellular assays were conducted to demonstrate the impact of TBX20 clinical mutations on DNA recognition and binding.

Results: The TBX20 DBD protein was purified to a purity level above 95%. Subsequently, the TBX20 DBD and dsDNA crystal were obtained at a concentration of 10 mg/ml and a temperature of 16 ℃ using hanging drop method. The purified TBX20 DBD protein was then subjected to Electrophoretic Mobility Shift Assay (EMSA) analysis, wherein they were incubated for 20 minutes in the presence of varying concentrations of dsDNA (250, 500, 750 nM). The observed results indicate a dose-dependent augmentation in TBX20 binding.

Conclusions: We conducted in vitro expression of TBX20 DNA binding domain (DBD) protein and determined the crystal structure of the TBX20 DBD and dsDNA complex. By studying clinical cases, we identified mutations in TBX20 DBD and demonstrated their impact on the recognition and binding of DNA in CHD using a series of experiments. Ultimately, our study shed light on the regulatory molecular mechanism of CHD by elucidating the role of TBX20.

Key words: TBX20 DBD; crystal structure; congenital heart disease; clinical mutations; mechanism

P8-8 Bruton tyrosine kinase inhibitor ibrutinib induces hypertension by upregulating transcription of $Ca_V1.2$ calcium channel

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Ibrutinib, as the first approved BTK inhibitor, is currently a first-line targeted drug for the treatment of chronic lymphocytic leukemia (CLL), but with a key limitation of cardiovascular adverse effects. Hypertension is a common side effect of ibrutinib therapy. Though previous studies suggest that ibrutinib-induced hypertension is related to the disturbance of intracellular calcium concentration, the underlying mechanisms are largely unknown. The analysis of clinical CLL patients' data found that ibrutinib treatment of CLL results in ~30% of hypertension, and ~6% of the patients even develop to grade 3 hypertension. To investigate the blood pressure (BP) change associated with a clinically relevant dose of ibrutinib, the mice were treated with ibrutinib (25 mg/kg per day) by oral gavage for 28 days, and their BP was monitored. Ibrutinib treatment increased SBP in these mice. By using the animal model, we found that 28 days' oral gavage of ibrutinib in mice induce the increased $Ca_V1.2$ expression and current density, and also increases K^+-induced vasoconstriction in the mesenteric artery (MA), suggesting enhanced functions of the $Ca_V1.2$ channel might mediate the enhanced vasoconstriction. Of significance, by monitoring the real-time intracellular calcium concentration ($[Ca^{2+}]_i$) in VSMCs by using 4 μmol/L Fluo-4 AM, we found ibrutinib increases K^+-triggered $[Ca^{2+}]_i$ elevation. By using whole-cell patch clamp, we found that application with ibrutinib exhibited hyperpolarized current-voltage and activation curve of $Ca_V1.2$ channels in vascular smooth muscle cells (VSMCs) from mice treated with ibrutinib, which facilitates the channel function. Unexpectedly, Masson and HE staining of MAs didn't show the obvious morphological change of ibrutinib-treated mice in comparison to control mice, indicating there is no structural remodeling in the MAs from the mice feeding with ibrutinib. For investigating the possible mechanisms, we applied RNA-seq, and the data identified that the expression of transcription factor C/EBP-β is specifically upregulated in the MA from ibrutinib-treated mice. Chip experiments demonstrated that $Ca_V1.2$ encoding gene *Cacna1c* is

bound with C/EBP-β. Furthermore, C/EBP-β transcriptional expression level was increased under ibrutinib stimulation. SiRNA-mediated knockdown of C/EBP-β decreased $Ca_V1.2$ current size in VSMCs, and K^+-induced constriction of MAs, respectively. Thus, these results reveal that ibrutinib long-termly increases the expression of $Ca_V1.2$ transcription by upregulating the transcription factor C/EBP-β, thereby enhancing channel functions and increasing vasoconstriction. This study identified a specific molecular mechanism of enhanced vasoconstriction induced by ibrutinib, providing a potential target for the management of hypertension in CLL patients when using ibrutinib.

Keywords: ibrutinib; hypertension; $Ca_V1.2$ calcium channel

P8-9 HIF-1α 通过调节能量代谢适应途径降低小鼠移植心脏冷保存过程中的冷缺血损伤

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背景：冷缺血损伤是供体心脏冷保存过程中遭受的主要损伤，HIF-1α 在心脏缺血再灌注损伤中发挥重要作用，但 HIF-1α 在移植心脏冷保存过程中的作用机制尚无人报道。

方法：本研究使用 C57BL/6N 小鼠作为研究对象，应用 ES 打靶技术，通过 Cre/Loxp 系统繁配 HIF-1α 心肌敲除小鼠后建立供体心脏 UW 液中冷保存 6h 模型。过程中添加 PDK1 抑制剂进行实验组处理。我们评估了心脏组织的能量代谢状态，包括 ATP、糖代谢关键酶如葡萄糖转运蛋白酶 1（GLUT1）、己糖激酶（HK2）、乳酸脱氢酶 A（LDHA）丙酮酸脱氢酶激酶 1（PDK1）。脂肪酸代谢关键酶如肉毒碱棕榈酰基转移酶 1A （CPT1A）、中链酰基辅酶 A 脱氢酶（MCAD）及长链酰基辅酶 A 脱氢酶（LCAD）的表达水平。此外，我们还通过组织形态学、免疫组化、电镜、分子生物学方法对心脏组织的形态外观、微观结构和细胞凋亡进行了评估分析。

结果：敲除鼠的心脏组织中 HIF-1α 与野生型小鼠相比表达量明显降低，而冷保存 6h 后的 HIF-1α 表达水平两组均在原基础上显著增加。野生小鼠供体心脏经历 6h 冷保存后，脂肪酸代谢关键酶 CPT1A、MCAD、LCAD 明显减少；GLUT1、HK2、LDHA 等糖酵解关键酶及糖代谢开关 PDK1 的表达水平明显增高；丙酮酸脱氢酶（PDH）磷酸化水平上升，总体活性下降。敲除鼠供体心脏冷保存 6h 后较野生小鼠供体心脏冷保存组各组指标均呈相反趋势。此外在敲除鼠冷保存组中心肌细胞凋亡程度更高。给予野生型小鼠 PDK1 抑制剂（PS10）并进行 4℃冷保存后，抑制剂组的 PDH 活性明显升高，在无氧条件下打开了有氧开关，引起冷保存心脏不必要的“能量耗竭”，ATP 水平明显下降，有较多 TUNEL 阳性细胞。

结论：激活 HIF-1α 可以通过调节心脏组织的能量代谢状态减少冷缺血损伤并抑制冷保存过程中心肌细胞的凋亡。在无氧状态下抑制 PDK1 水平会减弱 HIF-1α 的保护作用。这些

发现为进一步研究 HIF-1α 作为治疗手段的潜在应用提供了理论依据。

关键词：心脏移植；能量代谢；HIF-1α；冷缺血损伤；冷保存

P8-10 交感中枢 RVLM 内 DPP3 促进血管紧张素-(5-7)生成参与高血压交感亢进的机制研究

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目的：原发性高血压病严重威胁人类健康，其发生与交感中枢 RVLM 神经元异常兴奋导致交感亢进密切相关。RVLM 内肾素-血管紧张素系统的主要成分血管紧张素 II（Angiotensin II，Ang II）和血管紧张素-(1-7)[Angiotensin-(1-7)，Ang-(1-7)]的动态平衡在正常血压维持中发挥重要作用，因此，明确参与调节 Ang II 和 Ang-(1-7)平衡的机制对高血压病的防治具有重要意义。二肽基肽酶 3（Dipeptidyl Peptidase3，DPP3）是一种锌依赖性水解酶，研究表明 Ang II 和 Ang-(1-7)均可被 DPP3 水解，产生血管紧张素-(3-7)[Angiotensin-(3-7)，Ang-(3-7)]和血管紧张素-(5-7)[Angiotensin-(5-7)，Ang-(5-7)]，其中 Ang-(3-7)已被证明可以升高血压，然而 Ang-(5-7)是否与 Ang-(3-7)一样具有血压中枢调控作用也不清楚。因此，本研究旨在明确中枢 RVLM 内 DPP3 调控 Ang II 和 Ang-(1-7)平衡增加 Ang-(5-7)产生参与高血压发生。

方法：首先，收集心血管疾病患者血浆，检测血浆中 DPP3 及去甲肾上腺素（Norepinephrine，NE）水平。其次，比较观察不同周龄正常血压的 Wistar-Kyoto（WKY）大鼠和自发性高血压大鼠（Spontaneously Hypertensive Rat，SHR）血浆中 DPP3 及 NE 水平以及心血管系统和相关组织器官中 DPP3 的表达情况；并过表达或干扰 DPP3，观察中枢 DPP3 对 Ang-(5-7)产生和血压调控的作用。最后，观察中枢给予 Ang-(5-7)对血压、心率和肾交感活性的影响，同时证实 RVLM 内经 DPP3 酶促产生的 Ang-(5-7)可以激活交感神经活性促进高血压的发生发展。

结果：在心血管疾病患者和大鼠血浆中，DPP3 水平与 NE 水平呈正相关。免疫荧光检测表明 RVLM 神经元上存在 DPP3 表达，并且 SHR 的 RVLM 内 DPP3 表达明显高于 WKY 大鼠。此外，随着年龄的增加，SHR 的 RVLM 中 DPP3 表达水平也升高。进一步，在 RVLM 微量注射 DPP3 可升高交感神经活性和血压。WKY 大鼠 RVLM 内过表达 DPP3 后 Ang-(5-7)产生增加，SHR 的 RVLM 内干扰 DPP3 后 Ang-(5-7)产生减少。RVLM 内急性微量注射 Ang-(5-7)以及第四脑室慢性灌流 Ang-(5-7)均可增加肾交感活性，升高血压。

结论：RVLM 内 DPP3 通过增加 Ang-(5-7)产生导致交感输出亢进，血压升高。

关键词：高血压，RVLM，DPP3，Ang-(5-7)，交感亢进

P8-11 The hippocampus works as a potential crosslink between hypertension and Alzheimer's disease

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Objective Hypertension is related to cognitive impairment and increased risk for Alzheimer's disease (AD). While the brain renin-angiotensin system (RAS) contributes to hypertension, its overactivation also induces cerebrovascular dysfunction. Hereby we hypothesize that brain RAS overactivation serves as a shared etiology in both hypertension and AD. To selectively increase the activity of brain RAS, a deoxycorticosterone acetate (DOCA)–salt model was introduced in the current study. **Methods** DOCA-salt treatment (1 mg/g s.c.; 1%NaCl, 28 days) was applied to C57BL/6j male and female mice (20-22 weeks). BP was monitored via tail-cuff. Novel object recognition (NOR), Barnes maze, and nesting test were performed to assess the cognitive function. Later, cerebra blood flow (CBF) was measured by laser doppler flowmetry. Further molecular analysis was performed using single-cell RNA sequencing (sc-seq) and immunofluorescent staining (IF). **Results** DOCA-salt treatment induced cognitive impairment and inadequate functional hyperemia in both male and female C57BL/6j mice. Treating DOCA-salt hypertension through direct vasodilation or reducing blood volume improved only the performance in the first stage of Barnes maze test. In specific, neither hydralazine (75mg/L, o.a.) or empagliflozin (10 mg/kg/day, o.a.) increased novel object recognition preference or whisker-stimulated functional hyperemia. In contrast, hippocampal cognitive impairment, indicated by Barnes maze test, responded well to the two anti-hypertensive drugs, showing that hydralazine and empagliflozin effectively shortened the latency time on checkpoint of the 1st phase. Discrepancy between NOR and Barnes maze test suggested that the hippocampus might be differently affected by DOCA-salt, compared to the cortex. This was further confirmed by sc-seq using tissues from both regions. Although loss of endothelial cells was not observed (also confirmed by IF), there were transcriptome alterations following DOCA-salt treatment. By searching KEGG, the hippocampal markers highlighted infiltration of immune cells, neurodegeneration pathways, and AD, while those from the cortex were enriched in energy metabolism, platelet activation, and hypoxia-related

signaling pathway. **Conclusions** Our data provided evidence that cortex and hippocampus are differently affected by hypertension. This helps to distinguish contributions of hypertension to AD from those to vascular dementia, and to indicate which types of hypertension are with higher risk for AD.

Keywords: hypertension; cognitive impairment; hippocampus;

P8-12 Ibrutinib induces cardiac arrhythmia by targeting $Ca_V1.2$ calcium channel

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Background: Ibrutinib is a Bruton tyrosine kinase inhibitor that has shown significant efficacy against chronic lymphocytic leukemia (CLL). Clinical studies have found that ibrutinib increases the risk of cardiac arrhythmia, but the underlying molecular mechanisms are still unclear. $Ca_V1.2$ calcium channel is indispensable for the cardiac excitations, its dysregulations indeed lead to arrhythmia. However, the associations between Ibrutinib and cardiac $Ca_V1.2$ calcium channel and calcium-dependent signaling remain unknown.

Methods: We collected clinical history of the CLL patients treated with Ibrutinib to analyze possible factors which might associated with cardiac arrhythmia. Electrophysiological experiments were conducted in the hearts from mouse model and neonatal rat ventricular myocytes (NRVMs) to assess ibrutinib induced arrhythmia. mRNA transcriptomic of cardiac tissue was performed to screen the potential target genes of Ibrutinib-induced arrhythmia. The pathogenesis of arrhythmia was further studied at mouse models and cellular experiments.

Results: Clinical data show that the incidence of arrhythmia with ibrutinib is 16% and can be as high as 30% after discontinuation. At animal model, the mouse treated with Ibrutinib (25 mg/kg/d) were more likely to develop spontaneous ventricular arrhythmias, and M-mode echocardiography indicated systolic dysfunction of ibrutinib-treated mouse. The expression levels of $Ca_V1.2$ protein and the phosphorylated CaMKII, which were identified by RNA-seq, in mouse hearts and ibrutinib-treated NRVMs were significantly increased. Whole-cell patch clamp showed

that the activation kinetics of cardiac $Ca_V1.2$ calcium channel of ibrutinib-treated NRVMs shifts towards hyperpolarization, indicating the channel can be opened easier. Furthermore, the intracellular calcium concentration that detected with Fluo-4 AM was found to be increased after application with Ibrutinib in NRVMs.

Conclusions: These findings suggest that Ibrutinib could increase $Ca_V1.2$ expression of myocardial cells, and also shifted the *I-V* curve of $Ca_V1.2$ channels towards hyperpolarization. Thus, this cause intracellular calcium signaling disturbance and triggering cardiac arrhythmia.

Keywords: Ibrutinib; cardiac arrhythmia; $Ca_V1.2$ calcium channel

P8-13 GADD45G 在心肌肥厚中的表达调控及其介导表观遗传重编程的分子机制研究

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心肌肥厚是多种心血管疾病共同的病理过程，表观遗传调控在心肌肥厚基因表达重编程的过程中发挥重要作用，但不同表观遗传修饰间的协同调控机理尚未阐明。我们的研究发现，DNA 损伤诱导蛋白 GADD45G 在心肌肥厚中表达上调，敲低转录因子 ATF6 可逆转 GADD45G 在肥厚性刺激后的表达上调。在新生大鼠心肌细胞（NRVM）中过表达 GADD45G 可诱发心肌细胞肥大，而敲低 GADD45G 则抑制苯肾上腺素（PE）所诱导的心肌细胞肥大。小鼠心脏特异敲除 GADD45G 显著抑制主动脉狭窄术（TAC）所诱导的心肌肥厚。转录组学分析显示，GADD45G 过表达显著抑制扩张性心肌病相关的收缩功能蛋白、结构蛋白和离子通道蛋白等的转录表达，且差异表达基因与 H3K27me3 修饰位点在基因组尺度上存在广泛重合；但 GADD45G 对组蛋白 H3K9me3 和 H3K27me3 修饰的整体水平没有影响，反而特异地负向调控 H3K9ac 和 H3K27ac 修饰。ChIP-seq 结果显示，过表达 GADD45G 后，H3K9ac 和 H3K27ac 在基因组上的富集度显著降低。通过组蛋白去乙酰化酶（HDACs）的筛选实验发现，GADD45G 与 HDAC5 存在直接相互作用，敲低 HDAC5 可显著逆转 GADD45G 过表达所诱导的病理基因启动子区域的 H3K9ac 和 H3K27ac 富集减少。本研究结果表明，在心肌细胞遭受压力胁迫时，GADD45G 受 ATF6 调控表达升高，通过招募 HDAC5 抑制 H3K27me3 标定基因区域的组蛋白乙酰化修饰，导致染色质开放程度降低，介导心肌肥厚中的病理基因表达重编程。

关键词：心肌肥厚，表观遗传学，GADD45G，HDAC5，ATF6

P8-14 Deletion of CX3CR1^{+} macrophage inhibits the thoracic aortic aneurysm procession in Marfan syndrome

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The mechanistic studies on thoracic aortic aneurysm (TAA) in Marfan Syndrome (MFS) mainly focus on the pathological changes of vascular smooth muscle cells (VSMCs). However, whether inflammation is involved in the TAA formation in MFS is still elusive. First, we performed single cell RNA sequencing and identified a increased group of CX3CR1^{+} macrophages in thoracic aortas from 5-month old *Fbn*$^{C1041G/+}$ mice (MFS mouse model) than in aortas from WT. Furthermore, we validated the infiltration of increased CX3CR1^{+} macrophages in aortic root aortas from MFS mice than controls by flow cytometry since 6 weeks, when there were non-obvious expansion of aortic root and ascending aorta in MFS mice. Meantime, the results were confirmed by immunofluorescent staining in MFS aorta from both mice and patients. Moreover, elimination of CX3CR1^{+} macrophages by diphtheria toxin (DT) ameliorated the thoracic aortic aneurysm in MFS mice than vehicle from 11 weeks to 21 weeks by echocardiography and Verhoeff's Van Gieson (EVG) staning. In addition, we found aggravated VSMCs inflammation by pseudo-temporal analysis and KEGG pathway analysis, and we identified there were 5 potential pairs between CX3CR1^{+} macrophages and SMCs by ligand-receptor analysis, including IGF-1 and its receptor IGF1R; TNF and its receptor DAG1 or TNFRSF1a; PDGF-B and its receptor PDGFRB and LRP1. Then, we isolated macrophages form MFS patient aorta, and identified increased TNF and IGF-1 from CX3CR1^{+} macrophage cell media than CX3CR1^{-} macrophage by ELISA after culture. We induced pluripotent stem cells (iPSCs) derived VSMCs from MFS patients and cultured them with CX3CR1^{+} or CX3CR1^{-} macrophage media. And we clarified that CX3CR1^{+} macrophages aggravated the

VSMCs inflammation genes expression, especially *Il-6, Mcp1, Tnf, Cxcl1/2/5*. Anti-secreted TNF antibody or inhibited IGF-1 activity both ameliorated the VSMCs inflammation after co-culture iPSCs induced VSMCs with macrophages media. Next, bone marrow transplantation (BMT) assay and parabiosis assay suggested that the $CX3CR1^{+}$ macrophages were mainly derived from peripheral blood monocytes, in TAA of MFS mice. Furthermore, inhibition of monocyte recruitment into aortic wall by CCR2 antagonist RS504393 significantly alleviated the expansion of TAA in MFS mice. Overall, our results uncover the inflammatory mechanism and potential intervention strategy on TAA formation in MFS.

Key words： $CX3CR1^{+}$ macrophage; Marfan syndrome; thoracic aortic aneurysm; inflammation; CCR2 inhibitor; single-cell RNA sequencing;

P8-15 Metabolic changes of glycerophospholipids during the reparative phase after myocardial infarction injury

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Myocardial infarction (MI), commonly known as a heart attack, is an acute and fatal cardiovascular disease caused by a sharp decrease or cessation of blood supply to the heart muscle, leading to heart damage. It is the leading cause of morbidity and mortality worldwide. Diabetes, hypertension, cholesterol and smoking are important risk factors of MI, but the pathogenesis of MI remains poorly understood.

Glycerophospholipids (GPLs) or phosphoglycerides, glycerol-based phospholipids, are the main components of the cell membrane and important bioactive lipids. Phosphatidic acid and a substituent group (X) linked to phosphate formed the basic structure of GPLs. According to the different substituent groups linked to phosphate, GPLs can be divided into several classes, including phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PG) and phosphatidylinositol (PI).

Although GPLs members have been reported to be involved post-MI, the underlying mechanism of GPLs-associated post-MI is unclear. Cardiac repair after MI is a biphasic wound-healing response that involves an initial inflammatory phase (post-MI days 0–4) and a resolution phase (post-MI days 4–14). In the initial inflammatory phase, infiltrating neutrophils, monocytes and proinflammatory macrophages in the heart serve to clear damaged cells and matrix debris. During the resolution phase (post-MI days 4–14), activation of reparative cells relieves

inflammation and promotes scar formation and neovascularization. Reports have indicated that oral PS markedly reduced MI size and prevented adverse left ventricular remodeling in a mouse model of acute MI. Therefore, PS plays a pivotal role in cardiac repair after MI.

Lipid levels and composition alterations predict the risk of MI complications. Glycerophospholipids (GPLs) are important bioactive lipids and play a crucial role in the development of cardiovascular diseases. However, the metabolic changes in the GPLs profile during post-MI injury remain unknown.

In the current study, we constructed a classic MI model by ligating the left anterior descending branch and assessed the alterations in both plasma and myocardial GPLs profiles during the reparative phase post-MI by liquid chromatography–tandem mass spectrometry analysis.

We found that myocardial GPLs, but not plasma GPLs, were markedly changed after MI injury. Importantly, MI injury is associated with decreased phosphatidylserine (PS) levels. Consistently, the expression of phosphatidylserine synthase 1 (PSS1), which catalyzes the formation of PS from its substrate phosphatidylcholine, was significantly reduced in heart tissues after MI injury.

Furthermore, oxygen-glucose deprivation (OGD) inhibited PSS1 expression and reduced PS levels in primary neonatal rat cardiomyocytes, while overexpression of PSS1 restored the inhibition of PSS1 and the reduction in PS levels caused by OGD. Moreover, overexpression of PSS1 abrogated, whereas knockdown of PSS1 aggravated, OGD-induced cardiomyocyte apoptosis. Our findings revealed that GPLs metabolism was involved in the reparative phase post-MI, and cardiac decreased PS levels, resulting from inhibition of PSS1, are important contributor to the reparative phase post-MI. PSS1 overexpression represents a promising therapeutic strategy to attenuate MI injury.

Keywords: myocardial infarction, metabonomics, glycerophospholipids, phosphatidylserine, phosphatidylserine synthase 1

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P8-16 Heterogeneity of common carotid artery and abdominal aorta: an angle of sphingolipid metabolism

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Vascular heterogeneity in physiological or pathological modulations has been convinced, the details of which, however remain to be fully elucidated. Sphingolipids (SL) take extensive effects in cellular homeostasis. This study aimed to explore the difference in SL between common carotid artery (CA) and abdominal aorta (AA) of rats. UPLC-QTOF-MS -based lipidomics and qRT-PCR were conducted to detect SL species and expression of enzymes controlling SL metabolism. Meanwhile, subcellular organelles of vascular smooth muscle cells (VSMCs) were observed by transmission electron microscopy (TEM). Totally, 8 SL classes involving 137 species were identified. Among them, sphingomyelin (SM) and ceramides constitutes the majority, containing 56 and 58 species respectively. In addition to the SM, most SLs were significantly higher in CA than AA, including ceramide, 2-glucocerebroside ceramide (CerG2), ganglioside/monosialo trihexosyl ceramide (GM3), phytosphingosine (phSM), and sphingosines (So). Most SL metabolites contain long fatty acyl chains with more than 12 carbon atoms. The double bond numbers of ceramide and SM were 0-6 and 0-8, but the dominant range were 0-4 and 1-5 respectively. As for enzymes and organelles, the expression of *Cers1-4, Smpd1,* and *Sgms1/2* were higher in CA than AA. *Cert1, Sgpp1,* and *Sphk2* displayed a lower expression in CA than AA. The VSMCs of CA had more lysosomes and less Golgi apparatus than AA. Endoplasmic reticulum (ER) and mitochondria showed no significant differences between the two tissues. In summary, we revealed differences in SL metabolism between AA and CA, providing a new perspective for the role of lipids in vascular heterogeneity.

Keywords: Common carotid artery; Abdominal aorta; Vascular heterogeneity; Sphingolipid, Lipidomics

P8-17 骨髓间充质干细胞来源的微颗粒通过抑制铁死亡减轻阿霉素诱导心肌细胞损伤的作用研究

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背景：化疗药物阿霉素（Doxorubicin, DOX）被广泛用于多种癌症的治疗，但高心脏毒性限制了其临床应用。DOX 诱导的心脏毒性可导致心力衰竭和死亡，如何减轻 DOX 诱导的心脏毒性，仍亟需研究。**目的：**观察骨髓间充质干细胞来源的微颗粒（Bone Marrow Mesenchymal Stem Cell-derived Microparticles, BMSC-MPs）对 DOX 诱导心肌细胞损伤的作用，并探究其机制。**方法：**通过显微镜、成骨和成脂分化试剂盒鉴定 BMSC。差速离心法获

取 BMSC-MPs，利用 TEM、DLS 及 Zeta 电位仪进行鉴定。实验分为对照组、DOX 组、BMSC-MPs 干预组、Erastin 组，心肌细胞经相应处理后，通过 CCK-8 检测细胞活力、试剂盒检测 LDH 活性、Fe^{2+}、MDA、GSH 含量和 ROS 水平；Western blot 检测铁死亡相关蛋白 Ptgs2、ACSL4、GPx4 的表达水平。**结果：**1. 显微镜下可见 BMSC，梭形形态。成骨成脂诱导分化后可见明显的红色骨结节和深红色大小不一的脂滴。TEM 观察显示 BMSC-MPs 形态为圆形或椭圆形，膜结构完整。DLS 及 Zeta 电位检测显示 BMSC-MPs 的直径为 544±139.29 nm、Zeta 电位为-13.91±1.65 mV。2. BMSC-MPs 对 DOX 诱导的心肌细胞活力和 LDH 活性的影响：与对照组相比，DOX 组细胞活力明显下降、LDH 活性明显增加；BMSC-MPs 预处理 24h 后，细胞活力明显增加、LDH 活性明显下降；加入 Erastin 可部分逆转 BMSC-MPs 的作用。3. BMSC-MPs 对 ROS 水平和 MDA、Fe^{2+}、GSH 含量的影响：与对照组相比，DOX 组 ROS 水平、MDA 及 Fe^{2+}含量明显升高，GSH 含量明显降低；BMSC-MPs 干预后 ROS 水平、MDA 以及 Fe^{2+}含量明显下降，GSH 含量明显升高；加入 Erastin 可部分逆转 BMSC-MPs 的作用。4. BMSC-MPs 对 Ptgs2、ACSL4、GPx4 蛋白表达水平的影响：与对照组相比，DOX 组铁死亡标志蛋白 Ptgs2、ACSL4 表达明显升高，GPx4 表达明显降低，BMSC-MPs 干预后 Ptgs2、ACSL4 明显降低，GPx4 明显升高，加入 Erastin 可部分逆转 BMSC-MPs 的作用。**结论：BMSC-MPs 可显著减轻 DOX 诱导的心肌细胞损伤，这一作用与其抑制心肌细胞铁死亡有关。**

关键词：骨髓间充质干细胞；微颗粒；阿霉素；心肌细胞损伤；铁死亡

P8-18 Cocktail containing Pitavastatin and Resveratrol Alleviate hyperhomocytinemia-induced atherosclerosis through inhibiting ferroptosis and metabolitics change

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Cardiovascular disease (CVD) caused by atherosclerosis has become a main threaten for human health. As an independent risk factor, hyperhomocysteinemia (HHcy) played an important role in the pathogenesis of atherosclerosis by regulating metabolism and ferroptosis of macrophages. In this study, we constructed a new kind of liposome and PLGA nanoparticle by hybridizing liposome with macrophages membranes (Møm) to encapsulated resveratrol (Res) and PLGA to encapsulated pitavastatin (Pit). Assertion of hyaluronic acid (HA) on the macro-liposome and PLGA NPs was adopted to endow nanodrug targeting ability. *In vitro* results showed that the prepared nanoparticle cocktail can significantly enhance **Rps27l, orm1 and bdh1 protein expression**, while inhibit macrophage ferroptosis to alleviate lipid accumulation and inflammation, as well. *In vivo* studies have shown that the HA modification made the mix NPs an ideal decoy for targeting plaques. Thus, NPs mixture with prolonged blood circulation time, and improved targeting ability can achieve optimal Res and Pit accumulation at the region of atherosclerotic plaques to obtain high efficacy. According to our point, the nano-drug delivery system with high immune escape capability provided a feasible therapeutic strategy for efficient atherosclerosis therapy.

Keyword: homocysteine; atherosclerotic; macrophage; pitavastatin; resveratrol; Bio-NPs

P8-19 低氧诱导因子 HIF2α 对新生内膜增生的作用和机制研究

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背景：冠脉支架植入术后再狭窄（In-stent Restenosis, ISR）在临床发生率高达 5 ~ 10%，显著影响患者的远期临床结局。新生内膜增生是 ISR 的主要发病机制。在血管损伤后，血管平滑肌细胞（Vascular smooth muscle cell, VSMC）增殖迁移到受损部位，形成新生内膜，而内皮作为血管壁和循环血液之间的屏障，再内皮化可以抑制 VSMC 增殖，有效防止血管再狭窄。低氧诱导因子（Hypoxia-inducible factor, HIF）参与多种重塑性心血管疾病的发生发展，而 HIF2a 在新生内膜增生中的作用及潜在机制尚不明确。

结果：HIF2a 在股动脉导丝拉伤术后小鼠的血管平滑肌细胞中表达水平升高。小鼠 VSMC 特异性 *Hif2a* 的缺失减弱了导丝拉伤后的内膜增生。低氧条件下抑制 HIF2a 表达后 VSMC 迁移数明显降低。我们收集了 VSMC 培养基上清，并体外刺激内皮细胞，通过划痕实验、Transwell 迁移实验和 HUVEC 成管实验发现 *Hif2a* 敲除后的 SMC 上清促进 HUVEC 增殖迁移和管形成。我们通过超速离心法提取 VSMC 外泌体并进行芯片测序分析，发现 Hif2a 影响外泌体中 43 个 microRNA 的差异表达，其中 21 个在 *Hif2a* 敲除组表达上调，22 个表达下调。鉴于 *Hif2a* 的正向调控作用，我们发现在 *Hif2a* 敲除组下调的外泌体 miR-671 可以从 VSMCs 转移到 ECs。通过 KEGG 数据库对 miR-671 调控的信号通路进行分析定位到 Wnt 信号通路，在基因水平上验证发现 *Wnt3a* 在过表达 miR-671 后表达下降，而敲低 miR-671 后表达增加。通过 Targerscan 和 miRanda 数据库共同预测并取交集发现 miR-671-3p 的靶基因是 Ctnnd1，在 ECs 中过表达 miR-671 证实在基因和蛋白水平都能够抑制下游靶基因 Ctnnd1 的表达，并抑制内皮细胞的增殖迁移和成管，促进新生内膜增生。

结论：结果表明，VSMC 特异性 *Hif2a* 敲除后，既可以抑制 VSMC 自身迁移，又抑制了外泌体 miR-671 表达，通过旁分泌负向调控 ECs 中 Ctnnd1 表达促进内皮细胞增殖迁移和成管，从而减少血管损伤后的新生内膜增生。Hif2a 可能作为新的心血管治疗工具，在术后再狭窄的预防中发挥作用。

关键词：冠脉支架植入术后再狭窄；血管平滑肌细胞；外泌体；低氧诱导因子；miR-671

P8-20 PFKFB3-driven vascular smooth muscle cell glycolysis promotes vascular calcification via the altered FoxO3 and lactate production

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A link between increased glycolysis and vascular calcification has recently been reported, but it remains unclear how increased glycolysis contributes to vascular calcification. We therefore investigated the role of PFKFB3, a critical enzyme of glycolysis, in vascular calcification. We found that PFKFB3 expression was up-regulated in calcified mouse VSMCs and arteries. We showed that expression of miR-26a-5p and miR-26b-5p in calcified mouse arteries was significantly decreased, and a negative correlation between Pfkfb3 mRNA expression and miR-26a-5p or miR-26b-5p was seen in these samples. Overexpression of miR-26a/b-5p significantly inhibited PFKFB3 expression in VSMCs. Intriguingly, pharmacological inhibition of PFKFB3 using PFK15 or knockdown of PFKFB3 ameliorated vascular calcification in vD3-overloaded mice in vivo, or attenuated high phosphate (Pi)-induced VSMC calcification in vitro. Consistently, knockdown of PFKFB3 significantly reduced glycolysis and osteogenic transdifferentiation of VSMCs, whereas overexpression of PFKFB3 in VSMCs induced opposite effects. RNA-seq analysis and subsequent experiments revealed that silencing of PFKFB3 inhibited FoxO3 expression in VSMCs. Silencing of FoxO3 phenocopied the effects of PFKFB3 depletion on Ocn and Opg expression but not Alpl in VSMCs. Pyruvate or lactate supplementation, the product of glycolysis, reversed the PFKFB3 depletion-mediated effects on ALP activity and OPG protein expression in VSMCs. Our results reveal that the blockade of PFKFB3-mediated glycolysis inhibits vascular calcification in vitro and in vivo. Mechanistically, we show that FoxO3 and lactate production are involved in PFKFB3-driven osteogenic transdifferentiation of VSMCs. PFKFB3 may be a promising therapeutic target for the treatment of vascular calcification.

Keywords: Vascular calcification, PFKFB3, Glycolysis, Osteogenic transdifferentiation

P8-21 Exogenous H_2S initiating Nrf2/GPx4/GSH pathway through promoting Syvn1-Keap1 interaction in diabetic hearts

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Excessive ROS accumulation contributes to cardiac injury in type 2 diabetes mellitus. Hydrogen sulfide (H_2S) is a vital endogenous gasotransmitter to alleviate cardiac damage in diabetic cardiomyopathy (DCM). However, the underlying mechanisms remain unclear. In this study, we investigated the effects of NaHS administration in db/db mice via intraperitoneal injection for twenty weeks and treatment of high glucose (HG), palmitate (PA) and NaHS in HL-1 cardiomyocytes for 48 hours,respectively. H_2S levels were decreased in hearts of db/db mice and HL-1 cardiomyocytes exposed to HG and PA, which were restored by NaHS. Exogenous H_2S activated the nuclear factor erythroid 2-related factor 2 (Nrf2)/glutathione peroxidase 4 (GPx4)/glutathione (GSH) pathway, suppressed ferroptosis and mitigated mitochondrial apoptosis in db/db mice. However, these effects were abrogated after Nrf2 knockdown. NaHS treatment elevated the ubiquitination level of Kelch-like ECH-associated protein (Keap1) by preserving its E3 ligase synoviolin (Syvn1), resulting in Nrf2 nuclear translocation. H_2S facilitated the sulfhydration of Syvn1-cys115 site, a post-translational modification. Transfecting Syvn1 C115A in cardiomyocytes exposed to HG and PA partially attenuated the effects of NaHS on Nrf2 and cell death. Our findings suggest that exogenous H_2S regulates Nrf2/GPx4/GSH pathway by promoting the Syvn1-Keap1 interaction to reduce ferroptosis and mitochondrial apoptosis in DCM.

Keywords: Diabetic cardiomyopathy (DCM); hydrogen sulfide (H_2S); nuclear factor erythroid 2-related factor 2 (Nrf2); synoviolin (Syvn1); ferroptosis; mitochondrial apoptosis

P8-22 巨噬细胞中 NLRC5 缺失加重心肌重构和心力衰竭及其机制研究

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目的：巨噬细胞在心肌梗死早期的组织修复中起重要作用。然而，巨噬细胞在慢性心脏重构微环境中的作用尚未被阐明。NLRC5 作为巨噬细胞炎症相关通路激活的负调控因子，探讨巨噬细胞 NLRC5 在心力衰竭中的作用及机制。

方法：雄性 C57BL/6J 野生型(WT)和 NLRC5 基因敲除($NLRC5^{-/-}$)小鼠采用主动脉缩窄术(TAC)进行压力超载诱导的心力衰竭实验。流式细胞术检测 TAC 小鼠巨噬细胞、单核细胞和 T 细胞的数量。髓系巨噬细胞特异性敲除小鼠和骨髓移植小鼠也用于识别 NLRC5 具体作用细胞类别。高效液相色谱质谱、免疫共沉淀和免疫荧光被用来调查与 NLRC5 互动的靶蛋白，免疫印迹和 RNA 测序技术被用来揭示 NLRC5 在心力衰竭中通过巨噬细胞影响心肌细胞和纤维细胞的潜在机制。

结果：心力衰竭患者外周血单核细胞中 NLRC5 表达明显升高，而中性粒细胞、T 淋巴细胞和 B 淋巴细胞无明显变化。NLRC5 在心衰小鼠心脏中也高表达，其变化主要在人和小鼠心肌组织巨噬细胞中表达。重要的是，NLRC5 基因缺失、髓系巨噬细胞特异性敲除 NLRC5 和骨髓移植实验均发现 NLRC5 基因缺失加重了压力负荷诱导的病理性心脏重构和炎症因此，NLRC5 主要通过巨噬细胞影响心衰的进展。机制上，NLRC5 缺失巨噬细胞比 WT 小鼠巨噬细胞表达更多的炎症反应，并分泌更多的白细胞介素 6 (IL-6)分子，促进心肌细胞肥大和纤维化细胞的激活、增殖和迁移。同时，通过高效液相色谱质谱和转录组测序表明 NLRC5 可以通过结合伴侣 HSPA8 抑制下游 NF-κB 通路的激活，减少 IL-6 的分泌，缓解心脏重构微环境。

结论：我们的研究发现，巨噬细胞中 NLRC5 缺失可通过 NLRC5- hspa8 通路促进巨噬细胞浸润和 IL-6 分泌，加速压力超载诱导的心脏重构和炎症反应，最终加重心力衰竭的进展。且 IL-6 受体抑制剂可能成为心衰治疗策略的有用靶点。

关键词：心肌重构；巨噬细胞；模式识别受体

P8-23 病理性心肌肥厚治疗新策略：调控线粒体功能的 lncRNAs 网络构建

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我国心血管疾病的死亡率占疾病总死亡率的 40%，心血管疾病带来的社会和医疗压力仍在持续增加。而目前尚无有效且稳定的治疗策略。病理性心肌肥厚作为多种心血管疾病的相对早期的共同的病理变化，有效抑制甚至是消除病理性心肌肥厚，是许多心血管疾病防治的突破口。线粒体是细胞的“能量工厂”，心脏所需能量的 90%来自于线粒体氧化磷酸化。研究显示，线粒体结构和功能障碍导致的心肌细胞内能量缺乏是导致病理性心肌肥厚的关键因素。因此，寻找能够有效调控线粒体结构和功能的上游分子，并以此为靶点抑制病理性心肌肥厚，以实现安全的、有效治疗多种心血管疾病的目标。

我们前期实验通过对病理性心肌肥厚小鼠模型进行基因芯片筛查并利用生物信息技术分析芯片结果，发现了一些与病理性心肌肥厚密切相关 lncRNAs。进一步，采用生物信息学技术分析后发现 lncRNA Gm20257 及 lncRNA AK084656 与线粒体能量代谢高度相关，更让人惊喜的是预测结果显示这两个 lncRNAs 具有作为药物研发靶点的潜能。因此我们推测 lncRNA Gm20257 和 lncRNA AK084656 可能通过作用于线粒体调控病理性心肌肥厚。进一步，构建心肌肥厚的在体和离体模型，通过 RT-PCR 进行验证，体内外结果均显示这两个 lncRNAs 在病理性心肌肥厚时表达明显下调。过表达 lncRNA Gm20257 或 lncRNA AK084656 可抑制主动脉弓缩窄手术（TAC）或血管紧张素 II（Ang II）引起的心肌细胞肥厚及的线粒

体膜电位降低、ATP 合成减少。以上结果证实 lncRNA Gm20257 及 lncRNA AK084656 参与病理性心肌肥厚的调控过程，并且这种调控作用与线粒体功能有关。进一步机制研究发现 lncRNA Gm20257 通过调控 PGC-1α 促进线粒体生物合成；lncRNA AK084656 通过促进 GPX4 表达抑制线粒体损伤引起的心肌细胞铁死亡。

本项目以坚实的理论结合充分的前期研究基础，揭示调控线粒体结构及功能影响心肌肥厚的独特视角，以此为基础系统挖掘线粒体相关 lncRNAs，构建 lncRNAs 调控网络。为以肥厚为切入点治疗心血管疾病提供新靶点及思路。

关键词：病理性心肌肥厚；线粒体；长链非编码 RNA；调控网络

P8-24 Smooth muscle-conditional knock-in A‐kinase anchoring protein 150 (AKAP150) exacerbates insulin resistance-related cardiovascular dysfunction

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Background: Pathological remodeling of vascular structure and function is an important factor in insulin resistant vascular complications. Ca^{2+} acts as a second messenger to regulate the phenotype switching of smooth muscle through an excitation-transcriptional coupling pathway. This study investigates the role of A-kinase anchoring protein 150 (AKAP150), a scaffolding protein, in regulating kinases/phosphatases in the membrane of vascular smooth muscle cells. Specifically, it aims to explore the impact of smooth muscle AKAP150 on cardiovascular function in insulin-resistant mice. **Methods:** To assess metabolic differences, fasting blood glucose (FBG), glucose tolerance, and fasting insulin (FINS) were measured in 5-week-old AKAP150 smooth muscle-conditional knock-in (smKI) mice and wild-type (WT) mice. In order to explore the effects of smooth muscle AKAP150 on cardiovascular function in mice fed with 24 weeks high fat diet (HFD) and normal chow diet (NCD), Vascular and cardiac morphology and function in the context of hyperglycaemia were examined by cardiac ultrasound and heart and blood vessel morphology. **Results:** (1) The levels of FINS and the homeostatic model assessment of insulin resistance (HOMA-IR) were significantly higher in 5-week-old AKAP150 smKI mice compared to WT mice. Following 24 weeks of high-fat feeding, HFD-WT mice exhibited elevated levels of body fat% (P<0.0001), FBG (P<0.001), area under curve of blood glucose (P<0.0001), FINS (P<0.001), and HOMA-IR (P<0.001), compared with NCD-WT mice. It is noteworthy that, compared to HFD-WT, HFD-AKAP150 shows a more significant increase in these indicators. (2) The assessment of cardiomyocyte cross-sectional area using FITC-conjugated wheat germ staining sections revealed a

significant increase in cardiomyocyte hypertrophy following HFD feeding (P<0.0001). Moreover, HFD-AKAP150 smKI mice exhibited further exacerbation of cardiomyocyte hypertrophy (P<0.0001). Echocardiography was employed to evaluate cardiac function. NCD-AKAP150 smKI mice exhibited a significant decrease in ejection fraction (EF%) (P<0.05) and fractional shortening (FS%) (P<0.01) compared to NCD-WT mice. Additionally, HFD feeding for 24 weeks resulted in significant reductions in both EF% (P<0.0001) and FS% (P<0.0001) compared to mice fed a regular diet. Compared to HFD-WT mice, HFD-AKAP150 smKI mice displayed impaired systolic function, including EF% (P<0.05) and FS% (P<0.05). (3) The mesenteric grade 2 artery exhibited a significant increase in intima-media thickness in NCD-AKAP150 smKI mice compared to NCD-WT mice (P<0.01). Similarly, the HFD-WT group demonstrated a notable increase in intima-media thickness compared to the NCD-WT group (P<0.001). Both smooth muscle AKAP150 overexpression (P<0.01) and HFD feeding (P<0.0001) independently contributed to an increased ratio of intima-medial layer thickness to lumen diameter in the NCD-AKAP150 smKI, HFD-WT, and HFD-AKAP150 smKI groups, respectively. Importantly, the data revealed a significant elevation in the ratio of intima-medial layer thickness to lumen diameter in the HFD-AKAP150 smKI group compared to both the NCD-AKAP150 smKI group (P<0.01) and the HFD-WT group (P<0.05). **Conclusions:** Smooth muscle-specific overexpression of AKAP150 increased insulin secretion. Furthermore, high-fat diet and smooth muscle AKAP150 overexpression led to cardiac structure and function disorders. The presence of smooth muscle AKAP150 overexpression in the context of high-fat feeding rendered the vasculature and heart more susceptible to remodeling. Smooth muscle AKAP150 enhances the susceptibility of heart and blood vessels to high-fat-induced lesions, leading to more severe disease progression.

Keywords: smooth muscle, AKAP150, high-fat diet, cardiovascular dysfunction

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P8-25 Myeloid leukemia factor 1 is an epigenetic orchestrator facilitating chromatin opening in cardiac aging

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Aging-associated cardiac hypertrophy (AACH) increases susceptibility to heart failure in the elderly. Chromatin remodeling contributes to the gene reprogramming in AACH; however, the intrinsic regulations remain elusive. We performed a transcriptome analysis for AACH in comparison with pressure-overload-induced pathological cardiac hypertrophy in mice, and identified myeloid leukemia factor 1 (MLF1) as an aging-sensitive factor. In human AC16 cardiomyocytes, silencing MLF1 suppressed H2O2-induced cell senescence, while the phenotype was exacerbated by MLF1 overexpression. Combined ATAC-seq and RNA-seq analyses revealed reduced chromatin accessibility after MLF1 knockdown at H3K27me3-enriched genes related to inflammation and development. Despite of a direct interaction between MLF1 and polycomb repressive complex 2 (PRC2), its inhibition failed to reverse the impact of MLF1 knockdown. Instead, MLF1 promoted H3K27 acetylation at target promoters through directly binding to the HAT domain of EP300. Thus, MLF1 is a pro-aging epigenetic orchestrator by recognizing PRC2-resident loci and recruiting EP300 to facilitate chromatin opening.

Keywords: MLF1; cardiac aging; cardiac hypertrophy; histone acetylation; chromatin opening

P8-26 TKT 通过损害线粒体生物能学参与主动脉夹层的发生发展

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主动脉夹层（Aortic Dissection，AD）是一种危及生命的血管疾病，发病急，病情进展快。尽管在诊断技术和治疗方案取得了一定的进步，但 AD 的死亡率依旧很高，缺乏有效的诊断预警是临床上面临的最大问题之一。团队队列研究表明肥胖患者 AD 发病率是非肥胖患者 1.7 倍，AD 的发病风险与 BMI 指数显著相关，并且 AD 患者处于糖尿病前期的比例显著高于非 AD 患者；同时蛋白质组学、基因组学、单细胞测序及多组学联合分析发现 AD 患者糖脂代谢通路发生显著变化，表明糖脂代谢异常与 AD 的发生发展之间存在着密切关系。转酮醇酶（Transketolase，TKT）是介导糖酵解和磷酸戊糖途径的重要桥梁，是参与调控糖代谢关键酶，前期研究结果发现 TKT 在 AD 患者组织中显著上调。

目的：探索糖代谢在主动脉夹层发生中的作用，观察 TKT 变化与 AD 发生发展的关系，并挖掘糖代谢关键酶 TKT 在 AD 发生中的作用，进一步评估 TKT 成为 AD 早期预警生物标

志物的可能性。

方法：(1)采用人群队列研究，明确诱发 AD 的危险因素和关键因子；(2)收集临床标本组织进行基因组学测序、蛋白组学测序；(3)构建 AD 动物模型，采用 Elisa 技术观察关键因子与 AD 发展进程的关系；(4)利用单细胞测序筛选下游通路。

结果：(1)通过大型自然人群队列研究完成初期预警体系的建设，发现糖代谢异常是 AD 发生的主要危险因素，而 TKT 是其中的关键因子。(2)对 AD 患者组织进行蛋白组学测序，结果显示 TKT 表达上调；同时对 AD 患者血浆进行 Elisa 检测，发现 TKT 含量升高。(3)AD 动物模型中发现随着 AD 的发生发展，AD 小鼠血浆中 TKT 含量逐渐上调。(4) 透射电镜、流式细胞术、激光共聚焦结果显示 TKT 通过 AKT/MDM2/NDUFS1 通路影响糖代谢、线粒体功能等相关分子机制参与调控 AD。

结论：糖代谢异常与主动脉夹层密切相关，糖代谢关键酶 TKT 具有成为 AD 早期诊断生物标志物的价值。

关键词：主动脉夹层；糖代谢；转酮醇酶；诊断标志物

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P8-27 BACH1 缺失通过调节染色质开放性维持血管平滑肌细胞收缩表型抑制新生内膜增生

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研究目的： 心血管疾病的共同病理基础是由于血管功能及结构异常导致的血管病理性改变。转录因子BACH1在哺乳动物的多种细胞组织中表达，发挥转录激活或抑制等重要调控作用。通过人类基因组关联研究发现*BACH1*基因变异可能与冠心病相关，但是BACH1在血管损伤后新生内膜形成中的作用及机制还不清楚，因此本文旨在探究BACH1在血管平滑肌细胞表型转换和血管损伤后新生内膜形成中的作用及机制。

研究方法：我们构建了血管平滑肌特异性*Bach1*基因敲除小鼠，建立小鼠下肢股动脉导丝损伤模型，以明确血管平滑肌*Bach1*在血管损伤后新生内膜形成中的作用。在人主动脉平滑肌细胞上，通过CUT&Tag，ChIP-seq，RNA-seq以及ATAC-seq等技术，明确BACH1在血管平滑肌细胞表型转换中的作用和机制。

实验结果：我们分析发现在人冠状动脉粥样硬化斑块的平滑肌中有较高的 BACH1 转录因子活性，进一步我们发现冠心病病人冠状动脉增厚区域平滑肌的 BACH1 表达上调。血管平滑肌细胞特异性敲除 *Bach1* 可抑制导丝损伤后血管新生内膜增生，并维持平滑肌细胞收缩型表型，抑制平滑肌细胞增殖。

机制上，我们通过 Cut&Tag，ChIP-seq 和 ATAC-seq 分析发现在人主动脉平滑肌细胞中 BACH1 和 YAP 共同富集在平滑肌细胞中开放的染色质上，BACH1 可以直接结合在平滑肌收缩型标志基因的启动子区，抑制其表达。进一步我们发现在人主动脉平滑肌细胞中 BACH1 与 G9a 和 YAP 结合，ChIP-seq 显示 BACH1 可以通过招募 G9a 至平滑肌收缩型标志基因的启动子区，并维持其 H3K9me2 水平，进而抑制其染色质开放性。抑制 G9a 或者抑制 YAP 可恢复 BACH1 过表达引起的平滑肌收缩型标志基因表达的降低。

研究结论：我们的研究证实 BACH1 通过招募 YAP 和 G9a 促进血管平滑肌收缩型标志基因 H3K9me2 修饰，抑制平滑肌收缩型标志基因的表达，促进平滑肌细胞增殖，进而促进血管损伤后的新生内膜形成。这项研究阐明了 BACH1 在血管损伤后新生内膜形成和血管平滑肌细胞表型转换中的重要作用，为心血管疾病的防治提供了新靶点。

关键词: BACH1，染色质开放性，H3K9me2，甲基转移酶 G9a，YAP。

P8-28 Identifying Nox3 and differences between Paraventricular nucleus of hypothalamus (PVN) and rostral ventrolateral medulla (RVLM) and physiological role

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Nox proteins participate in cellular signaling and oxidative damage in the central nervous system (CNS). Paraventricular nucleus of hypothalamus (PVN) and rostral ventrolateral medulla (RVLM) are the CNS centers for sympathetic control of cardiovascular function. Recent advances demonstrate a role of Nox2 and Nox4 in pathologies. However, new Nox subtypes, tissue-specific characteristics of reactive oxygen species (ROS) generation, and the physiological role are little studied. This study aimed to identify novel Nox subtypes in PVN and RVLM under physiological conditions. PVN and RVLM regions were obtained from mice by stereotaxic dissection. Peripheral tissues were isolated under microscopic guidance. Western blot, immunofluorescence and confocal imaging determined Nox subtypes and tissue distributions. qRT-PCR quantified mRNAs. Lucigenin-enhanced chemiluminescence measured NADPH-dependent superoxide production. Intra-RVLM microinjection and hemodynamics were performed in vivo using rats.

Nox1, Nox2, Nox3 and Nox4 subtypes were expressed and colocalized with neurons in PVN and RVLM. Nox3 expression in RVLM was 5-fold greater than in PVN. RVLM produced 5 times more superoxide than PVN. PVN and RVLM generated more sustained superoxide than aortic and cardiac tissues. Nox inhibitor diphenyleneiodonium (DPI) suppressed over 95% superoxide production in PVN and RVLM. Pro-inflammatory factors TNF-α and IL-6 differentially enhanced ROS production in PVN and RVLM. DPI microinjection to RVLM suppressed the blood pressure in rats in vivo. These results provide the first data on Nox subtype spectrum in PVN and RVLM and characteristics of Nox-derived ROS production, and identify Nox3 predominance in RVLM and its contribution to higher ROS generation and its physiological role.

Key words: NADPH oxidase, reactive oxygen species, Paraventricular nucleus of hypothalamus (PVN), rostral ventrolateral medulla (RVLM), blood pressure

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P8-29 ATP promotes resident vascular wall CD34$^+$ cells migration mainly through P2Y2-STIM1-ERK/p38 pathway

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Extracellular Adenosine triphosphate (ATP) is one of the most abundant biochemical constitutes within the stem cell microenvironment and is postulated to play critical roles in cell migration under stress conditions. However, it is unclear whether ATP regulates the cell migration of CD34$^+$ vascular wall-resident stem/progenitor cells (VW-SCs) and participates in angiogenesis. Therefore, the biological mechanisms of cell migration mediated by ATP was determined by *in vivo* subcutaneous matrigel plug assay, *ex vivo* aortic ring assay, *in vitro* transwell migration assay and other molecular methods. In present study, ATP dose-dependently promoted CD34$^+$ VW-SCs migration, which were more obviously attenuated by inhibition or knocking down P2Y2 than P2Y6. Furthermore, it was

confirmed that ATP potently promoted the migration of resident $CD34^+$ cells from cultured aortic artery and differentiation into endothelial cells in matrigel plugs by using inducible lineage tracing Cd34-$CreER^{T2}$; R26-tdTomato mice, while P2Y2 and P2Y6 blocker greatly inhibited the effect of ATP. Additionally, ATP enhanced the membrane protein expression of Stromal Interaction Molecule 1 (STIM1), blocking CRAC channel with shSTIM1or BTP2 apparently inhibited ATP evoked elevation in intracellular Ca^{2+} concentration and channel opening, thereby suppressed ATP-driven cell migration. Moreover, extracellular signal regulated protein kinase (ERK) inhibitor PD98059, p38 inhibitor SB203580 remarkably inhibited ERK and p38 phosphorylation, cytoskeleton rearrangement and subsequent cell migration. Interestingly, it was unexpectedly to find that knocking down STIM1 greatly inhibited ATP triggered ERK/p38 activation. Taken together, it was suggested that P2Y2 signaled through CRAC channel mediated Ca^{2+} influx and ERK/p38 pathway to reorganize cytoskeleton and promoted the migration of vascular wall resident $CD34^+$ cells.

Keywords: Adenosine triphosphate; resident vascular wall $CD34^+$ cells; STIM1; purinergic P2Y receptor; MAPK pathway

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P8-30 Cardiomyocyte peroxisome proliferator-activated receptor α alleviates heart failure with preserved ejection fraction by inhibiting ferroptosis

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Rationale: Heart failure with preserved ejection fraction (HFpEF) has become the predominant type of heart failure with limited effective treatment. Cardiac lipid overload is crucial in the development of HFpEF. However, the underlying mechanism remains poorly understood.

Objective: This study aimed to decipher the key transcription factor responsible for the cardiac lipid overload and the critical pathway for lipotoxicity during HFpEF by multiple-omics,

including transcriptomics and lipidomics.

Methods and results: Analyses for public transcriptomic database of HFpEF patients showed that PPARα and its pathway was significantly downregulated in HFpEF hearts, which was confirmed in a high-fat diet and L-NAME-induced HFpEF mouse model. When challenged with high-fat diet itself, cardiomyocyte-specific *Ppara* knockout mice (*Ppara*$^{\Delta CM}$) exhibited cardiac diastolic dysfunction, decreased global longitudinal strain (GLS) and global circumferential strain (GCS), increased level of NT-pro BNP, and exacerbated exercise exhaustion damage, whereas ejection fraction (EF) was preserved, indicating that these mice had accelerated HFpEF. Oil red O staining and transmission electron microscopic analyses showed excess lipid accumulation in *Ppara*$^{\Delta CM}$ cardiomyocytes. Lipidomics for heart tissue and serum demonstrated an increased phospholipid and oxidized phospholipid in *Ppara*$^{\Delta CM}$ mice. ELISA analyses confirmed increased content of MDA and LPO in cardiac tissue and plasma in *Ppara*$^{\Delta CM}$ mice. Mechanistically, RNA sequencing revealed that *Gpx4*, a key component protecting cells from ferroptosis, was significantly decreased in *Ppara*$^{\Delta CM}$ mice. Consistent with the decreasing of GPX4 level in heart tissue, the activity of GPX and GSH contents in heart tissue and plasma were also remarkedly declined in *Ppara*$^{\Delta CM}$ mice. *In vitro*, PPARα knockdown by siRNA in H9C2 cells dramatically increased lipid peroxidation and decreased GPX4 levels. Ferroptosis inhibitor Fer1 treatment markedly improved the above damage in H9C2 cells.

Conclusions: These findings suggest that impaired PPARα signaling is critical for HFpEF, phospholipid and oxidized phospholipid accumulation is a characteristic for HFpEF mouse model induced by cardiomyocyte PPARα deficiency and a HFD treatment, thus raise up PPARα-GPX4-ferroptosis axis as potential therapeutic targets for HFpEF.

Keywords: heart failure with preserved ejection fraction, peroxisome proliferator-activated receptor α, phospholipid, ferroptosis, glutathione peroxidase 4.

P8-31 Activation of endothelial Transient Receptor Potential Vanilloid 4 exacerbates myocardial ischemia-reperfusion injury via vascular integrity impairment

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Background: TRPV4 activation exacerbates myocardial ischemia-reperfusion (IR) injury and is abundantly expressed in vascular endothelial cells. However, the specific role of TRPV4 in

endothelial cells during myocardial IR remains ambiguous.

Methods: Myocardial IR was induced in C57BL/6 WT, $Trpv4^{-/-}$, tamoxifen-inducible endothelial Trpv4 knockout ($Trpv4_{EC}$-/-), and tamoxifen-treated control ($Trpv4^{fl/fl}$) mice. WT mice were treated with TRPV4-specific antagonist GSK2193874 (1mg/kg) or agonist GSK101790A (1mg/kg). Human umbilical vein endothelial cells (HUVECs) were studied after hypoxia-reoxygenation (HR).

Results: $TRPV4^{-/-}$ mice showed reduced IR-induced infarct size, preserved endothelial integrity, decreased permeability, upregulated VE-cadherin, claudin-5, occludin, and reduced inflammation. Pre-treatment of WT mice with GSK2193874 mimicked these effects, while TRPV4 agonist worsened injury. HUVECs displayed similar responses to TRPV4 modulation. Furthermore, $TRPV4_{EC}$-/- mice also exhibit reduced post-ischemic heart infarct size and better endothelial integrity. Mechanistically, activation of endothelial TRPV4 leads to increased endothelial permeability through the Ca^{2+}/PKC/RhoA/MLC pathway, inhibiting the expression of VE-cadherin, claudin-5, and occludin, consequently exacerbating IR injury.

Conclusion: Endothelial TRPV4 influences post-IR vascular permeability and inflammation. Targeting TRPV4 may hold promise for mitigating myocardial IR injury.

Keywords: endothelial TRPV4, myocardial IR, vascular integrity

P8-32 恩帕格列净挽救主动脉缩窄诱导的小鼠心律失常和钙稳态

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钠-葡萄糖共转运蛋白 2（SGLT2）抑制剂具有潜在的心力衰竭治疗作用。我们采用主动脉收缩术（TAC）建立心力衰竭小鼠模型，2 周后给予 SGLT2 抑制剂恩帕列净 4 周。结果发现，与 TAC 组和假手术组比较，恩帕格列净减少了晚期 Na^+电流，增加了磷酸化（p-）CaMK II 和 Nav1.5，但没有增加总（t）-CaMK II 以及 Na^+/Ca^{2+}交换体的表达。恩帕列净挽救了 TAC 引起的超声心动图射血分数和缩短分数的降低，以及舒张期的前壁和后壁增厚。采用 Optical mapping 同步检测 Langendorff 灌注的心脏的电压和 Ca^{2+}信号，结果证明了恩帕格列净挽救了 TAC 诱导的动作电位复极 80%时间（APD80）、Ca^{2+}信号恢复 80%恢复时间（CaTD80）、

常规 10Hz 刺激期间 Ca^{2+}达峰时间（TTP100）和 Ca^{2+}衰变常数（Decay30-90）的增加，以及 Ca^{2+}瞬态交替随循环长度缩短。异丙肾上腺素缩短了假手术组和 TAC 组小鼠心脏的 APD80，缩短了 CaTD80 和 Decay30-90，但在所有组中都保留了 TTP100 和 Ca^{2+}瞬时交替。在异丙肾上腺素刺激后，所有组都显示出相似的 APD80，而仅 TAC 的心脏显示出更大的 CaTD80 异质性。在异丙肾上腺素激发的 TAC 操作的心脏中，连续突发起搏发作后，恩帕列净消除或减少了室性心动过速和室性早搏以及相关的再入传导模式。因此，恩帕列净可以挽救 TAC 诱导的心室肥大和完整心脏的收缩功能、Ca^{2+}稳态和促心律失常变化。

P8-33 S-propargyl-cysteine promotes the stability of atherosclerotic plaque via maintaining vascular muscle contractile phenotype

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Objective: SPRC (S-propargyl-cysteine), a new sulfide-containing donor, has been reported to exert a positive role in cardioprotection, with possible mechanisms involve its anti-inflammation, anti-oxidation and anti-atherogenic activities. However, it is not clear whether SPRC is effective in atherosclerotic plaque stabilization. Moreover, we are particularly interested in whether SPRC have some effects on vascular smooth muscle cells' phenotype switching, since the latter is a major risk factor for atherosclerosis, stenosis and calcification in the plaque.

Methods and Results: An atherosclerotic unstable plaque mice model was established by using $APOE^{-/-}$ mice to perform tandem stenosis of the right carotid artery combined with the Western diet. $APOE^{-/-}$ mice were fed with western diet and received SPRC administration daily for 13 weeks. TS surgery was introduced 6 weeks after the onset of experiments. Our findings showed that SPRC treatment not only lowered plasma lipid levels, but also significantly enhanced plaque stability by increasing collagen content and decreasing cell apoptosis in atherosclerotic plaque compared to the model group. Enhanced plaque stability by SPRC was associated with maintaining the contractile phenotype of VSMCs by up-regulating the miR-143 expression, suggesting its distinct mechanisms of plaque stabilization. In *in vitro* studies we used platelet-derived growth factor-BB (PDGF-BB) to stimulate human artery vascular smooth muscle cells (VSMCs) with or without 100μM SPRC treatment. We found that SPRC increased contractile marker expression in VSMCs via up-regulating micro RNA-143 level by Western blot and Real-time PCR. BrdU cell proliferation kit and immunofluorescence of Ki-67 were used to

detect cell proliferation, while scratch wound healing and transwell assay were used to measure cell migration. We observed that SPRC administration significantly reduced the excessive proliferation and migration of VSMCs compared to PDGF-BB-stimulated model group. Overall, these findings suggest that the inhibiting effect of SPRC on phenotype switching from contractile to synthetic VSMCs may contribute to its beneficial role in plaque stability.

Conclusions: SPRC has protective effects on plaque stabilization via reducing necrotic core size, increasing collagen content The effect of SPRC may associate with its role in inhibiting phenotype switching of VSMCs.

Keywords: atherosclerosis; S-propargyl-cysteine; plaque stabilization; VSMCs; phenotype switching.

P8-34 RNA 可变剪接调控与慢性心衰

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基因表达调控与慢性心衰密切相关。90%的基因通过可变剪接，产生多种蛋白。可变剪接在心衰中的功能和调控机制仍未阐明。我们分析二代测序数据，发现除了可变剪接发生明显改变，可能涉及钙离子调控、心肌收缩、转录调控、miRNA 加工成熟等方面。我们通过实验对一部分进行了验证，例如 ATP2a2、PDLIM3、MEF2C、YAP1 等。YAP1 Exon6 的跳跃在组织中广泛存在，在物种间高度保守，在蛋白结构上存在明显差别。Exon 6 心肌特异敲除不影响心脏的结构和功能。TAC 后，Exon6 敲除小鼠的死亡率明显降低，心肌肥厚的相关指标明显改善。YAP1 的长短亚型的降解速率存在明显不同，短的亚型更容易与 HIPPO 信号通路相互作用，更容易被磷酸化而降解。短的亚型更容易与 b-Catenin 结合，导致 b-Catenin 的降解。除了 YAP1 外，miRNA 加工关键蛋白 Drosha 的 Exon7 出现外显子跳跃。Exon7 敲除大鼠在 1 年龄心功能改善明显，机制分析显示 Exon7 敲除影响 miRNA 的成熟，进而调控了 MAPK、mTOR 等信号通路，引发生理性心肌肥厚。为了研究 YAP1、Drosha 等基因的剪接调控机制，我们通过相关性分析和生物信息学方法，建立了心肌中可变剪接的调控网络。将调控网络应用到 YAP1 可变剪接，提出调控模型：CLK1 磷酸化 SR 蛋白，SR 蛋白结合到 YAP1 的 Exon6，调控 Exon6 可变剪接。我们通过实验验证了这个模型。这种通过大数据分析，构建的调控模型，可以应用到心衰中任何可变剪接事件，也可以应用到反向剪接环状 RNA 的调控机制研究。环状 RNA 和线性 RNA 之间存在此消彼长的关系，环状 RNA 的形成可能通过调控线性 RNA 发挥功能，探讨一些心血管重要基因的反向剪接调控方式具有重要意义，例如 PALLD。我们发现 HnRNPAB 和 NONO 在 PALLD 的反向剪接中发

挥关键作用。正向剪接和反向剪接都会形成没有蛋白编码能力的 RNA。这些异常 RNA 的降解主要通过无义介导 RNA 降解途径。我们发现无义介导 RNA 降解相关分子在心衰的过程中会富集。然而无义介导 RNA 降解在心血管中的功能研究较少。我们在成年小鼠的心肌中特异敲除其中的关键基因 UPF1 后，发现导致小鼠死亡。综上所述，RNA 可变剪接的异常调控与心衰的发生密切相关。

关键词：RNA 可变剪接、慢性心衰、环状 RNA、剪接调控网络

P8-35 富勒醇对心肌细胞增殖的调节作用及机制探讨

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背景和目的：新生哺乳动物的心脏拥有强大的心肌增殖能力，在心脏受损后可以通过心肌再生完全恢复其结构和功能；但在出生后一周心肌细胞退出细胞周期，心脏的增殖能力基本丧失。而出生后心肌细胞产生活性氧（ROS）引起的氧化损伤是导致心肌细胞细胞周期停滞的一个主要原因。富勒醇是富勒烯的水溶性衍生物，可以作为生物系统中的自由基清除剂或抗氧化剂来治疗与氧化应激相关的疾病。因此，本研究的主要目的是探究富勒醇对小鼠心肌细胞增殖的调控作用以及相关的分子机制。

实验方法和结果：在新生小鼠原代心肌细胞上给与不同浓度的富勒醇处理，结果发现 0.5 μM 的富勒醇可以明显增加 PH3 和 Ki67 阳性心肌细胞量。紧接着，我们给与新生小鼠每日腹腔注射富勒醇，于出生后 7 天（P7）及 P14 时收取心脏进行检测，结果发现富勒醇降低了心肌细胞的横截面积，并增加小鼠心脏的心肌细胞总数、单核心肌细胞数量，降低了双核和多核心肌细胞数量；进一步的免疫荧光染色发现富勒醇提高了小鼠心肌细胞的 PH3 和 Ki67 阳性细胞数，且 P14 时，富勒醇对小鼠心肌细胞增殖的促进作用高于 P7。以上实验结果表明，富勒醇可以促进发育期小鼠心肌细胞的增殖，延长了出生后小鼠心肌细胞增殖的窗口期。接下来，我们对富勒醇处理的原代小鼠心肌细胞进行了转录组测序，结果分析得出共有 202 个差异基因表达，其中有 100 个基因表达上调，102 个基因表达下调。我们根据基因表达变化筛选出 8 个介导富勒醇调控心肌细胞增殖的可能靶分子，并通过 qRT-PCR 和 Western blot 实验对其表达进行验证，最后筛选出下调基因 NR4A1 作为靶分子；同时我们通过药理性激活 NR4A1 后，发现活化 NR4A1 抑制心肌细胞增殖，并阻断了富勒醇对心肌细胞增殖的促进作用，提示富勒醇对心肌细胞增殖的调节作用可能是通过 NR4A1 介导。

结论：我们的实验表明，富勒醇可能通过下调基因 NR4A1 的表达促进了心肌细胞的增殖，从而延长了出生后小鼠心脏的增殖窗口期。

关键词：富勒醇；心肌细胞；细胞增殖；NR4A1

P8-36 Lack of PGC-1α in the hypothalamus paraventricular nucleus leads to mitochondrial malfunction and hypertension

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Paraventricular nucleus of hypothalamus (PVN) is one of the most important pivots regulating cardiovascular activities. PVN mitochondrial dysfunction with electron transport chain damage and elevated reactive oxygen species (ROS) production can lead to oxidation-antioxidant imbalance, and consequently cardiovascular diseases. Peroxisome proliferator-activated receptor γ coactiva-tor-1α (PGC-1α) plays a critical role in regulating mitochondrial biogenesis. Our pilot study found reduction of PGC-1α expression in the PVN of hypertensive rats, leading to the hypothesis that PGC-1α may be involved in the pathogenesis of hypertension. To test the hypothesis, we used adeno-associated virus to overexpress or knockdown Pgc-1α gene in the PVN of Spontaneously Hypertensive Rats (SHR) and their normotensive control Wistar Kyoto (WKY) Rats, respectively. The changes of blood pressure were monitored, and the levels of inflammatory cytokines (PIC), activation levels of estrogen associated receptor α (ERRα) / recombinant nuclear respiratory factor 2 (NRF2) pathway and other mitochondrial function indicators in the PVN were examined. Results showed that overexpression of Pgc-1α in the PVN of SHR could significantly reduce blood pressure and lowered the level of inflammation and oxidative stress in the PVN. Additionally, the activation level of ERRα / NRF2 pathway was elevated while the expression level of mitochondrial biogenesis related factors and respiratory chain complex subunits was changed, and the ATP production and membrane potential were restored. Oppositely, Pgc-1α knockdown in the PVN of WKY rats resulted in significantly elevated blood pressure and malfunction of mitochondrion. Together, these results suggested that PGC-1α can regulate blood pressure in PVN by participating in the regulation of mitochondrial biogenesis, controlling mitochondrial function and cell oxidation-antioxidant balance, possibly through modulating ERRα / NRF2 pathway activation. This study provided new experimental evidence to support a critical role of PGC-1α in blood pressure regulation, and it could be considered as a new therapeutic target for the clinical treatment.

Keywords: Hypertension, Mitochondrial biogenesis, PGC-1α, Oxidative stress, Mitochondrial respiratory chain.

P8-37 Whole brain mapping for afferent and efferent connections of PNMT-expressing neurons in the nucleus tractus solitarii

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Phenylethanolamine N-methyltransferase (PNMT) expressing neurons in the nucleus tractus solitarii (NTS) are recognized as adrenergic neurons and involved in regulation of many physiological functions including blood pressure, respiration, endocrine, and stress. Despite extensive research on the vital role of PNMT expressing neurons of the NTS (NTS^{PNMT} neurons), the neural circuits linking these neurons to other brain regions remain unclear and require further investigation. By using retrograde and anterograde tracing vector, we mapped the inputs and outputs of NTS^{PNMT} neurons in PNMT-Cre mice throughout whole brain. We found that there were 44 upstream nuclei innervating PNMT neurons in the NTS, and 43 discrete brain regions received axonal projections from NTS^{PNMT} neurons in the whole brain. NTS^{PNMT} neurons established neural circuits with functional nuclei regulating blood pressure (rostroventrolateral medulla, centroventrolateral medulla, ambiguus nucleus), breathing (pre-Botzinger complex, locus coeruleus), sleep-wake (laterodorsal tegmenal nucleus, lateral hypothalamic, paraventricular thalamic nucleus) and metabolism (parabrachial nucleus, arcuate hypothalamic nucleus, dorsomedial hypothalamic). Overall, this study provides a structural framework for further research into the neural mechanisms underlying the potential functions of PNMT neurons in the NTS.

Keywords: PNMT, Nucleus tractus solitarii, Neural circuit, Breathing

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P8-38 Diagnostic and prognostic value of Lp-PLA2, H-FABP and ST2 in patients with septic cardiomyopathy: A retrospective case-control study

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Background: Septic cardiomyopathy (SCM) is one of the main factors of mortality in the intensive care unit (ICU), and directly affects the development and prognosis of sepsis patients. At present, there are no good early diagnostic biomarkers for SCM. This study evaluated the levels of serum lipoprotein-associated phospholipase A2 (Lp-PLA2), heart-type fatty acid-binding protein (H-FABP), and growth stimulation expressed gene 2 (ST2) in patients with sepsis and explored their diagnostic and prognostic value for SCM.

Methods: The sepsis patients admitted to the ICU of Tianjin Medical University General Hospital were selected. They were divided into the septic cardiomyopathy group (n=139) and septic non-cardiomyopathy (n=138). The multivariate Logistics regression analysis, correlation analysis and receiver operating characteristic curve (ROC) were carried out to test the diagnostic value of indexes Lp-PLA2, H-FABP and ST2 in SCM. In addition, the 28-day mortality was compared between the two groups and multivariate COX analysis of survival risk factors was performed to determine the prognostic value of Lp-PLA2, H-FABP and ST2.

Results: The data showed that Lp-PLA2 (Odds ratio, OR 1.529, 95%CI 1.106-2.114, *P*=0.010), H-FABP (OR 1.530, 95%CI 1.018-2.300, *P*=0.041), and ST2 (OR 1.182, 95%CI 1.018-1.373, *P*=0.028) were independent risk factors for myocardial injury in sepsis. Moreover, Lp-PLA2 (AUC:0.964, *P*<0.001), H-FABP (AUC:0.951, *P*<0.001), and ST2 (AUC: 0.901, *P*<0.001) had good diagnostic capability and were positively correlated with myocardial injury indexes. The 28-day mortality rate in the SCM group was significantly higher than that in the non-SCM group, but the COX analysis showed that Lp-PLA2 (Hazard ratio, HR 1.013, 95%CI 0.997-1.030, *P*=0.117), H-FABP (HR 1.004, 95%CI 0.993-1.016, *P*=0.451), and ST2 (HR 0.999, 95%CI 0.993-1.004, *P*=0.590) were not independent risk factors.

Conclusion: Lp-PLA2, H-FABP, and ST2 had good diagnostic value, but had no associated with prognostic value.

P8-39 α-ketoglutarate promotes cardiomyocyte proliferation and heart regeneration after myocardial infarction

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The neonatal mammalian heart is capable of substantial regeneration following injury through cardiomyocyte proliferation. However, this regenerative capacity is lost by postnatal (P) day 7. How to stimulate the adult cardiomyocyte re-enter cell cycle is still unsolved. Accumulating evidence suggests that cardiomyocyte proliferation depends on its metabolic state. Due to the tight connection between tricarboxylic acid cycle (TCA) metabolism and proliferation, we analyzed the TCA metabolites between P0.5 and P7 mouse hearts and found that α-ketoglutarate (α-KG) ranked the first among the decreased metabolites. Injection of exogenous α-KG extended the window of cardiomyocyte proliferation during heart development and promoted heart regeneration after myocardial infarction (MI) by inducing adult cardiomyocyte proliferation, which was confirmed by increased endogenous α-KG in *Ogdh*-siRNA treated mice. Mechanistically, α-KG activates Jmjd3, a histone lysine demethylase-regulated H3K27me3 and the transcription of cell cycle genes in cardiomyocytes. Our present study indicates that α-KG promotes cardiomyocyte proliferation by Jmjd3-dependent demethylation and inactivation of H3K27me3, which is a potential therapeutic approach for treating MI and heart failure.

Key Words: Cardiomyocyte proliferation; Myocardial infarction; TCA metabolite; Cell cycle; Histone modification.

P8-40 Reversing metabolic reprogramming by CPT1 inhibition, via DUSP1 ADP-ribosylation-mediated p38 MAPK phosphorylation, promotes cardiomyocyte proliferation and heart regeneration

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The neonatal mammalian heart has a remarkable regenerative capacity, while the adult heart has difficulty regenerating. A metabolic reprogramming from glycolysis to fatty acid oxidation (FAO) occurs along with the loss of cardiomyocyte proliferative capacity shortly after birth. In this study, we sought to determine if and how metabolic reprogramming regulates cardiomyocyte proliferation. Reversing metabolic reprogramming by CPT1 inhibition, using cardiac-specific Cpt1a and Cpt1b knockout mice promoted cardiomyocyte proliferation and improved cardiac function post-myocardial infarction (MI). The inhibition of CPT1 is of pharmacological significance because those protective effects were replicated by etomoxir, a CPT1 inhibitor. CPT1 inhibition, by decreasing PARP1 expression, reduced ADP-ribosylation of DUSP1 in cardiomyocytes, leading to decreased p38 MAPK phosphorylation, and stimulation of cardiomyocyte proliferation. Our present study indicates that reversing metabolic reprogramming is an effective strategy to stimulate adult cardiomyocyte proliferation. CPT1 is a potential therapeutic target for promoting heart regeneration and MI treatment.

Keywords: metabolic reprogramming, cardiomyocyte proliferation, CPT1 inhibition, p38 MAPK phosphorylation, ADP-ribosylation

P8-41 SMOC1 通过影响血管平滑肌钙化介导主动脉夹层发生进展

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目的：主动脉夹层(aortic dissection, AD)是主动脉内膜上形成一个原发破口，血流冲刷进入主动脉中膜内，使得管壁形成真假两腔，薄弱的血管外壁容易发生破裂、出血。主动脉夹层患者钙化相关基因显著上调，微钙化与 AD 之间是否关联尚不清楚。血管平滑肌细胞是主动脉中膜内的主要细胞组分，在维持主动脉收缩功能和稳态中具有重要作用。在多种病理生理因素及外界压力刺激下，细胞的结构和功能完整性受损，丧失原有的生物力学特性，最终形成主动脉疾病。课题组前期研究通过蛋白组学测序发现 SMOC1 在 AD 患者组织中明显下调。目前对 SMOC1 的生理功能研究主要集中在调节细胞周期进程、细胞附着于细胞外基质、组织纤维化、钙化、血管生成中，但相关机制尚不明确。本研究从 SMOC1 着手，对其在主动脉中的生理功能及其相关机制进行深入研究，发掘其在 AD 发生发展中的作用，为

AD 的预防及治疗提供新策略。

方法：收集 AD 患者和正常组织进行高通量蛋白组学测序和单细胞测序，筛选与 AD 相关因子。在血管平滑肌上调控 SMOC1 基因表达进行转录组学测序，寻找 SMOC1 相关机制。从临床样本，AD 动物模型构建，离体细胞实验三个方面进行研究，通过蛋白质印迹法、免疫组化法、免疫荧光、实时荧光定量 PCR，酶联接免疫吸附剂测定法对实验相关因子的表达进行测定。通过苏木精-伊红染色、弹性纤维染色法、Masson 三色染色法、透射电镜等观察主动脉壁结构和形态。通过细胞划痕实验和流式细胞术以及茜素红染色验证 SMOC1 对血管平滑肌细胞的细胞功能影响。

结果：相较于正常组，夹层样本的血管平滑肌细胞数量减少，排列紊乱，收缩型 VSMC 转化为合成型并向骨/软骨化表型转化。通过蛋白质印迹法和免疫组化法，发现 SMOC1 在 AD 样本、人主动脉血管平滑肌细胞 AD 模型中显著降低，SMOC1 通过影响 VSMC 胞内钙离子的释放，从而调控血管平滑肌细胞的收缩功能。在体内实验中 SMOC1 可减弱维生素 D3 给药小鼠的主动脉钙化程度。AD 小鼠中主动脉破裂的钙化更为严重; 通过对动脉壁进行分析发现，不同部位钙化水平具有明显差异，SMOC1 的敲除引起主动脉钙化加剧 AD 的发生发展。

结论：SMOC1 与 AD 密切相关，在调控血管平滑肌细胞稳态和主动脉夹层病理生理发挥重要作用。SMOC1 很有可能成为诊断标志物和治疗靶点。血管钙化相关的靶点很有可能为预防、诊断和治疗 AD 提供新策略。

关键词：主动脉夹层;SMOC1;钙化；血管平滑肌细胞

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P8-42 TSPAN8 介导血管平滑肌细胞表型转换参与主动脉夹层的发生发展

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目的：主动脉夹层（aortic dissection，AD）是一种因主动脉内膜层撕裂，导致主动脉壁的内膜层和中膜层分离的凶险疾病。由于 AD 的病理表现不具有特异性，发病机制至今尚未明确。血管平滑肌细胞（vascular smooth muscle cell，VSMC）表型转换是 AD 主要的病理变化之一，VSMC 表型转换能够导致促炎反应和 MMPs 生成增加促进疾病的发生和发展。TSPAN8 能够促进多种癌症细胞的增殖、迁移、侵袭和转移，与表型转换部分表现一致。因此本实验从 VSMC 表型转换入手，验证 TSPAN8 与 AD 发生发展的关系。

方法：从临床样本、细胞模型实验、小鼠模型实验三方面探讨 TSPAN8 介导 VSMC 表型转换参与主动脉夹层发生发展的机制：（1）临床样本：采用 RT-PCR、Western Blot、病理染色等实验方法，确认 AD 患者中 TSPAN8 的表达位置和变化；（2）细胞模型实验：VSMC AD 造模后对 TSPAN8 基因进行过表达/敲除，细胞增殖实验、细胞划痕实验观察 VSMC 的变化，Western Blot 的实验方法确认 TSPAN8 过表达/敲除对 VSMC 收缩表型蛋白、炎症因子、MMPs 表达的影响；CHIP-seq 确定 TSPAN8 控制的下游靶基因；（3）小鼠模型实验：设置正常对照组、AD 组、干预组，通过小鼠死亡率，主动脉病理染色判断造模是否成功，确定干预药物是否有效；取主动脉进行 RT-PCR、Western Blot 实验验证干预药物和 TSPAN8 影响 AD 发生的机制。

结果：Western Blot、IHC、IF 等实验结果显示 AD 患者主动脉组织中 TSPAN8 表达明显升高。细胞实验中发现 Ang II 能够上调 TSPAN8 的表达，而 VSMC 收缩蛋白表达下降。通过过表达/敲除实验发现细胞增殖和迁移现象明显，其他实验方法也验证了 TSPAN8 能够影响 VSMC 的表型转换并增加炎症因子和 MMPs 的表达。

结论：TSPAN8 通过调控 VSMC 表型转换参与 AD 的发生发展，其表达变化可能对 AD 的发生提供诊断价值。

关键词：主动脉夹层；血管平滑肌细胞；表型转换

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P8-43 巨噬细胞通过 C5a/C5AR1 信号轴参与主动脉夹层发生进展

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目的：主动脉夹层（aortic dissection，AD）是指主动脉内膜撕裂后，腔内的血液通过内膜破口进入动脉壁中层形成夹层血肿，并沿血管长轴方向扩展，形成动脉真、假腔病理改变的严重主动脉疾病。而主动脉夹层的发病机制至今仍未明确。目前有研究表明血管炎症与夹层的发生发展存在密切联系，其中巨噬细胞浸润是主动脉夹层的发病特征之一。然而巨噬细胞发挥的作用及其机制尚不清楚。本研究从巨噬细胞着手，深入研究主动脉夹层发病机制，为该疾病的预防及治疗提供新策略。

方法：收集 AD 患者和正常组织进行高通量蛋白组学测序和单细胞测序，筛选与巨噬细胞的相关因子。从临床样本，AD 动物模型构建，离体细胞实验三个方面进行研究，通过蛋白质印迹法、免疫组化法、免疫荧光、实时荧光定量 PCR 对巨噬细胞相关因子，包括基质金属蛋白酶 2/9、白细胞介素-1β/6、肿瘤坏死因子 α 等的表达。通过苏木精-伊红染色、弹性

纤维染色法、Masson 三色染色法等观察主动脉壁结构和形态及巨噬细胞浸润程度。

结果：相较于正常组，夹层样本的中外膜层的巨噬细胞数量增加。通过蛋白质印迹法和 PCR 法，发现 C5AR1 在 AD 样本高表达。通过蛋白质印迹法，发现 C5AR1 在巨噬细胞炎症模型中表达升高，且炎症因子 TNF-α 显著升高，表明巨噬细胞通过 C5a/C5AR1 信号轴促进血管炎症的发生发展，加重 AD 发展进程。

结论：血管炎症与 AD 密切相关，巨噬细胞通过 C5a/C5AR1 信号通路促进血管炎症发生发展，从而推进 AD 的发生发展。C5AR1 很有可能成为诊断标志物和治疗靶点。

关键词：主动脉夹层；巨噬细胞浸润；补体受体；炎症

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P8-44 经典蒙药“四味土木香散”通过影响 miR-34a-5p/Notch1 信号通路改善压力超负荷性心肌肥厚

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目的：探究蒙药四味土木香散（STP）对机械牵张诱导的大鼠 H9c2 心肌细胞肥大模型的保护作用及作用机制。方法：1. 制备 STP 含药血清。2. 验证机械牵张诱导的细胞肥大模型的造模效果。3. 通过检测乳酸脱氢酶（LDH）活性确定 STP 含药血清最适剂量与作用时间。4. 检测 miR-34a-5p mRNA 及 ANP、BNP mRNA 和蛋白的表达水平，验证 STP 是否通过下调 miR-34a-5p 的表达对机械牵张诱导的 H9c2 心肌细胞肥大发挥保护作用。5.采用 siRNA 敲低 Notch1 表达，验证 STP 是否通过上调 Notch1 信号通路对机械牵张诱导的 H9c2 心肌细胞肥大发挥保护作用。6. TargetScan 8.0 预测潜在靶点，双荧光素酶检测 miR-34a-5p 能否直接靶向调控 Notch1，以及 STP 是否通过调控 miR-34a-5p/Notch1 通路对心肌细胞肥大模型的保护作用。结果：1. 与 Control 组相比，MS 组 ANP、BNP 的 mRNA 和蛋白表达水平升高（P<0.01）。2. STP 含药血清干预模型细胞最适剂量为低剂量（0.972g/kg）、作用时间 24 h。3. 与 MS 组相比，MS+STP 组 ANP、BNP mRNA 和蛋白表达下调（P<0.01）。4. 与 MS 组相比，MS+STP 组 miR-34a-5p 表达下调（*P*<0.01），与 MS+STP+NC 组相比，MS+STP+miR-34a-5p mimics 组 ANP、BNP 蛋白表达升高（*P*<0.01）。5. WB 验证了 siRNA 敲低 Notch1 表达，与 MS+STP+si-NC 组相比，MS+STP+si-Notch1 组 ANP、BNP 蛋白表达升高（*P*<0.01）。6. TargetScan 8.0 预测显示 miR-34a-5p 与 Notch1 3’UTR 有 4 个保守的结合序列，与 Notch1 3’UTR-WT+NC 共转染相比，Notch1 3’UTR-WT+miR-34a-5p mimic 荧光素酶活性下降（*P*<0.01），与 Notch1 3’UTR-MUT+NC 共转染相比，Notch1 3’UTR-MUT+miR-34a-5p mimic 荧光素酶活性无明显差异（*P*＞0.05）。miR-34a-5p 降低心

肌细胞中 Notch1 的表达（*P*<0.01）。WB 检测参与 Notch1 通路的关键因子 Notch1、NICD1、Hes1 的表达，与 Control 组相比，MS 组 Notch1、NICD1、Hes1 蛋白表达降低（*P*<0.01），与 MS 组相比，MS+STP 组 Notch1、NICD1、Hes1 蛋白表达升高（*P* <0.01），与 MS+STP+NC 组相比，MS+STP+miR-34a-5p mimics 组 Notch1、NICD1、Hes1 蛋白表达降低（*P* <0.05）。

结论：STP 对压力超负荷性心肌肥厚具有保护作用，其机制可能是通过影响 miR-34a-5p 负调控 Notch1 信号通路实现的。

关键词：心肌肥厚；四味土木香散；miRNA-34a-5p；Notch1 信号通路

The classical mongolian medicine "Siwei Tumuxiang Powder" improves pressure overload induced myocardial hypertrophy by regulating the miR-34a-5p/Notch1 signal pathway

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Objective: To investigate the protective effect and mechanism of Siwei Tumuxiang Powde (STP) on the model of H9c2 cardiomyoblast hypertrophy induced by mechanical stretching. **Method:** 1. Preparation of STP drug-containing serum. 2. Verify the modeling effect of the mechanical stretch-induced cell hypertrophy model. 3. Determine the optimal dose and time of action of STP drug-containing serum by detecting lactate dehydrogenase (LDH) activity. 4. The expression level of STP to ANP, BNP mRNA and protein was detected to verify whether STP exerted a protective effect on mechanical stretch-induced H9c2 cardiomyoblasts hypertrophy by downregulating the expression of miR-*34*a-5p. 5. siRNA knockdown Notch1 expression was used to verify whether STP exerts a protective effect on mechanical stretch-induced H9c2 cardiomyoblasts hypertrophy by upregulating the Notch1 signaling pathway. 6. TargetScan 8.0 predicts potential targets, and diluciferase detects whether miR-34a-5p can directly target and regulate Notch1, and whether STP protects cardiomyoblasts hypertrophy models by regulating the miR-34a-5p/Notch1 pathway. **Results:**1. Compared with the control group, the mRNA and protein expression levels of ANP and BNP were increased in the model group (*P*<0.01). 2. The optimal dose of drug-containing serum intervention model cells was a low dose (0.972g/kg) and the action time was 24h. 3. Compared with the MS group, the expression of ANP, BNP mRNA and protein in the MS+STP group was downregulated (*P*<0.01). 4. Compared with the MS group, the expression of miR-34a-5p in the MS+STP group was downregulated (*P*<0.01), and compared with the

MS+STP+NC group, the expression of ANP and BNP proteins in the MS+STP+miR-34a-5p mimics group was increased (P<0.01). 5. WB verified siRNA knockdown Notch1 expression, compared with MS+STP+si-NC group, the expression of ANP and BNP proteins in MS+STP+si-Notch1 group was elevated (P<0.01). 6. TargetScan 8.0 predictions showed that miR-34a-5p had 4 conserved binding sequences with Notch1 3'UTR, and Notch1 3'UTR-WT+NC cotransfection showed decreased Notch1 3'UTR-WT+miR-34a-5p mimic luciferase activity compared to Notch1 3'UTR-WT+NC cotransfection (P<0.01), there was no significant difference in Notch1 3'UTR-MUT+miR-34a-5p mimic luciferase activity compared to Notch1 3'UTR-MUT+NC cotransfection (P>0.05). miR-34a-5p reduces the expression of Notch1 in cardiomyoblasts (P<0.01). Compared with the Control group, the expression of Notch1, NICD1 and Hes1 proteins in the MS group was reduced (P<0.01), compared with the MS group, the expression of Notch1, NICD1 and Hes1 proteins in the MS+STP group was increased (P<0.01), and compared with the MS+STP+NC group, the expression of Notch1, NICD1 and Hes1 proteins in the MS+STP+miR-34a-5p mimics group was reduced (P<0.05).

Conclusion: STP has a protective effect on stress overload myocardial hypertrophy, and its mechanism may be realized by influencing the negative regulation of the Notch1 signaling pathway of miR-34a-5p.

Keywords: Myocardial hypertrophy; Siwei Tumuxiang Powder; miRNA-34a-5p; Notch1 signaling pathway

P9 肾脏生理

P9-1 Tiliroside protects against lipopolysaccharide-induced acute kidney injury via intrarenal renin-angiotensin system in mice

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Tiliroside, a natural flavonoid, has various biological activities and improves several

inflammatory diseases in rodents. However, the effect of tiliroside on LPS-induced acute kidney injury (AKI) and the underlying mechanisms are still unclear. The purpose of this study was to evaluate the potential renoprotective effect of tiliroside on LPS-induced AKI in mice. Male C57BL/6 mice were intraperitoneally injected with LPS (a single dose, 3 mg/kg) with or without tiliroside (50 or 200 mg/kg, one time every day for 8 days). Tiliroside administration protected against LPS-induced AKI, as reflected by ameliorated renal dysfunction and histological alterations. LPS-stimulated renal expression of inflammatory cytokines, fibrosis markers, and kidney injury markers in mice was significantly abolished by tiliroside. This flavonoid also stimulated autophagy but inhibited oxidative stress and tubular cell apoptosis in kidneys from LPS-injected mice. Mechanistically, our study showed the regulation of tiliroside on the intrarenal renin-angiotensin system in LPS-induced AKI mice. Tiliroside treatment suppressed intrarenal AGT, Renin, ACE, and AngII, but upregulated intrarenal ACE2 and Ang1-7. Collectively, our data highlight the renoprotective action of tiliroside on LPS-induced AKI by suppressing inflammation, oxidative stress, and tubular cell apoptosis and activating autophagy via the shift towards the intrarenal ACE2/Ang1-7 axis and away from the intrarenal ACE/AngII axis.

Keywords: Tiliroside; acute kidney injury; intrarenal RAS; ACE; ACE2

P9-2 Phosphoglycerate kinase 1 (PGK1) contributes to the development of diabetic nephropathy in enzyme-dependent and -independent manners

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Diabetic nephropathy (DN) is the one of the leading causes of end-stage kidney disease. Unraveling novel biomarker signatures or therapeutic targets capable to identify and treat patients

with DN may be favorable for tackle the burden. Metabolites are the end product of biochemical processes, and their changes can directly and accurately reflect metabolic alterations in the pathogenesis of DN. However, the key metabolites underlying DN progression remain to be elucidated. The non-target metabolomics and targeted metabolomics revealed that serum levels of 3-phosphoglycerate (3-PG) in DN patients was significantly elevated in the discovery and four validation sets. The level of 3-PG showed a positive association with urinary albumin creatinine ratio (UACR) in DN patients. The expression of phosphoglycerate kinase 1 (PGK1) responsible for the generation of 3-PG was also upregulated in the kidneys for humans, type 1 diabetes (T1D) mice and type 2 diabetes (T2D) mice, as well as high glucose (HG)-exposed HK-2 cells. The transcription factor paired box 5 (PAX5) was found to mediate the upregulation of PGK1 in DN. The progression of DN is robustly mitigated by renal specific knockdown of PGK1, and significantly aggravated by PGK1 overexpression or 3-PG infusion *in vivo* and *in vitro*. Through the proteomics and molecular validation, 3-PG downregulated the expression of glutathione peroxidase 1 (GPX1) and activated the NLRP3 inflammasome in HK-2 cells. Mass spectrometry and co-immunoprecipitation analyses showed that PGK1 interacted with aldehyde dehydrogenase 1 family member L1 (Aldh1l1). RNA sequencing disclosed that the PGK1/Aldh1l1 complex triggered unc-5 family C-terminal like (UN5CL)-mediated activation of nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase, leading to renal epithelial inflammation. We further screened and confirmed that three compounds had favorable binding affinity to PGK1, based on the virtual screening from 1.6 million compounds, or actual screening from a pool of natural compounds and FDA-approved drugs. Subsequently, we ascertained the therapeutic capacity of these compounds in DN mice by suppressing the protein expression and activity of PGK1. Therefore, our data showed that targeting both PGK1 and its metabolite 3-PG might be therapeutically promising for the treatment of DN.

Keywords: Diabetic nephropathy, PGK1, 3-phosphoglycerate, metabolomics; RNA sequencing; proteomics

P9-3 基于肾病综合征探讨 AQPs 在肝心脾肺肾上腺的变化

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目的 尾静脉注射盐酸阿霉素建立肾病综合征(NS)大鼠模型，观察 AQPs 在肝、心、脾、肺、肾上腺的分布及表达变化，探讨各组织水转运情况。**方法** 将 20 只 SD 大鼠随机分为模

型组和对照组。模型组予尾静脉注射盐酸阿霉素（6.0mg/kg），对照组注射等量生理盐水。造模成功后对各组织进行病理学观察，免疫组化法检测 AQP1、AQP2、AQP3、AQP9 在对应组织的分布，免疫印迹（WB）法和 RT-PCR 法检测各脏腑中 AQP1、AQP9 的蛋白和 mRNA 表达水平。**结果** 结果显示，与对照组相比，NS 大鼠脾血液充盈不足，肝、心、肺、肾上腺均出现不同程度的水肿和病理损伤；WB 和 RT-PCR 结果显示模型组中肾上腺 AQP1 和脾脏 AQP9 蛋白和 mRNA 表达水平均显著降低（P<0.05），心脏中 AQP1 蛋白和 mRNA 表达水平均显著增高（P<0.05），肝脏 AQP1 蛋白与 mRNA 表达水平无显著差异。**结论** NS 可引起肝、心、脾、肺、肾上腺等器官不同程度的病理损伤以及与水液代谢相关器官 AQPs 的表达变化。

关键词：阿霉素肾病；AQPs；肝心脾肺肾上腺；

P9-4 中性粒细胞胞外诱捕网在转基因高血压小鼠肾损伤中作用

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应用血管紧张素原（Angiotensinogen，AGT）-肾素（Renin，REN）（AGT-REN）双转基因高血压（hypertension, HT）小鼠探讨 RAS 失衡对高血压小鼠肾脏 NETs 表达水平影响；应用人急性早幼粒细胞白血病细胞系（HL-60）探讨 AngII/Ang(1-7)失衡诱导成熟中性粒细胞（dHL-60）形成中性粒细胞胞外诱捕网（NETs）的作用机制。动物实验发现，给予坎地沙坦干预后 HT 组小鼠血压显著降低，AVE0991 对小鼠血压无明显影响。HT 组小鼠肾脏重量和肾脏脏器系数均降低，两种药物干预后肾脏系数显著升高。HT 组小鼠血清和肾组织 KIM-1、血清尿素、肌酐、尿微量白蛋白及 24h 尿蛋白含量均高于野生型（WT）组，两种药无干预后上述指标均下降。HT 组小鼠肾组织出现明显肾小球纤维化和炎细胞浸润，两种药物干预减轻了小鼠肾脏病理损伤。与 WT 组小鼠相比，HT 组小鼠血清 AngII 水平升高，血清 Ang(1-7)水平降低，二者比值升高；两种药物干预后 AngII 水平降低，Ang(1-7)水平无显著变化，二者比值降低；与 WT 组小鼠相比，HT 组小鼠局部肾组织 AngII 和 Ang(1-7)水平升高，二者比值降低；两种药物干预后 Ang II 和 Ang(1-7)水平减低，但二者比值均升高。与 WT 组小鼠相比，HT 组小鼠肾组织 MPO、Cit-H3 的表达升高，两种药物干预后蛋白表达水平均降低。细胞实验发现流式细胞术检测 CD11b +细胞表达增高，视黄醇 ATRA 明显促进 HL-60 细胞成熟，细胞存活率最高。与对照组相比，Ang II 组 NETs 标志性蛋白 NE 和 Cit-H3 蛋白表达升高，AngⅡ+Ang(1-7)组和 AngⅡ+坎地沙坦组 NETs 生成减少，NE、Cit-H3 蛋白表达降低，AngⅡ+ PAD4 抑制剂 GSK 组 NETs 生成减少，NE、Cit-H3 蛋白表达降低。结果表明，AngII/Ang(1-7)失衡促进高血压肾损伤小鼠肾脏 NETs 的表达；AngII/Ang(1-7)失衡刺

激 dHL-60 细胞生成 NETs 可能与 PAD4 蛋白激活有关。

关键词：高血压；血管紧张素Ⅱ；血管紧张素 1-7；中性粒细胞胞外诱捕网；肾损伤

P9-5 刺激钙离子敏感受体对 C57BL/6 小鼠肾脏 DCT 钾离子通道 Kir4.1/Kir5.1 调控机制的研究

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目的: 刺激钙离子敏感受体(Ca^{2+}-sensing receptor，CaSR）对 C57BL/6 小鼠肾脏 DCT 钾离子通道 Kir4.1/Kir5.1 调控机制的研究。Kir4.1/Kir5.1 通道是肾远曲小管（The early distal convoluted tubule，DCT）细胞管周膜上唯一的功能性钾通道，相关研究显示，Kir4.1/Kir5.1 通道与 NCC（Na/Cl cotransporter，NCC）、ENaC (Epithelial Na^+ channel，ENaC）及钠泵等管腔/管周膜通道蛋白、转运体蛋白之间的协同作用，铸就了跨 DCT 管腔膜 Na^+的吸收及 K^+的分泌。本课题组已证实，低浓度 Ca^{2+}对大鼠肾脏髓袢升支粗段管周膜 50pS 和 100pS 钾通道具有激活作用，并且此作用是通过抑制钙敏感受体（CaSR）实现的。基于上述研究结果观察刺激钙离子敏感受体(Ca^{2+}-sensing receptor，CaSR）对 C57BL/6 小鼠肾脏 DCT 钾离子通道 Kir4.1/Kir5.1 通道活性的影响，并进一步探究其调控机制。

方法：膜片钳技术：本实验采用细胞贴附式单通道膜片钳技术、穿孔膜片钳技术、全细胞膜片钳技术，分别检测 CaSR 激动剂及抑制剂对 DCT 管周膜 Kir4.1/Kir5.1 通道的活性、DCT 细胞膜电位以及全细胞钾电流的影响。采用 Western Blotting 实验技术观察 CaSR 激动剂及抑制剂对 Na^+重吸收相关转运体及通道蛋白表达的影响。

结果：1. 膜片钳实验结果显示，CaSR 激动剂 Neomycin 降低了 C57BL/6 小鼠 DCT 管周膜 Kir4.1/Kir5.1 单通道 K^+电流的通道开放概率（Open probability，NPo）以及 DCT 全细胞 K^+电流，并且使细胞膜发生去极化。 2. 膜片钳实验结果显示，CaSR 拮抗剂 NPS2390 增加了 C57BL/6 小鼠 DCT 管周膜 Kir4.1/Kir5.1 单通道 K^+电流的通道开放概率（Open probability，NPo）以及 DCT 全细胞 K^+电流，并且使细胞膜发生超极化。3.Western Blotting 实验结果显示，CaSR 激动剂 Neomycin 能够降低 C57BL/6 小鼠肾 NCC 转运体总蛋白（tNCC）及其磷酸化（pNCC）表达水平。4. Western Blotting 实验结果显示，CaSR 体拮抗剂 NPS2390 能够增加 C57BL/6 小鼠肾 NCC 转运体总蛋白（tNCC）及其磷酸化（pNCC）表达水平。

结论：1.CaSR 激动剂 Neomycin 对 DCT 管周膜 Kir4.1/Kir5.1 通道具有抑制作用，降低 tNCC 及 pNCC 转运体蛋白表达。2.CaSR 体拮抗剂 NPS2390 对 DCT 管周膜 Kir4.1/Kir5.1 通道具有激活作用，增加 tNCC 及 pNCC 转运体蛋白表达。

关键词：膜片钳技术；远曲小管管周膜；Kir4.1/Kir5.1；钙敏感受体

P9-6 The role and mechanism of XBP1S in hyperuricemic nephropathy

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Endoplasmic reticulum stress (ERS) is closely related to the pathological process of hyperuricemic nephropathy (HN). Adenosine triphosphate binding cassette of half transporter protein (ABCG2) helps uric acid excretion. Moderate activation of XBP1S can alleviate ERS. XBP1S can directly regulate ABCG2, but the role of XBP1S in HN is still unclear. Therefore, we investigate whether XBP1S alleviates the renal damage caused by hyperuricemia through regulating ABCG2 gene In this study, Adeno-associated virus (1.7×10^{12}vg/ml) induced the overexpression of XBP1S in mice, and HN mice were generated by intragastric administration of potassium oxonate (250mg/kg/day) combined with adenine(50mg/kg/day) for 28 days. The concentrations of uric acid, creatinine and blood urea nitrogen in serum were determined by enzyme colorimetry, sarcosine oxidase method and urease method respectively; The pathological changes of the kidneys were observed using HE and Masson staining techniques; Real-time quantitative PCR and Western blot were used to detect the expression level of related genes. Furthermore, NRK-52E cells were treated with uric acid (UA, 0.9mmol/L) for 48 hours. Adeno-associated virus (1.7×10^{11}vg/ml) induced overexpression of XBP1S in NRK-52E cells. The levels of blood uric acid, creatinine and blood urea nitrogen in HN mice increased significantly, while the overexpression of XBP1S effectively weakened these changes. HE and Masson staining results showed that overexpression of XBP1S could significantly reduce renal tubular dilatation, epithelial cell loss, and tubulointerstitial fibrosis induced by hyperuricemia. In vivo and in vitro experiments have shown that the decrease in ABCG2 mRNA and protein levels induced by high uric acid can be reversed by overexpression of XBP1S. RT-qPCR and WB results showed that overexpression of XBP1S alleviated the high expression of Fibronectin and Collagen I induced by high uric acid. This study shows that XBP1S may assist excretion of uric acid and alleviate renal injury by positively regulating the gene expression of ABCG2 in HN. Targeted regulation of XBP1S is expected to become a new drug target of HN.

Keywords: Hyperuricemic nephropathy ERS XBP1S ABCG2

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P9-7 Latanoprost stimulates the basolateral Kir4.1/5.1 channel in the distal convoluted tubule

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Latanoprost is a selective FP receptor agonist, has been widely used for glaucoma treatment. The aim of the present study is to test whether Latanoprost stimulates the basolateral Kir4.1/5.1 channel in the distal convoluted tubule (DCT). Single channel and whole cell recordings demonstrated that Latanoprost stimulated the Kir4.1/5.1 channel in the DCT *in vitro* or *in vivo*. The inhibition of PLC or PKC had no significant effect on the Kir4.1/5.1 channel, and both of them failed to block the stimulatory effect of Latanoprost on the K channel. In contrast, inhibition of p38 MAPK or JNK but not ERK blocked the effect of Latanoprost on the Kir4.1/5.1 channel. Inhibition of NADPH oxidase also abrogated the stimulatory effect of Latanoprost on the Kir4.1/5.1 channel, while the addition of 1μM H_2O_2 mimicked the stimulatory effect of Latanoprost on the Kir4.1/5.1 channel. Moreover, superoxide-related species may mediate the stimulatory effect of Latanoprost on the Kir4.1/5.1 channel because the stimulatory effect of Latanoprost and H_2O_2 was not additive. Western blot analysis showed that infusion of Latanoprost *in vivo* not only increased the expression of Kir4.1 but also increased the expression of Kir5.1. We conclude that Latanoprost stimulates the basolateral Kir4.1/5.1 channel in the DCT by activating FP receptor through p38 MAPK/JNK and NADPH oxidase-dependent pathways. The stimulatory effects of Latanoprost on the Kir4.1/5.1 channel may contribute to Latanoprost-induced increases in NaCl reabsorption in the DCT.

Keywords: Latanoprost, Kir4.1/5.1 channel, distal convoluted tubule, FP receptor

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P9-8 维持性血液透析患者低相位角与全因死亡风险增加有关——项前瞻性队列研究

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背景：维持性血液透析（maintenance hemodialysis，MHD）患者普遍存在营养不良、蛋白质能量消耗、身体活动能力下降等多种并发症，降低生活质量，导致心血管事件以及死亡风险增加。而由生物电阻抗分析法测定的相位角是反映 MHD 患者营养状态及身体活动能力的良好标志物。据此，我们推测相位角可能是患者不良预后的预测指标。本研究的目的旨在确定在 MHD 患者中，相位角与全因死亡风险、住院以及主要心血管事件等不良临床预后的关系。

方法：这是一项单中心、前瞻性、观察性研究。纳入 2020 年 10 月至 2022 年 1 月在本中心透析的患者。采用生物电阻抗技术测定患者的体成分及 50kHz 相位角。采用握力、简易体能状况量表（Short Physical Performance Battery, SPPB）、4 米步速以及计时起立-步行测验（Timed Up and Go Test，TUGT）评估患者的肌力及身体活动能力。通过营养不良炎症评分（Malnutrition-Inflammation Score，MIS）评估患者的营养状况。根据相位角的中位数（4.3°）将患者分为两组：低相位角组（n=71），相位角范围（最小-最大值）2.3-4.2°；高相位角组（n=71），相位角范围 4.3-6.8°。主要结局为全因死亡，生存时间定义为从纳入研究到出现主要临床结局或完成 1 年的随访。同时记录患者 1 年内的住院次数以及主要不良心血管事件（MACE）。生存分析采用 Cox 比例风险模型，评价指标为风险比（Hazard Ratio，HR），并使用 Kaplan-Meier 方法绘制生存曲线。

结果：本研究最终纳入 142 名 MHD 患者，中位年龄(四分位数间距)为 66 岁(58 - 72 岁)，其中 59%为男性。两组基线比较显示，高相位角组患者更年轻、男性比例更高、合并心血管疾病、糖尿病及营养不良比例更低，而血红蛋白、转铁蛋白饱和度、血清白蛋白水平显著升高。体成分比较显示，高相位角组患者细胞外水比率（ECW/TBW）显著下降，骨骼肌指数（SMI）显著升高。高相位角患者的各项活动能力表现更好（SPPB， P <0.001；步速，P=0.003；TUGT，P <0.001；握力，P <0.001）。

所有患者平均随访时间 439 天，期间 14 名患者死亡，其中脓毒症 6 例、脑出血 3 例、心力衰竭 3 例、心肌梗死 1 例、肿瘤 1 例。低相位角组患者死亡 12 例，高相位角组死亡 2 例。随访期间共有 70 名患者曾住院治疗，其中低相位角组 40 例（56.3%），高相位角组 30 例（42.3%）。1 年内发生主要不良心血管事件 13 次，低相位角组 8 次（11.3%），高相位角组 5 次（7.0%）。单因素 Logistics 回归分析显示，相位角、MIS、SPPB 是全因死亡率和住院的预测因素。校正了年龄、性别、MIS 以及 SPPB 后，低相位角组全因死亡风险显著高于高相位角组（HR：6.67；95%CI：1.22-36.57；P=0.029）。

结论：本研究表明，在维持性血透患者中，低相位角与 1 年全因死亡风险增加显著相关。可以考虑在临床实践中常态化监测相位角变化，以预判患者的预后情况。

关键词：血液透析，相位角，全因死亡

P9-9 基于临床数据库建立急性肾损伤风险预测模型

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背景：急性肾损伤(acute kidney disease, AKI)是一种以肾脏功能快速降低为特点的临床综合征。我国的流行病学资料显示，每年至少有 290 万例成年 AKI 患者住院治疗，其中约 70 万例死亡，存活的患者中约 2/3 进展到慢性肾脏疾病（chronic kidney disease，CKD）。早期识别 AKI 风险并及时干预是改善 AKI 患者预后的关键环节。目前针对 AKI 风险预测模型多基于单一病因建立 AKI 风险预测模型，然而临床患者发生 AKI 前尚无法预计是何种病因导致 AKI。本研究中，我们基于大样本数据库平台，应用 R 语言、机器学习及传统统计学方法构建 AKI 的发病风险因素的预测模型，同时验证模型的准确性。

方法：根据 KDIGO 中 AKI 诊断标准筛选 2021 年 1 月 1 日至 2021 年 12 月 31 日同济医院就诊患者中符合 AKI 诊断标准的患者，同时纳入 48 小时内监测血清肌酐水平但未发生 AKI 患者作为对照组。最终，总共 5671 名患者被分为 AKI 组和非 AKI 组，收集两组患者的慢性疾病史、手术史、用药史以及实验室检查数据等，以评估临床上发生 AKI 的风险因素。应用列线图模型和机械学习模型来评估 AKI 发病因素的预测价值。首先，基于多变量逻辑回归分析及逐步回归分析，筛选 P 值 < 0.05 的变量包括在最终模型中，将这些风险预测因子构建了列线图模型和机械学习模型，并收集了外院患者信息进行了外部验证，并通过说明受试者工作曲线和计算曲线下面积（area under curve，AUC）来确定模型的区分度，同时进行决策曲线分析（decision curve analysis，DCA）以评估临床净效益。最后，运用逻辑回归（logistic regression，）、决策树（decision tree）、极端梯度提升（eXtreme gradient boosting，Xgboost）、支持向量机（support Vector Machine，SVM）、随机森林（random forest，RF），梯度提升树（gradient boosted decision tree, GBDT），、梯度提升机（gradient boosting machine，GBM）共 7 种模型对发生 AKI 的预测变量进行分析，通过准确率（accuracy）、精确率（precision）、召回率（recall）、AUC、F1 值（F1score）综合评价预测效能，并根据预测效能选择最适宜的模型，从而建立可视化决策树模型。

结果：纳入研究的 AKI 患者有 1884 例(33.2%)。多因素逻辑分析显示，血肌酐、性别、慢性肾脏疾病、高血压、糖尿病、脑血管意外、手术史、尿素氮是 AKI 发生的独立风险因素。构建纳入慢性肾脏疾病、高血压、肌红蛋白、血肌酐、尿素氮等元素的列线图模型，该预测模型的 AUC 为 0.919 [95%CI:0.911-0.927；P < 0.001],校准曲线显示，列线图的校准效果良好(p 值>0.05)，决策曲线结果显示当列线图模型阈值>0.04 时，该模型构建在临床上是有用的。各种机械学习分类器显示，Accuracy>0.79 说明该预测模型的准确率较高；

Precision>0.78 说明该模型的精确率较高；除 Logist 和 SVM 外，其余分类器显示 Recall>0.81，说明 AKI 检测率较高；Logist、Decision tree、Xgboost、SVM、Random forest，GBDT、GBM 的 AUC 值依次为 0.87、0.86、0.92、0.84、0.97，0.98 和 0.98。综合上述指标，本研究最终使用 GBM 模型筛选出的预测变量建立可视化决策树模型。

结论：本研究建立了预测 AKI 发生的列线图模型及可视化决策树预测模型，这两种模型的建立有助于临床医师及早发现高危患者，预防 AKI 的发生，及时干预，改善预后。

关键词：急性肾损伤，临床数据库，机械学习，决策树模型，列线图

P9-10 A small natural molecule targets cdc42-mediated gsk-3β/β-catenin signaling to combat kidney fibrosis

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Renal fibrosis is a common fate of chronic kidney diseases (CKD) that eventually leads to renal dysfunction. Yet, there is no effective treatment for this pathological process. During our bioassay-guided chemical investigation of medicinal plant W*ikstroemia chamaedaphne*, a daphne diterpenoid, daphnepedunin A (diterpenoid 15), is identified as a promising anti-renal fibrotic lead. Diterpenoid 15 shows significant anti-renal fibrosis effects in cultured renal fibroblasts and unilateral ureteral obstruction-induced kidney fibrosis, more potent than the clinical trial drug pirfenidone. Leveraging the MS-CETSA and proteomic techniques, we find cell division cycle 42 (Cdc42), a GTPase, as the direct target of diterpenoid 15. Mechanistically, diterpenoid 15 targets to reduce Cdc42 activity and down-regulate its downstream phospho-PKCζ/GSK-3β, which in turn promotes β-catenin Ser33/37/Thr41 phosphorylation and primes β-catenin for ubiquitin proteolysis, and finally blocks the classical pro-fibrotic β-catenin signaling. These findings suggest that Cdc42 is a possible therapeutic target for renal fibrosis, and diterpenoid 15 has great potential as a Cdc42 inhibitor for the treatment of CKD.

Keywords: Renal fibrosis; Small natural molecule; GSK-3β/β-catenin; Cdc42

P9-11 Biochanin A suppressed Klf6-Smad3 signaling to attenuate renal fibrosis

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TGF-β/Smad3 signaling is the master pathway controlling renal fibrosis in chronic kidney disease. Biochanin A (BCA), a botanical isoflavone, has multiple pharmaceutic activities. Our previous data showed that BCA can attenuate renal fibrosis by specifically down-regulating the RNA and protein levels of pro-fibrotic *Smad3*, suggesting the suppressed *Smad3* transcription. However, the underlying mechanism remains unclear. In this study, the combination of RNA-seq and transcriptional factor binding prediction was used to uncover the upstream mechanism mediating the suppressed transcription of *Smad3* by BCA, which was further validated in vitro and in vivo. RNA-seq analysis found that BCA treatment significantly affect the gene expression of TGF-β signaling in mouse renal tubular cells (TCMK1). Again, RNA-seq also confirmed that *Smad3* but not *Smad2* was transcriptionally down-regulated by BCA. Promoter binding prediction found 711 potential transcriptional factors on the 2-kb Smad3 promoter region, among which 95 transcriptional factor shows differential expression following BCA treatment. In those transcriptional factors, Klf6 was found to be upregulated by TGF-β1 stimulation and further down-regulated by BCA treatment. Overexpression of Klf6 promoted the transcriptional activity of the *Smad3* promoter-driven luciferase reporter vector, as well as the mRNA and protein expression of endogenous *Smad3* gene in TCMK1 cells. Most importantly, BCA treatment attenuated the fibrotic gene expression including a-SMA, fibronectin, and Col1a1 in TGF-β1-stimualted TCMK1 cells and in mice with unilateral ureter ligation, which, however, was abolished by Klf6 overexpression. Collectively, our findings demonstrated that BCA executes its anti-renal fibrosis effect by suppressing Klf6-mediated Smad3 expression.

Keywords: biochanin A, UUO, Smad3, Klf6, renal fibrosis

P9-12 Integrin αVβ6 induces macrophage infiltration and activation to promote renal inflammation and fibrosis through activating tubular production of IL-34

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Objective: Integrin αVβ6 is a promising therapeutic target for renal fibrosis. However, the use of αVβ6 inhibitors in fibrosis has been hampered by concerns about severe inflammatory effects. Clarifying the role of αVβ6 on renal inflammation is crucial for the feasibility of αVβ6-targeted therapy for CKD.

Methods: In the mouse model of unilateral renal ischemia-reperfusion injury (uIRI), expression and correlation of αvβ6, inflammatory markers and immune cells in the kidney were detected. Wild-type and ITGB6 knockout uIRI were established, and renal inflammation and fibrosis phenotypes were assessed by flow cytometry to detect immune cells and q-PCR to detect inflammation indicators. In vitro, tubular epithelial cells (TECs) transfected with si-NC or si-ITGB6 were co-cultured with macrophages RAW264.7 under hypoxia/reoxygenation (H/R) conditions to elucidate the mechanism of crosstalk.

Results: Increased tubular αVβ6 expression during renal fibrosis was positively correlated with the accumulation of macrophages and inflammatory cytokines, including IL-1β, TNF-α, and MCP-1. Compared to the controls, ITGB6$^{-/-}$ strikingly alleviated renal inflammation and fibrosis. Kidney immune cell profiling showed that the proportion of macrophages was markedly reduced in ITGB6$^{-/-}$ kidneys, while T cells, B cells, neutrophils, and dendritic cells were largely unchanged. In co-cultures, knockdown of tubular αVβ6 effectively blocked macrophage migration and proliferation, as well as differentiation into M1 after H/R injury, as demonstrated by down-regulation of IL-1β, IL-6, TNF-α, MCP-1, and IL-12. Mechanistically, by detecting key cytokines involved in the crosstalk between TECs and macrophages, it was found that the secretion of IL-34 by TECs was significantly reduced after αVβ6 silencing. Supplementation of IL-34 in conditioned supernatants of si-ITGB6 transfections restored macrophage activation by TECs.

Conclusions: Tubular αVβ6 promotes the differentiation, migration and proliferation of macrophages by activating the secretion of IL-34, exacerbating the inflammatory response in the process of renal fibrosis.

Key words: renal fibrosis, inflammation, αVβ6, macrophage

P9-13 Inhibition of ACSS2-mediated H3K9 crotonylation alleviates kidney fibrosis via IL-1β-dependent macrophage activation and tubular cell senescence

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Chronic kidney disease (CKD) is characterized by sustained inflammation and progressive fibrosis, where therapies to slow CKD progression are limited. Histone lysine crotonylation (Kcr), a novel posttranslational modification, is widespread as acetylation (Kac); however, its roles in CKD are largely unknown. In this study, we report that histone Kcr of tubular epithelial cells was significantly elevated in the fibrotic kidneys of patients and mice, positively correlating with disease progression. Interestingly, abnormal increases in histone 3 lysine 9 crotonylation (H3K9cr) among kidneys with unilateral ureteric obstruction (UUO) and folic acid nephropathy (FAN) completely differed from the stable expression of H3K9ac, indicating that H3K9cr may exert extraordinary functions in kidney fibrosis. By screening these crotonylated/acetylated factors, a crotonyl-CoA-producing enzyme—ACSS2 (acyl-CoA synthetase short chain family member 2)—was found to remarkably promote H3K9cr without influencing H3K9ac. Combined analysis of ChIP and RNA sequencing revealed that the hub proinflammatory cytokine, IL-1β (which is regulated by H3K9cr), may play a significant role in kidney fibrosis. Genetic and pharmacologic inhibition of ACSS2 both attenuated kidney injury and fibrosis, as well as suppressed H3K9cr-mediated IL-1β expression, which thereby alleviated IL-1β-dependent macrophage activation and tubular cell senescence. Collectively, our findings uncover that H3K9cr plays a critical, previously unrecognized role in kidney fibrosis, where ACSS2 represents an attractive target for strategies that aim to slow fibrotic kidney disease progression.

Keywords: Kidney fibrosis, histone crotonylation, **acyl-CoA synthetase short chain family member 2,** macrophage activation, tubular cell senescence

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P9-14 慢性肾病患者的生物补充剂:随机对照试验的荟萃分析

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目的:肠道菌群失衡是慢性肾病(CKD)患者的特征。尽管生物补充剂已被提出可以减轻炎症和氧化应激，从而降低进行性肾损伤和心血管疾病的风险，但其效果仍存在争议。我们进行了一项荟萃分析，以评估生物制剂对慢性肾病的治疗益处。

方法:系统地检索 PubMed, Embase 和 Cochrane 数据库，以评估 CKD (CKD, 3-4 期至终末期肾病)患者的任何生物(益生元，益生菌，合成制剂)补充剂的随机对照试验。主要终点包括肾功能、炎症标志物和氧化应激的变化。次要终点包括尿毒症毒素水平的变化和脂质代谢的变化。

结果:23 项符合条件的研究包括 842 名参与者。在一项综合分析中，益生元没有改变肾小球滤过率(平均差值[MD] = 0.08, P =.92)或血清白蛋白(MD = 20.01, P =.86)，尽管益生元降低了血清肌酐(标准化平均差值[SMD] = 20.23, P . =.009)和血尿素氮(MD = -6.05, P <.00001)。生物制剂提高了总抗氧化能力(smd= 0.37, P =.007)和丙二醛(smd= -0.96, P =.006)，降低了炎症标志物白介素-6 (smd= -0.30, P =.01)，但没有降低 c 反应蛋白(smd= -0.22, P =.20)。生物干预减少了一些尿毒症毒素，包括对甲酚硫酸盐(SMD = -2.18, P <.0001)和吲哚酚硫酸盐(SMD = -5.14, P <.0009)，这些毒素在透析依赖患者中减少。另一种毒素吲哚-3-乙酸(MD = -0.22, P = .63)没有变化。生物干预对血脂没有影响(总胆固醇:smd5 20.01, P 5.89;高密度脂蛋白:smd= -0.08, p= .76;低密度脂蛋白:md=3.54, p=.28;甘油三酯:MD = -2.26, P =.58)。

结论:结果表明，生物制剂对 CKD 患者循环指标肌酐、氧化应激(丙二醛、总抗氧化能力)、炎症(白细胞介素-6)和尿毒症毒素(对甲酚硫酸盐)有良好影响。在透析前或透析患者中，生物制剂不影响肾小球滤过率、白蛋白、吲哚-3-乙酸或脂质。

关键词：慢性肾脏病；生物补充剂；荟萃分析

P9-15 Btg2 promotes focal segmental glomerulosclerosis via smad3-dependent podocyte-mesenchymal transition

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Podocyte injury plays a critical role in the progression of focal segmental glomerulosclerosis (FSGS). Here we report that B-cell translocation gene 2 (Btg2) promotes Adriamycin (ADR)-induced FSGS via Smad3-dependent podocyte-mesenchymal transition. It was found that in FSGS patients and animal models, Btg2 was markedly upregulated by podocytes and correlated with progressive renal injury. Podocyte-specific deletion of Btg2 protected against the onset of proteinuria and glomerulosclerosis in ADR-treated mice along with inhibition of EMT markers such as α-SMA and vimentin while restoring epithelial marker E-cadherin. In cultured MPC5 podocytes, overexpression of Btg2 largely promoted ADR and TGF-β1-induced EMT and fibrosis, which was further enhanced by overexpressing Btg2 but blocked by disrupting Btg2. Mechanistically, Btg2 was rapidly induced by TGF-β1 and then bound Smad3 but not Smad2 to promote Smad3 signaling and podocyte EMT, which was again exacerbated by overexpressing Btg2 but blocked by deleting Btg2 in MPC5 podocytes. Interestingly, blockade of Smad3 signaling with a Smad3 inhibitor SIS3 was also capable of inhibiting Btg2 expression and Btg2-mediated podocyte EMT, revealing a TGF-β/Smad3-Btg2 circuit mechanism in Btg2-mediated podocyte injury in FSGS. In conclusion, Btg2 is pathogenic in FSGS and promotes podocyte injury via a Smad3-dependent EMT pathway.

Keywords: focal segmental glomerulosclerosis, Btg2, epithelial-mesenchymal transition, podocyte, TGF-β/Smad3 signaling

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P9-16 LncRNA-gm33782 activates MLL3/MLL4 complex regulated H3K4 methylation to exacerbate renal injury in AKI mice

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Numerous studies have shown that long chain non coding RNAs play an important role in AKI renal injury. However, the epigenetic mechanism by which LncRNA participates in the regulation of AKI injury is still unclear. In this study, we found through LncRNA sequencing and validation that LncR-gm33782 is highly expressed in mouse kidneys in both cisplatin induced AKI and ischemia-reperfusion induced AKI. The FISH results indicated that LncR-gm33782 is mainly expressed in renal tubular cells. Knocking down LncR-gm33782 in situ in kidney through CRISPR/CAS13d technology based electrotransfection can significantly downregulate ischemia-reperfusion induced renal injury. Knockdown or overexpression of LncR-gm33782 in vitro cell also demonstrated the key role of LncR-gm33782 in maintaining cisplatin stimulated renal cell damage. The subsequent transcriptome sequencing results of LncR-gm33782 overexpression cells showed that overexpression of LncR-gm33782 strongly activated the MLL3/4 complex (PA1, MLL3 and MLL4), which was mainly involved in H3K4 methylation. Overexpression of LncR-gm33782 upregulates PTIP, H3K4 dimethylation and trimethylation activity, indicating that LncR-gm33782 can regulate H3K4 methylation through MLL3/4 complex. This finding suggests that LncR-gm33782 mainly promotes AKI renal injury through epigenetics based on methylation modification in AKI, and its potential mechanism is related to regulating the MLL3/4 complex.

Keywords: LncR-gm33782; Methylation; MLL3/4 complex; AKI; PA1

P9-17 前列环素及其受体在肾脏纤维化中的作用及机制

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方法 构建单侧输尿管结扎（UUO)模型及单侧缺血再灌注（IR)联合肾切除模型。分析纳入 CKD 患者及健康对照的单细胞测序数据库。

结果

1、分析数据库发现，CKD 时，人肾脏的前列环素合成酶（PTGIS）的 mRNA 水平显著增加，且与 eGFR 成负相关。

2、UUO 后，*Ptgis* 全身敲除杂合子（$Ptgis^{+/-}$）小鼠和 $Ptgis^{+/+}$小鼠的肾脏 PGIS 表达均较对应假手术组小鼠显著增加，$Ptgis^{+/-}$小鼠肾脏 PGIS 水平显著低于 $Ptgis^{+/+}$小鼠。UUO 后，$Ptgis^{+/-}$小鼠肾脏的纤维化程度较野生型小鼠更重。

3、通过分析单细胞测序的结果，明确内皮细胞是人肾脏表达 *PTGIS* 的主要细胞。UUO 后，内皮细胞特异性 PGIS 基因敲除小鼠（ $Ptgis^{fl/fl}$ Tek^{Cre+} ）肾脏的纤维化程度较对照组小

鼠更重。

4、在 IR 后 6 周诱导内皮细胞 *Ptgis* 敲除，IR 后 12、20、30 周时 $Ptgis^{fl/fl}$ $Tek^{CreERT2+}$小鼠的肾脏纤维化程度较对照组小鼠更重。 IR 后 20、30 周时，$Ptgis^{fl/fl}$ $Tek^{CreERT2+}$小鼠的 Scr 及 BUN 较对照组小鼠显著增加。

5、野生型小鼠在 IR 后 32 天灌胃给予每天两次 PGI_2 类似物，IR 后 56 天时给药组的肾脏纤维化程度更轻。

6、前列环素受体（PTGIR）是 PGI_2 的细胞膜受体，亦有研究表明 PPARδ 也是 PGI_2 的受体之一。UUO 模型中，$Ptgir^{+/-}$小鼠的肾脏纤维化程度较对照组小鼠更重，而 $Ppard^{+/-}$小鼠的肾脏纤维化程度与对照组小鼠无显著差异。

7、野生型小鼠在 IR 后 32 天灌胃给予每天两次 PTGIR 特异性激动剂，IR 后 56 天时给药组的肾脏纤维化程度更轻。

8、单细胞测序结果显示，在人肾脏发生纤维化时，成纤维细胞和肌成纤维细胞是表达 PTGIR 的主要细胞。

9、UUO 后，$Ptgir^{fl/fl}$ $Col1a2^{CreER+}$小鼠肾脏的纤维化程度较对照组小鼠更重。

10、在大鼠肾成纤维细胞系和人原代肾成纤维细胞中，PGI_2 类似物或 PTGIR 特异性激动剂可以减少 TGF-β 诱导的成纤维细胞活化。激活 PTGIR 可以通过活化 PKA 增加 CREB 磷酸化水平。免疫共沉淀显示，增加的 p-CREB 通过与 CBP 结合，竞争性抑制 p-SMAD2 与 CBP 结合，最终可降低 Fibronectin 以及 α-SMA 的转录。

结论 肾脏纤维化时，肾脏 PTGIS 表达增加，抑制 PGI_2 产生会加重肾脏纤维化程度。PGI_2 的类似物或 PTGIR 特异性激动剂可以减轻 IR 模型导致的肾脏纤维化。PGI_2 可能通过作用于成纤维细胞和肌成纤维细胞的 PTGIR 保护肾脏纤维化。

关键词：前列环素 纤维化 成纤维细胞

P9-18 血管紧张素 II 激活高钾饮食小鼠肾远曲小管末段 ROMK 通道

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摘 要：本文旨在研究血管紧张素 II (Angiotensin II，Ang II)对高钾饮食小鼠肾远曲小管末段(late distal convoluted tubule，DCT2) 肾外髓钾通道(renal outer medullary potassium channel，ROMK)活动的影响，从离子通道水平揭示高钾饮食条件下 Ang II 对肾脏的保护作

用及可能机制。膜片钳结果显示，Ang II 能够增加高钾饮食小鼠肾 DCT2 管腔膜 ROMK 通道活性，且具有剂量依赖性；血管紧张素 1 型受体(Angiotensin type 1 receptor，AT_1R)拮抗药 Losartan 并未阻断 Ang II 对高钾饮食小鼠肾 DCT2 管腔膜 ROMK 通道的激活作用；而血管紧张素 2 型受体(Angiotensin type 2 receptor，AT_2R)拮抗药 PD123319 能够完全阻断该激活作用，AT_2R 激动药 CGP-42112 可模拟 Ang II 对 ROMK 通道的激活作用。免疫组织化学结果显示，AT_2R 在小鼠肾远曲小管(distal convoluted tubule，DCT)管腔膜上呈特异性表达。Western blot 结果显示，与正常钾饮食组相比，高钾饮食能够显著增加小鼠肾组织 AT_2R 蛋白表达水平(P<0.05)；Ang II 能够显著上调高钾饮食小鼠肾组织 ROMK 通道蛋白表达(P<0.01)。此外，Ang II 灌注能明显增加高钾饮食小鼠尿钾排泄量(P<0.01)。上述结果提示，Ang II 通过 AT_2R 介导高钾饮食小鼠肾远曲小管末段 ROMK 通道的激活作用，促进尿钾排泄。

关键词：血管紧张素 II；血管紧张素 2 型受体；肾外髓钾通道；远曲小管末段；高钾饮食；膜片钳

Activation of renal outer medullary potassium channel in the late distal convoluted tubule by Angiotensin II on a high potassium diet

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The purpose of the present study was mainly to investigate the effects of Angiotensin II (Ang II) on the renal outer medullary potassium (ROMK) channels in the apical membrane of renal late distal convoluted tubules (DCT2) during high potassium (HK) intake conditions and to elucidate the protective effects of Ang II and possible mechanism of kidney on high potassium diet from ion channel levels. Patch-clamp results showed that the channel open probability (NPo) of ROMK channels were increased by Ang II in a dose-dependent manner in the renal apical membrane of DCT2 during HK intake. AT_1R antagonist Losartan did not block the activation of Ang II on ROMK channels in the renal DCT2 during HK intake; While AT_2R antagonist PD123319 was able to completely block this activating effect, AT_2R agonist CGP-42112 could mimic the activation effect of Ang II on ROMK channels. Immunohistochemistry showed that AT_2R was specifically expressed in the apical membrane of renal distal convoluted tubules (DCT). Western blot showed

that HK diet significantly increased the protein expression of AT_2R in renal tissues (P <0.05) but not AT_1R (P> 0.05) compared to the NK group; Ang II significantly upregulated ROMK channel protein expression during HK intake (P <0.01). In addition, Ang II perfusion significantly increased urinary potassium excretion during HK intake (P <0.01). These results suggest that AT_2R non-AT_1R mediates the activation of Ang II on ROMK channels in the apical membrane of renal DCT2 during HK intake and promotes urinary potassium excretion.

Key words: Ang II; AT_2R; ROMK; DCT2; high potassium diet; patch-clamp

P9-19 RfxCas13d-mediated inhibition of Circ1647 alleviates renal fibrosis via PI3K/Akt signaling pathway

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Background: Circular RNAs (CircRNAs) have been shown to be involved in the development of chronic kidney disease (CKD). However, only a limited number of CircRNAs have been reported, and their functions remain largely unknown. This study aimed to investigate the role of *Circ1647* in renal fibrosis, which is a hallmark of CKD.

Methods: In this study, we established a unilateral ureteral obstruction (UUO) model and delivered *Circ1647* RfxCas13d knockdown plasmid into renal parenchymal cells via renal vein injection followed by electroporation. Immediately after that, the pathological changes were determined by Hematoxylin and Eosin. Meanwhile, Immunohistochemistry, Real-time PCR and Western blot were conducted to assess the degree of fibrosis. In addition, overexpressing of *Circ1647* in renal tubular epithelial cells (TCMK1) was performed to investigate the underlying mechanisms of *Circ1647*.

Results: Our results displayed that electroporation-mediated knockdown of *Circ1647* by

RfxCas13d knockdown plasmid significantly inhibited renal fibrosis in UUO mice as evidenced by reduced expression of α-SMA and fibronectin. Conversely, overexpression of *Circ1647* in TCMK1 cells promoted the fibrosis. In terms of mechanism, *Circ1647* may mediate the PI3K/AKT Signaling Pathway as demonstrated by the balance of the phosphorylation of PI3K and AKT in vivo and the aggravated phosphorylation of PI3K and AKT in vitro.

Conclusion: Our study suggests that *Circ1647* plays a significant role in renal fibrosis by mediating the PI3K/Akt signaling pathway. RfxCas13d-mediated inhibition of *Circ1647* may serve as a therapeutic target for renal fibrosis in CKD. These findings provide new insights into the pathogenesis of CKD and potential therapeutic targets for the disease.

Keywords: *Circ1647*, CKD, Akt, RfxCas13d

P9-20 柴胡皂苷 D 通过抑制 TGF-β/Smad3/HK2 信号通路活化介导的糖酵解反应改善 CKD 肾脏纤维化的作用机制研究

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背景：慢性肾病（chronic kidney disease，CKD）常对人类生命健康构成巨大危害，柴胡皂苷 D（SSD）具有良好抗纤维化效果，但是在慢性肾病作及用机制尚有待研究，已有研究表明 HK2 是受 TGF-β 诱导升高的参与糖酵解反应的关键激酶能够促进肾脏纤维化的发生，TGF-β/Smad3 信号通路的激活也被广泛报道称对肾脏纤维化起促进作用，然而 Smad3 对 HK2 的直接调控关系还有待验证。

方法：分别构建单侧输尿管梗阻（UUO）和腺嘌呤诱（ADE）诱导的 CKD 模型并给予低剂量（50mg/kg）、高剂量（100mg/kg）的 SSD 进行治疗干预，通过检测肾脏病理、肾功以及纤维化相关蛋白 FN、α-SMA 和 Col-Ⅰ的表达变化情况评价 SSD 对 CKD 的改善效果，体外通过 TGF-β 诱导 TCMK1 细胞纤维化进一步验证 SSD 对肾脏纤维化的作用。机制方面，采用转录组测序手段分析经 SSD 治疗和未经治疗的 CKD 小鼠肾脏基因并筛选差异基因进行研究；体外观察 SSD 对肾小管细胞糖酵解反应以及 TGF-β/Smad3 信号通路抑制效果，并检测 HK2 敲低后对细胞纤维化的改善作用。最后通过 Co-IP 实验明确 Smad3 与 HK2 的相互作用关系，开展回复实验给予糖酵解糖激动剂 TEPP46 以促进细胞糖酵解反应后观察 SSD 对肾小管细胞纤维化的改善作用是否受到抑制。

结果：SSD 高剂量能够明显减轻 UUO 和 ADE 诱导的小鼠 CKD 肾脏病理损伤和肾脏纤维化的发生，同时也能够改善肾功；80μg/ml 的 SSD 对 TCMK1 细胞纤维化蛋白表达有明显抑制效果。转录组测序结果显示，相对 CKD 模型组，SSD 给药干预后 HK2 显著下降，而体内外实验验证结果均显示 SSD 能够抑制 TGF-β/Smad3 信号通路和 HK2 在 CKD 模型中的

激活和表达，后续实验待开展 HK2 敲低后功能验证以及 Smad3 与 HK2 的相互作用关系验证。

结论：本研究明确了 SSD 是柴黄益肾颗粒剂中的主要成分，能够有效改善 CKD 肾脏纤维化的作用并有望阐明其通过阻断 Smad3 对 HK2 的调控作用抑制糖酵解反应的作用机制，为今后 CKD 的治疗方向提供新的思路。

P9-21 空间联合单细胞转录组测序揭示肾小球细胞分子特征及其机制研究

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目的：由多种细胞类型构成的肾小球发挥关键的滤过屏障作用，其中一种细胞的损伤均可导致滤过屏障的失衡，但是肾小球不同细胞的分子特征目前仍未明确。

方法：通过儿童肾脏的单细胞转录组测序与空间转录组测序，我们获取了肾小球毛细血管袢内皮细胞（EC-GC）、系膜细胞（Mes）和足细胞（Pod）的特征表达基因，并根据其特征基因富集了细胞类型特异性的功能与代谢特征。

结果：肾脏内皮细胞的重聚类分析和空间转录组数据证实 SOST 和 GATA5 是 EC-GC 特征转录因子，与小分子滤过相关的 GJA5 可能是人 EC-GC 新的标记分子。Mes 与血管平滑肌细胞具有类似的特征基因表达，但是 Mes 特征性表达 IL1RL1，POSTN，PDGFRA 和 CHRDL1 等基因，其中与细胞粘附相关的 RAPH1 可能是人 Mes 新的标记分子。人足细胞的不仅表达经典的标记分子，还特异性表达微管相关蛋白 TPPP3。肾组织免疫组化与免疫荧光结果均证实 TPPP3 在人肾小球中特异性表达，并发现足细胞病患儿肾小球中 TPPP3 显著降低。超分辨免疫荧光与免疫电镜提示 TPPP3 与足细胞中微管蛋白存在共定位关系。通过 siRNA 抑制足细胞系中 TPPP3 后发现微管结构解聚，形成不连续片段，与微管稳定性相关的乙酰化 tubulin 连续性显著破坏，形成点状不连续片段。CO-IP 实验证实 TPPP3 与 HDAC6 直接结合，抑制 TPPP3 后 HDAC6 去乙酰化酶活性显著增强。同时，体内外研究均证实给予特异性 HDAC6 抑制剂 TSA 后能够逆转抑制 TPPP3 后乙酰化 tubulin 的连续性中断。

结论：本研究明确了人 EC-GC，Mes 和 Pod 的分子特征，并证实人足细胞新标记分子 TPPP3 可能与足细胞的微管稳定性有关，TPPP3 通过与 HDAC6 直接结合抑制其去乙酰化酶活性，维持足细胞微管的高乙酰化水平。TPPP3 表达降低可能导致足细胞微管乙酰化水平降低从而导致足细胞微管紊乱，细胞骨架结构破坏。特异性抑制 HDAC6 可能通过保护足细胞微管乙酰化水平，可能是一种新的足细胞保护策略。

关键词：肾小球，足细胞，微管，TPPP3，HDAC6

P9-22 基于转录组测序分析黄芪三七合剂改善肾脏纤维化的关键 LncRNA

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目的 通过对单侧输尿管结扎小鼠组及黄芪三七合剂干预组的肾脏进行转录组测序，利用生物信息学验证差异显著的 lncRNA，探究黄芪三七合剂（AP）对改善肾脏纤维化的潜在机制。**方法** 将 24 只 C57 小鼠分为假手术组、肾脏纤维化组、黄芪三七合剂干预组（3.944 g/kg）及厄贝沙坦阳性对照干预组，每组 6 只小鼠。采用单侧输尿管结扎（UUO）建立肾纤维化小鼠模型。术后予以灌胃给药，连续给药 7 d 后处死动物并采集标本。通过 HE、Masson 染色分析黄芪三七合剂对肾纤维化病理损伤的改变，同时通过 Western blot、免疫组化检测各组肾脏组织 Fn、α-SMA 的蛋白水平，评估黄芪三七合剂对肾纤维化的缓解作用。随后通过转录组测序，获取了 lncRNA 的表达信息，在分析数据质量、GO 富集和差异 lncRNA 后进行 Real-time PCR 验证。**结果** 与模型组比较，黄芪三七合剂干预组小鼠的肾脏纤维化明显减轻，其肾脏组织中 α-SMA、Fn 的蛋白水平及 lncRNA 的表达量均显著下调。（$P<0.0001$）。筛选出 3 个 lncRNA 在模型组增加且 AP 干预后显著降低，分别为 lncRNA Gm29994、Gm51500 及 Gm35391。**结论** 黄芪三七合剂可改善肾脏纤维化，Gm29994、Gm51500 及 Gm35391 可能是黄芪三七合剂保护肾脏抑制纤维化的关键 lncRNA 靶点。

关键词：黄芪三七合剂； 肾脏纤维化； lncRNA； 高通量测序

Analysis of key LncRNA for HuangQi Sanqi Mixture to ameliorates renal interstitial fibrosis in UUO mice based on transcriptome sequencing

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Objective To explore the potential of Huangqi Sanqi mixture (AP) in improving renal fibrosis by performing transcriptome sequencing of the kidneys of the unilateral ureteral ligation mouse group and the Huangqi Sanqi mixture intervention group, and using bioinformatics to verify the signitficantly different IncRNAs mechanism. **Methods** Twenty-four C57 mice were divided into sham operation group, renal fibrosis group, Huangqi Sanqi mixture intervention

group (3. 944g/kg) and irbesartan positive control intervention group, with 6 mice in each group. A mouse model of renal fibrosis was established by unilateral ureteral ligation (UUO). The animals were given intragastric administration after operation, and the animals were sacrificed and the specimens were collected after seven consecutive days of administration. The changes of Huangqi Sanqi mixture on renal fibrosis pathological damage were analyzed by HE and Masson staining, and the protein levels of Fn and a-SMA in renal tissue of each group were detected by Western blot and immunohistochemistry. the alleviating effect.Subsequently,the expression information of IncRNA was obtained by transcriptome sequencing. and Real-time PCR was performed after analyzing data quality, GO enrichment and differential IncRNA. **Results** Compared with the model group, the renal fibrosis of the mice in the Huangqi Sanqi mixture intervention group was significantly reduced, and the protein levels of a-SMA and Fn and the expression of IncRNA in the renal tissue were significantly down-regulated. ($P<0.0001$). Three IncRNAs were screened that increased In the model group and significantly decreased after AP intervention, namely IncRNA Gm29994, Gm51500 and Gm35391. **Conclusion** Huangqi Sanqi mixture can ameliorate renal fibrosis, Gm29994、Gm51500 and Gm35391 may be the key IncRNA tarqets of Huangqi Sanqi mixture to protect kidney and inhibit fibrosis.

Key words: Huangqi sanqi mixture; renal fibrosis; lncRNA; high-throughput sequencing

P9-23 TGR5 activation ameliorated hypertension through inhibiting ENaC expression in the kidney of DOCA-salt treated mice

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Epithelial sodium channel (ENaC), located in the collecting duct principal cells of the kidney, plays a critical role in regulating sodium balance and blood pressure in the body. The G

protein-coupled bile acid receptor (TGR5) is a cell-surface receptor mediating bile acid effects and is implicated in several kidney diseases. In the current study, we investigated whether activation of TGR5 by lithocholic acid (LCA) regulated renal ENaC expression and blood pressure in deoxycorticosterone acetate (DOCA)-salt induced hypertensive mice and potential molecular mechanisms. Hypertension was induced in mice by subcutaneous implantation of DOCA pellets with 1% NaCl in drinking water. LCA was given by gavage. Immortalized mouse cortical collecting duct (mpkCCD) cells were treated with angiotensin II (Ang II) or aldosterone. LCA markedly decreased blood pressure induced by DOCA-salt in mice, which was associated with decreased expression levels of ENaC mRNA and protein in the kidney. Compared with wild type group, TGR5 knockout mice developed increased blood pressure and ENaC protein expression in the kidney after DOCA-salt treatment. Bioinformatic indicates H3K4me1,2,3 enrichment in the promotor of ENaC. DOCA-salt treatment was associated with increased H3K4me3 expression in the kidney cortex which was markedly inhibited by LCA, while TGR5 knockout caused further increased H3K4me3 expression mice with DOCA-salt. Interestingly the mRNA and protein expression of KDM5A, a lysine demethylase, was significantly decreased in the kidney of mice with DOCA-salt, which was also significantly prevented by LCA. These data likely suggests that TGR5 activation decreased H3K4me3 enrichment of ENaC thus downregulated ENaC mRNA and protein expression. In mpkCCD cells treated with either Ang II or aldosterone, the protein and mRNA expression levels of ENaC subunits were dramatically increased in association with increased protein expression of H3K4me3 and decreased mRNA and protein abundance of KDM5A, which were all inhibited by LCA treatment. Inhibition of KDM5 or KDM5A knockdown in mpkCCD cells treated with Ang II or aldosterone prevented the downregulation of ENaC expression by promoting H3K4me3 on the combination of ENaC transcription start site induced by LCA. In conclusion, LCA decreased blood pressure and ENaC protein expression in the kidney of mice with DOCA-salt, likely through increased KDM5A signal pathway mediated H3K4me3.

Keywords: ENaC, TGR5, H3K4 methylation, KDM5A, Kidney

P10 应激生理

P10-1 The role and mechanism of cardiovascular bioactive peptide intermedin in diabetic vascular calcification

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BACKGROUNDS Vascular calcification is an important cause of death and disability in patients with type 2 diabetes mellitus (T2DMs). Oxidative stress is one of the important drivers of vascular calcification in diabetes mellitus. However, there is still no effective treatment for vascular calcification in diabetes clinically. As a cardiovascular bioactive peptide, intermedin (IMD)/ adrenomedullin 2 (ADM2) plays a protective role in cardiovascular diseases by inhibiting oxidative stress and endoplasmic reticulum stress. However, the role and mechanism of IMD in diabetic vascular calcification remain unknown.

METHODS Plasma of T2DM patients and healthy controls were used for detecting IMD contents. *In vivo*, male Sprague-Dawley (SD) rats and *Adm2* knockout /transgenic mice were used in the experiment to induce diabetic vascular calcification, IMD was administered with subcutaneous Alzert mini-osmotic pumps in the last 4 weeks of the experiment. *In vitro*, rat and mouse vascular smooth muscle cells (VSMC) were treated to induce VSMC calcification. Histochemical staining was used to observe vascular morphology and calcium deposition in blood vessels. Enzyme-linked immunosorbent assay, colorimetric method, western blot and seahorse assay were performed to detect the levels of diabetes and vascular calcification-related molecules.

RESULTS IMD level was decreased in the plasma of diabetic patients and rats. Meanwhile, *Adm2* mRNA expression was significantly down-regulated in calcified aortas of diabetic rats, and its receptor calcitonin receptor-like receptor (CRLR) and receptor activity modifying protein 1 (RAMP1) were increased, RAMP3 was decreased. Exogenous IMD reduced fructose-induced calcium deposition, calcium contents and expression levels of VSMC osteogenic markers in diabetic rat aortas. Endogenous *Adm2* deficiency aggravated and *Adm2* overexpression attenuated vascular calcium deposition and alkaline phosphatase (ALP) activity in diabetic mice induced by high-fat diet. In addition, IMD significantly inhibited the high glucose induced rat VSMC calcium deposition, calcium contents, ALP activity and expression levels of osteogenic markers. *Adm2* deficiency exacerbated mouse VSMC calcium deposition and further decreased the expression levels of contractile markers induced by high glucose. Further studies showed that IMD diminished ROS production in diabetic rat calcified aortas and high glucose-treated VSMC. IMD reduced diabetic vascular calcification by inhibiting the rat plasma advanced glycation end products (AGEs) concentration and by reducing the receptor for AGEs (RAGE) expression level in calcified aortas and VSMCs. IMD inhibited glucose transporter 1 (GLUT1). The inhibitory

effects of IMD on RAGE protein level and lactate production were blocked by GLUT1 knockdown using small interfering RNA. RAGE knockdown had no influence on GLUT1. The inhibitory effect of IMD on rat VSMC calcification was also blocked by GLUT1 knockdown. IMD receptor antagonist IMD17-47, phosphatidylinositol 3 kinase (PI3K) inhibitor LY294002 and protein kinase A (PKA) inhibitor H89 blocked the effect of IMD on inhibiting GLUT1 and thus alleviating VSMC calcification, H89 reversed the effect of IMD on downregulating VSMC lactate production.

CONCLUSIONS This study found that both exogenous and endogenous IMD could reduce diabetic vascular calcification. Mechanistically, IMD inhibited GLUT1 to suppress AGEs/RAGE mediated oxidative stress and glycolysis via activating the cAMP/PKA signaling pathway.

KEY WORDS Intermedin, vascular calcification, diabetes, GLUT1, RAGE

P10-2 Intermedin inhibits DNA damage-mediated vascular aging by activating NAMPT/PARP1

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Backgrounds: Vascular aging is a crucial risk factor for the occurrence and development of cardiovascular diseases. Intermedin (IMD), a paracrine/autocrine peptide, has a protective effect on cardiovascular diseases. In this study, we aimed to explore the beneficial role of IMD in vascular aging. Vascular aging was induced by angiotensin II (Ang II) in wild-type (WT) and VSMC-specific IMD-deficient ($IMD^{SMC-/-}$) mice.

Methods: For the vascular aging model, 12- to 14-week-old male $IMD^{SMC-/-}$ mice and their age-matched WT littermates were subjected to subcutaneous implantation of an Alzet osmotic minipump containing only saline or Ang II dissolved in saline. Mice were then continuously infused with saline or Ang II (1.44 mg/kg/d) for 4 weeks. VSMCs were treated with IMD_{1-53} at a concentration of 10^{-7} mol/L for 30 min and treated with Ang II (10^{-7} mol/L).

Results: The protein and mRNA levels of IMD were significantly decreased in the aged

aortas. The activity of senescence-associated β-galactosidase and the protein levels of p16 and p21 were increased in the aortas of Ang II-treated WT mice and were further elevated in the aortas of Ang II-treated $IMD^{SMC-/-}$ mice. In addition, IMD deficiency increased the protein levels of DNA damage markers, 53BP1 and γH2AX in aged aortas and VSMCs induced by Ang II, which were mitigated by the administration of IMD. Mechanistically, IMD increased intracellular NAD^+ by activating nicotinamide phosphoribosyl transferase (NAMPT), followed by enhancing poly (ADP-ribose) polymerase-1 (PARP1) activity. Inhibitors of PARP1 or NAMPT effectively blocked the beneficial effect of IMD on VSMC DNA damage.

Conclusions: In conclusion, IMD might alleviate DNA damage by activating NAMPT/PARP1, thereby inhibiting vascular aging. These results might shed new light on the prevention of vascular aging.

Keywords: Aging; Intermedin; DNA damage; PARP1; NAD

P10-3 应激反应介导模拟失重大鼠血管内皮改变

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在失重/模拟失重暴露时，血管内皮出现形态异常、内皮型一氧化氮合酶（eNOS）表达水平和一氧化氮（NO）生成减少、氧化应激增强等变化，发生机制尚未完全阐明，应激是机体对外界刺激的生理反应，表现为儿茶酚胺类激素和糖皮质激素的分泌变化，可显著影响内皮状态，本研究旨在探讨应激反应激素在模拟失重大鼠血管内皮改变中的作用和机制。方法：采用后肢去负荷（HLU）大鼠模拟失重血流动力学变化，通过苏木精-伊红(HE)染色、免疫组织化学染色和酶联免疫吸附等技术，测定血管内皮结构、应激激素和内皮调控分子水平，采用酚托拉明和地塞米松进行干预。结果：HLU 1d 开始，内皮即出现损伤改变，表现为形态异常、内皮细胞塌陷或脱落，内皮素 1(ET1)和血管性血友病因子(vWF)增加，同时伴有 eNOS 表达降低和 NO 合成减少，ROS 生成增加。1-7d 中，损伤逐渐加重，14d 时，损伤略好转，但 28d 时又再次加重。HLU 1-7d 时，血清去甲肾上腺素（NE）增加，但皮质醇降低，HLU 14d 时，NE 降低，皮质醇恢复到正常水平；但 HLU 28d 时，NE 再次增加，而皮质醇再次降低。在 HLU 3d 大鼠中，酚妥拉明和地塞米松对 ET1、vWF、eNOS 和 NO 无影响，但显著降低血管组织 ROS 含量。在 HLU 28d 大鼠中，酚妥拉明显著恢复 ET1、vWF、eNOS 和 NO 水平，并降低 ROS 含量；地塞米松则恢复 eNOS 和 NO 水平，对 ET1、vWF、ROS 无明显影响。结论：HLU 大鼠内皮损伤以及应激激素呈现时程依赖的波动性变化，应

激激素在早期通过促进 ROS 生成，晚期通过增加 ET1、vWF，降低 eNOS 表达和 NO 生成导致内皮损伤。

关键词：模拟失重、血管内皮、应激、去甲肾上腺素、酚托拉明、地塞米松

P10-4 NLRP3 inflammasome-dependent pryptosis mediates CUMS-induced reproductive impairment in depressive male mice

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Background: Accumulating evidence indicates that major depressive disorder may have influence on the male reproductive function, like semen parameters and fertility. However, the relationship and specific pathogenesis are not so far clear. As chronic inflammation contributes to the pathological mechanism of both depression and unexplained male infertility, this study aimed to elucidate the immunological mechanisms of male reproductive impairment in depression.

Methods: Male C57BL/6 mice were subjected to chronic unpredictable mild stress (CUMS) for 8 weeks, treatment group were administered with the NLRP3 inhibitor MCC950 (20 mg/kg, i.p.). Then, the mice were assessed for depression-like behaviors. Testicular damage was assessed by testicular pathological evaluation, epididymal sperm concentration, sperm motility, serum testosterone levels, testicular apoptotic cell measurements analyses.

Results: CUMS-induced depressive mice exhibited decreased levels of serum testosterone, decreased epididymal sperm concentration and impaired sperm motility. Furthermore, CUMS exposure caused an increase expression of NLRP3 imflammasome pathway and activated pryptosis signaling in the testes. The NLRP3 inhibitor MCC950 significantly restored hyperglycemia-induced depression, reproductive impairment and the activation of the testis NLRP3 inflammasome, and reversed the damage effect on testicular cells markers.

Conclusions: NLRP3-depedent pryptosis mediates the male reproductive impairment evoked by CUMS-induced depression in mice. Targeting the NLRP3 inflammasome is a feasible strategy for the treatment of depression-related male infertility. This study provides new evidence for a comprehensive understanding of psychoneuroimmunology.

Keywords: Depression, Male reproductive, Spermatogenesis dysfunction, NLRP3 inflammasome, Pryptosis

P10-5 有氧运动调节伏隔核 D1R-MSN 谷氨酸能突触传递减少尼古丁复吸的机制研究

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目的：探究运动对成瘾模型戒断期伏隔核 D1R-MSN 谷氨酸能突触传递的影响，为运动防治成瘾提供实验依据。

方法：以清洁级、2 月龄、雄性 Drd1a-Tdtomato 小鼠作为研究对象，随机分为生理盐水+安静组（SS）、生理盐水+运动组（SE）、尼古丁+安静组（NS）、尼古丁+运动组（NE）。使用 CPP 行为学范式建立成瘾模型后，进行为期 2 周的戒断。在戒断期，运动组小鼠进行跑台运动干预（前 10 min，12 m/min，后 50 min，18 m/min，60 min/d，5 d/w），安静组小鼠自由饮食及饮水。2 周戒断后，再次进行 CPP 测试，评价尼古丁依赖性。免疫荧光染色检测 NAc c-fos 表达水平。脑片膜片钳记录 NAc D1R-MSN 的微小兴奋性突触后电流（mEPSC），分析其平均频率、平均幅度、间隔时间和波幅累积分布曲线。结果进行双因素方差分析，$P<0.05$ 具有显著性差异。

结果：（1）行为学结果显示，NS 组在戒断期 CPP 得分显著高于 SS 组（$P<0.001$）；NE 组 CPP 得分显著低于 NS 组（$P<0.05$），提示运动具有减少尼古丁复吸的作用。（2）免疫荧光染色结果显示，NS 组 NAc c-fos 荧光强度显著强于 SS 组（$P<0.05$）；NE 组 c-fos 荧光强度显著弱于 NS 组（$P<0.05$）。（3）mEPSC 结果显示，各组间 mEPSC 平均频率和间隔时间累积分布曲线无显著性差异（$P>0.05$）；同 SS 组相比，NS 组 mEPSC 平均幅度显著升高（$P<0.01$），波幅累积分布曲线右移（$P<0.01$）；同 NS 组相比，NE 组 mEPSC 平均幅度显著降低（$P<0.05$），波幅累积分布曲线左移（$P<0.05$）。以上结果提示，尼古丁戒断使 NAc 兴奋性增强，对 D1R-MSN 突触前谷氨酸释放无影响，使突触后受体的数量和/或功能增强；运动降低戒断小鼠 NAc 的兴奋性，下调 D1R-MSN 突触后受体的数量和/或功能，降低谷氨酸能突触传递效能。

结论：运动降低尼古丁戒断小鼠伏隔核过度激活，下调 D1R-MSN 突触后受体的数量和/或功能，降低谷氨酸能突触传递效能，这可能是运动减少成瘾戒断期尼古丁复吸的中枢机制之一。

关键词：有氧运动，成瘾，伏隔核，突触可塑性

P10-6 热射病诱导大鼠血管平滑肌细胞表型转化及血管损伤的初步研究

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目的 本研究通过建立体外热射病模型，初步探讨热射病大鼠胸主动脉血管平滑肌细胞表型转化及坏死性细胞凋亡的发生，为热应激相关的心血管疾病的发病防治提供研究基础。

方法 将 30 只 SPF 级雄性 SD 大鼠随机分为对照组、热射病恢复 0h、6h、12h 和 24h 组（n=6）。热射病组置于人工气候舱内（温度 40℃，相对湿度 50%），以大鼠核心温度达到 40.5℃且伴有四肢无力、不能爬行，认定大鼠热射病模型成功。评价大鼠的一般状态；ELISA 测定大鼠血清中 IL-1β、TNF-α、SOD 及 MDA 的水平；HE 染色观察大鼠胸主动脉血管组织形态结构的变化；免疫组织化学观察 α-SMA、OPN、RIPK1 和 RIPK3 的表达水平；Western Blot 检测 α-SMA、OPN、RIPK1、RIPK3、Bcl-2 和 Bax 蛋白表达水平。

结果 热射病组大鼠四肢无力和紫绀，毛发耸立、呼吸急促，口腔或鼻腔出现大量粉红色泡沫状液体，体重下降(P<0.05)。热射病组大鼠血清中 IL-1β、TNF-α 的表达增加是短暂的(P<0.05)。MDA 含量随着热射病恢复时间的延长逐渐升高，而 SOD 含量逐渐降低，具有统计学差异(P<0.05)；对照组血管未见明显病理损伤，热射病恢复各组血管内膜粗糙不平整，肌纤维排列杂乱无序，平滑肌层紊乱、断裂；免疫组化及 Western Blot 显示，对照组胸主动脉血管中 α-SMA 蛋白的表达最高，OPN 几乎不表达。随着热射病恢复时间的延长，α-SMA 表达逐渐下调， OPN 表达逐渐增加，具有统计学意义(P<0.05)。同时，与对照组相比，随着热射病恢复时间的延长，RIPK1 和 RIPK3 在 HS-6h 和 HS-24h 组呈现一致的升高趋势，且在 HS-24h 组表达最高，具有统计学差异(P<0.05)。同时热射病恢复 0h、6h、12h 和 24h 组 Bax 蛋白呈现升高的趋势，而 Bcl-2 蛋白呈现下降趋势，与对照组相比具有统计学差异(P<0.05)。

结论 热射病可能引起大鼠氧化应激损伤，促进了大鼠胸主动脉血管平滑肌表型转化和坏死性细胞凋亡的发生，提示热射病是促进血管损伤的主要原因之一。

关键词 热射病；血管平滑肌；表型转化；坏死性细胞凋亡

基金项目：宁夏自然科学基金（2023AAC0318）

P10-7 枸杞多糖对热射病大鼠结肠结构与紧密链接相关蛋白的影响

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[目的] 热应激对机体的影响是系统性的，肠道是热应激损伤的靶器官之一。由而肠上皮细胞、胞间紧密连接蛋白复合体及杯状细胞分泌的粘液构成的肠道黏膜是维护机体健康的重要生理屏障，在营养物质吸收、微生物稳态调节与免疫等起着重要作用。因此，本研究通过构建动物模型，探讨枸杞多糖（lycium barbarum polysaccharide, LBP）对热射病大鼠结肠组织的保护作用。

[方法] 将 6 周龄 40 只雄性 SPF 级正常大鼠随机分成 5 组：空白对照组（Con）、热射病组（HS），以及枸杞多糖低（$LBP_{(L)}$）、中（$LBP_{(M)}$）、高（$LBP_{(H)}$）剂量组分别为 50、150、450mg/kg d。适应性喂养 1 周，Con 组和 HS 组灌服纯水，剩余各组灌服对应剂量的 LBP 水溶液，为期 4 周。将 Con 组环境温度保持在 25℃，其余 4 组转移至 42℃。监测大鼠核心体温超过 40℃并稳定 3min 完成热射病大鼠造模。将热应激后的大鼠转移至 25℃恢复 12h。处死大鼠，取血清及横结肠组织备用。经 HE 染色、PAS 染色评价结肠组织病理变化；Western Blot 和 IF 法检测组织中 Occludin 和 ZO-1 的表达水平。

[结果] 根据 HE 和 PAS 染色结果，HS 组结肠黏膜层变薄，隐窝消失或缩短（$P<0.001$）、排列紊乱，固有层出现炎性细胞浸润，杯状细胞大小和数量显著降低（$P<0.001$）。接受 LBP 灌胃的各组，结肠黏膜层厚度和隐窝结构恢复，黏膜层厚度和隐窝结构随着剂量升高恢复至正常，隐窝的排列愈发规则，炎性细胞浸润的现象逐渐消失（$P<0.001$），杯状细胞逐步恢复到正常水平（$P<0.002$，$P<0.001$，$P<0.001$）。Western Blot 和 IF 的实验结果共同表明，HS 组中 Occludin 和 ZO-1 的表达水平均显著下降（$P<0.001$）。450mg/kg d 的 LBP 灌胃剂量下，Occludin 和 ZO-1 的表达水平均显著恢复（$P<0.001$，$P<0.033$）。

[结论] 枸杞多糖能有效保护热应激下大鼠结肠的结构（隐窝深度、黏液水平及杯状细胞状态），防止高温对胞间紧密连接蛋白的破坏，显著恢复 Occludin 和 ZO-1 蛋白的表达。

关键词：枸杞多糖；热射病；肠道黏膜屏障；结肠损伤

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P10-8 Preliminary observation of effects of flavanols on learning and memory functions in anxiety disorder model rats

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Objective: To exploring the effects of flavanols on the learning and memory functions in anxiety disorder model rats. **Methods:** Twenty-four adult male SD rats were randomly divided into control group (*n*=6) and modeling group (*n*=18). The method of single-cage rearing combined with chronic restraint stress was carried out for 3 consecutive weeks to prepare the anxiety disorder model rat. The model rat was identified using the elevated cross maze (ECM) and open field (OF) tests, and the successful modeling rats were randomly divided into the model, the low-dose flavanols (LDF), and the high-dose flavanols (HDF) group (*n*=6). The LDF and HDF

groups were given 30 mg/kg and 60 mg/kg of flavanols by gavage, respectively, while the model and control groups were given equal volumes of saline for 2 weeks. Afterwards, the anxiety-like activities of rats in each group were evaluated using ECM and OF tests, and the learning and memory functions were evaluated using the novel object recognition (NOR) and Y-maze experiment. **Results:** (1) After modeling, compared with the control rats, the ratio of the number of entries in the open arm and the ratio of the dwell time in the open arm of the ECM in the modeling group rats decreased (P<0.01 and P<0.05), and the total distance of traveling and the number of entries in the central area of OF also decreased (P<0.05 and P<0.01). (2) After treatment, compared with the control group, the total distance of traveling and the number of entries into the central area of OF were reduced in the model, LDF and HDF groups (P<0.01 and P<0.05). There was an increased tendency of the total distance of traveling and the number of entries into the central area of OF in the LDF but not HDF group compared with the model group. Compared with the model group, the ratio of the number of open arm entries in the LDF group was significantly higher (P<0.01). (3) Compared with the model group, there was an increasing trend of recognition index in the LDF, HDF and control group, of autonomous alternation rate and the residence time in the novel arms in the LDF group. Compared with the model group, there was an increase in the latency of the novel arm in the HDF group (P<0.05). **Conclusion:**The preliminary results suggest low-dose flavanol many alleviate anxiety-like behaviors in anxiety disorder model rats.

Keywords: Anxiety disorders; Learning and memory; Flavanols; Elevated cross maze test; Novel object recognition test

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P10-9 幼年高血压应激大鼠模型中肠道胶原纤维的变化特征

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背景和目的：高血压（Hypertension, HTN）已成为全球公共卫生关注的问题，并且是心-脑血管和肾脏疾病的主要危险因素。在中国根据流行病学调查显示，2015 年 HTN 的患病率为 27.9%，1.6 亿患者需要立即干预，150 万-170 万人由于高血压升相关疾病而过早的死亡，2012~2020 年，研究发现，中国≥ 18 岁居民血压正常高值检出率 39.1%，高血压患者超过 2.45 亿。大量研究表明应激与肠道炎症和黏膜屏障损害密切相关。然而，人们对高血压

伴有应激的肠道组织学变化知之甚少。为了探究应激对高血压状态下的肠道病理改变，本实验采用通过 Masson 染色检测结肠组织切片的胶原纤维含量。结果表明结肠在黏膜下层中表现出明显的胶原沉积。y-WKY-S 组的黏膜下胶原纤维面积比 y-WKY 组减少 2.48%（p<0.05，n=5）。与 y-SHR 组相比，masson 的阳性胶原纤维沉积在 y-SHR-S 中显著增加 3.17%（p<0.05，n=5）。为了进一步确认该现象，采用光学显微镜和偏光显微镜，分析 Sirius Red 染色的胶原纤维阳性区域的统计数据，与 y-SHR 组相比，y-SHR-S 组中的 Masson 三色和 Sirius Red 阳性纤维化区域均明显增加，而 y- WKY-S 组与 y-WKY 组相比胶原纤维区域却显著减少。为了进一步确认观察胶原纤维Ⅰ型在此过程中的变化，使用偏振光下观察，与 y-WKY 相比 y-WKY-S 结肠中胶原纤维Ⅰ型面积百分比从 9.79%减少至 6.12%（p<0.05，n=5）而 y-SHR-S 与 y-SHR 相比胶原纤维Ⅰ型面积百分比从 6.06%增至 8.79%（p<0.01，n=5）。进一步通过 TEM 进行观察，发现胶原纤维在电镜下是排列紧密的胶原纤维束，束内原纤维间的距离小于 0.2μm，并且进一步确定，应激大鼠的胶原纤维在 y-SHR-S 中变粗，在 y-WKY-S 中变细。根据以上所有内容，我们可以推测束缚应激可以加速 HTN 相关的肠道胶原纤维Ⅰ型的增加。上述结果表明，通过束缚应激处理可以诱导结肠的组织结构发生改变。

关键词：Masson 染色，Sirius Red 染色，高血压，应激，胶原纤维

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P10-10 SRT1720 ameliorates LPS-induced depressive-like behaviors and activates PINK1/Parkin mediated mitophagy in mice

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Background: Depression is a complex and detrimental psychiatric disorder that is characterized by persistent low mood, loss of interest or pleasure, fatigue or loss of energy, feelings of worthlessness or guilt and insomnia. Extensive studies have revealed that mitophagy, a specific mechanism of mitochondrial quality control is associated with depression. Furthermore, it has been demonstrated that sirtuin 1 (SIRT1) plays an important role in depression, though the potential mechanism is poorly understood. The current study aimed to investigate the effect of SIRT1 on depressive behaviors in mice, and to determine whether mitophagy is involved in it.

Methods: Male BALB/c mice were treated with lipopolysaccharide (LPS) to mimic depressive-like behaviors, and the treatment group was pre-administered with SRT1720 (50mg/kg, i.p.), a specific activator of SIRT1. Then, the depressive-like behaviors in mice were assessed by sucrose preference test (SPT) and forced swimming test (FST). Meanwhile, the ultrastructure

changes of hippocampal neurons were detected under transmission electron microscopy, and mitophagy-related proteins were examined by western blotting analysis. Additionally, the pathway of PINK1/Parkin mediated mitophagy was further examined in HT-22 cells.

Results: The results showed that activation of SIRT1 ameliorated LPS-induced depressive-like behaviors, as indicated by SPT and FST. Moreover, the activation of SIRT1 alleviated the damage of neuron and mitochondria in hippocampus after LPS treatment significantly increased the expression levels of LC3II, PINK1 and Parkin in hippocampus, representing the upregulation of mitophagy. In vitro experiment further proved that activation of SIRT1 in HT-22 cells restored the depolarization of mitochondrial membrane potential induced by LPS and promoted mitophagy via PINK1/Parkin pathway.

Conclusion: The findings from this study implied that SRT1720 could alleviate depressive-like behaviors after LPS challenge in mice, in which upregulation of PINK1/Parkin mediated mitophagy might be a potential mechanism.

Keywords: Depression, Mitophagy, SIRT1

P10-11 低氧应激神经内分泌反应对高原肺水肿发病的作用研究

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目的：通过应用低氧应激大鼠模型，研究低氧应激神经内分泌反应对高原肺水肿发病的作用机制。确定不同低氧应激条件对大鼠肺功能的影响。确定不同低氧应激条件对肺微血管通透性的影响。确定不同低氧应激条件对肺组织形态学的影响。

方法：将大鼠随机分为对照组和给药（阻断皮质醇生成）组，对照组处理条件为试验开始前 6 小时大鼠腹腔注射生理盐水，给药组处理条件为试验开始前 6 小时大鼠腹腔注射美替拉酮（皮质醇生成阻断剂）；将两组又分为常氧组及急性低氧不同时间组，低氧处理为 7000m 不同时间点（6h、12h、24h），取出各组大鼠进行相关实验。

① 肺功能评估

不同组大鼠于低压氧舱模拟海拔 7000 米低氧处理不同时间（6h、12h、24h）后取出，立即应用 DSI-BUXCO 无创呼吸功能检测系统（NAM 系统）检测大鼠肺呼吸功能改变。。

② 肺微血管通透性评估

应用伊文思蓝含量测定法，计算每克肺组织中伊文思蓝含量以反映毛细血管通透性。

③ 肺组织形态学改变

取各组大鼠肺组织，进行 HE 染色。

结果：1.测定肺功能结果显示，对照组急性低氧各组大鼠潮气量（TV）、每分通气量（MV）、呼气峰流值（PIF）、吸气峰流值（PEF）、肺活量 50%时的呼气流值（EF50）等指标较对照常氧组低，而气道阻力（Raw）较对照常氧组升高。给药急性低氧 24h 组呼吸频率（F）较给药常氧组和对照低氧 24h 组低，气道阻力较对照低氧 24h 组低，潮气量（TV）、每分通气量（MV）、呼气峰流值（PIF）、吸气峰流值（PEF）、肺活量 50%时的呼气流值（EF50）较给药低氧 6h 组高。

2.测定肺组织伊文思蓝含量结果显示，对照急性低氧各组较对照常氧组有上升趋势，但无显著差异；给药低氧各组与给药常氧组比较，给药低氧 12h 组、给药低氧 24h 组，伊文思蓝含量显著升高。

3.肺组织形态学观察，常氧组肺泡壁轮廓清晰结构完整，肺泡腔内无渗出，间质无渗出无炎性细胞浸润；低氧各组肺泡腔内有液体渗出，低氧 12h 肺泡腔内出现红细胞，低氧 24h 肺泡腔渗出量增多，间质有渗出增多。

结论：

1.急性低氧会造成大鼠气道阻力升高，给予皮质激素阻断剂后，会降低急性低氧时的呼吸频率和气道阻力，升高急性低氧时的潮气量、每分通气量。

2.给与美替拉酮药物组低氧 12 小时和 24 小时肺组织伊文思蓝含量明显增加，提示皮质醇在急性低氧应激过程中对肺微血管起保护作用。

3.根据观察肺组织 HE 染色，对照组与给药组的各低氧组，随着时间延长，肺组织器质性损伤逐渐出现，其中给药急性低氧 24 小时时渗出最明显。提示急性低氧会造成肺微血管和肺泡膜通透性发生改变，抑制皮质醇生成可能会加重肺损伤。

关键词：低氧应激 神经内分泌 肺功能 肺水肿

P10-12 NE-arranged fluctuation of BMP7 in hippocampus involves the dynamic effects of stress on rodent cognitions.

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Stress is a systemic response of the organism in the face of both physical and psychological adverse factors, which makes the performance of our organism display an inverted-U-shaped curve with rising stress duration or intensity; however, the detailed mechanisms underlying the transition from adaptation to damage are still elusive. Using mRNA sequencing analysis for

hippocampal transcriptome in rats receiving 3-days or 2-weeks or 6-weeks mild unexpected stress, we identified BMP7 showing a similar expressive pattern to the tendency of cognitive alteration in period-span stress, making it as a possible candidate involved in the dynamic regulation of stress. Presuming that the elevation of BMP7 level in 3-days or 2-weeks could antagonize stress-induced hippocampal damage, we further verified the neuroprotective effects of BMP7 by gain-of-function or loss-of-function both *in vitro* and *in vivo*. The results showed that BMP7 could suppress the increase of oxidative stress and damage of synaptic plasticity induced by GC, and enhance cell viability in PC12 cells. BMP7 could also alleviate chronic stress-induced cognitive impairment and ameliorates increased oxidative stress and impaired synaptic plasticity in the rat hippocampus. The regulation mechanisms for BMP7 fluctuation during period-span stress were also investigated in the present study. Results indicated that the rapid releasing of NE in early period of stress activates the downstream cAMP/PKA and Ca^{2+}/CaN signaling pathways by its binding to ADRB1, and subsequently promotes the binding of nuclear transcriptive factor NFATc4 to *Bmp7* promoter, which regulates the dynamic expression of BMP in stress. Our new data shed light on the novel mechanism for stress-associated fluctuation of BMP7 expression in hippocampus, and implied a possible mechanism for the regulation of dynamic effects of stress on rodent cognitions.

Key words: stress, dynamic regulation, BMP7, NE, cognition

P10-13 GLUT1-mediated microglia M1-polarization contributes to development of stress-related learning and memory dysfunction in mice

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Stress has been recognized as the risk of cognitive decline, especially of hippocampal-related spatial learning and memory dysfunction. But there is a lack of effective prevention and treatment methods due to the unclear pathological basis. Recent work suggests it is accompanied by neuroinflammation involving microglia activation. However, the specific mechanism of microglia inflammatory polarization and its involvement in stress-related learning and memory dysfunction are far from understood. In this study, we used the classical chronic unpredictable mild stress

(CUMS) model to explore the relationship between microglia activation, neuroinflammation and stress-induced learning and memory impairment. Our data showed that 8 weeks of CUMS induced remarkable spatial learning and memory impairment in mice, simultaneously causing hippocampal microglia M1 polarization. Likewise, upregulation of inflammatory mediators, including IL-1β, IL-6, and TNF-α, were also observed in the hippocampus after exposure to chronic stress. What's more, inhibiting microglia activation through minocycline alleviated stress-induced learning and memory decline. Mechanistically, elevated glucose level in hippocampus induced by chronic stress was revealed to be a key regulator for proinflammatory activation of microglia. Since the cellular transport of glucose is mediated via the glucose transporters (GLUTs), we examined the effect of chronic stress and high glucose on the expression of GLUTs and found that both stress and high glucose specifically upregulated the level of GLUT1 in microglia. Furthermore, GLUT1 overexpression promoted microglia M1 polarization, while antagonizing the function of GLUT1 inhibited the M1-polarized microglia cells induced by high glucose. In addition, the results of western blot and immunofluorescence suggested that GLUT1 activated the NF-κB signaling to realize its function in microglia. Finally, we specifically down regulated the expression of GLUT1 in stressed-mice hippocampal microglia using an adeno-associated virus (AAV). Intriguingly, the low-expression of GLUT1 in hippocampal microglia relieved stress-induced learning and memory injury, microglia M1 polarization, inflammatory factors secretion and NF-κB signaling activation. Cumulatively, here we demonstrate that high level of glucose and GLUT1 induced microglia proinflammatory polarization, which play an integral role in the promotion of stress-associated learning and memory dysfunction. Our findings reveal a remarkable crosstalk between metabolism and inflammation and provide a possible therapeutic target against stress-related cognitive disorders.

Key words: chronic stress, microglia, M1 polarization, GLUT1, learning and memory dysfunction.

P10-14 同型半胱氨酸通过上调 Rap1a 表达促进小鼠小胶质细胞 M1 型极化

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目的 研究高同型半胱氨酸对 BV2 小鼠小胶质细胞介导的炎性反应的影响，探讨 Ras 相关蛋白 1a（Rap1a）在 Hcy 促进的小鼠小胶质细胞炎性反应过程中的作用机制。**方法** 体

外培养小鼠小胶质细胞系 BV2 细胞，用 Hcy 干预，建立高同型半胱氨酸模型，首先探索 Hcy 促进小鼠小胶质细胞系 BV2 细胞发生 M1 型极化介导炎性反应的最佳浓度；将细胞分成空白对照组、Hcy50、100、150μmol/l 组，采用 RT-qPCR 法检测 BV2 细胞 M1 型极化标志物、炎性因子 IL-6、IL-1β、TNF-α 及 Rap1a 的 mRNA 表达水平，ELISA 法检测 BV2 细胞炎性因子 IL-6、IL-1β、TNF-α 的含量；Western Blot 法检测细胞内 Rap1a 的蛋白表达水平。其次过表达和敲低 Rap1a 探索其在 Hcy 促进的小胶质细胞炎性反应中的机制，过表达 Rap1a 条件下将细胞分成 oeRap1a-sc 组、oeRap1a 组、Hcy 组、Hcy-oeRap1a 组；敲低 Rap1a 条件下将细胞分成 shRap1a-sc 组、shRap1a 组、Hcy 组、Hcy-shRap1a 组。**结果** 1.与 Control 组相比，Hcy 组细胞在 Hcy 浓度为 100μmol/l 的条件下细胞 M1 型极化标志物 CD80、CD86mRNA 显著升高（P＜0.05），炎性因子 mRNA 及含量均显著升高（P＜0.05），Rap1a 蛋白及 mRNA 表达水平均显著升高（P＜0.05）；2.过表达 Rap1a，与 oeRap1a-sc 组相比，oeRap1a 组 BV2 细胞 M1 型极化标志物 CD80、CD86 及炎性反应均显著升高（P＜0.05）；3.敲低 Rap1a，与 Hcy 组相比，Hcy-shRap1a 组 BV2 细胞 M1 型极化标志物 CD80、CD86 及炎性反应均显著下降（P＜0.05）。**结论** Hcy 能够促进 BV2 小鼠小胶质细胞发生 M1 型极化，进一步介导炎性反应，其中 Rap1a 表达上调参与 Hcy 促进的 BV2 小鼠小胶质细胞炎性反应，这就为后期神经炎症性疾病的预防和治疗提供新的靶点。

P10-15 DDX3X 调控内质网应激功能转换在肝衰竭发病中的分子机制研究

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背景及目的：内质网应激（Endoplasmic reticulum stress, ERS）的功能转换对细胞命运的调控影响了肝衰竭（Liver failure, LF）的发生和发展，但参与 ERS 功能转换的具体分子机制尚不明确。DEAD-box 解旋酶 3X-连锁（DEAD-box helicase 3 X-linked, DDX3X）是一种依赖 ATP 的 RNA 解旋酶，它在真核细胞中普遍表达并且参与细胞内翻译、转录等多生理过程，但是其在 ERS 细胞中的作用还不清楚。在本研究中，我们探索了 DDX3X 及其信号通路调控 ERS 功能转换参与 LF 疾病进展的关键作用。

方法：分离 C57BL/6J 小鼠的原代肝细胞，用衣霉素（Tunicamycin, TM）诱导细胞 ERS；用 TM 诱导 C57BL/6J 小鼠体内 ERS。收集健康对照、慢性乙型肝炎（Chronic hepatitis B, CHB）患者和乙肝相关肝衰竭（Hepatitis B virus related liver failure, HBV-LF）患者样本，分析其肝组织及血清中 DDX3X 的表达情况。采用实时荧光定量 PCR（Quantitative real-time PCR, qRT-PCR）方法、免疫印迹（Western blotting, WB）方法检测相关基因、蛋白的表达情况；

细胞计数试剂盒-8（Cell counting kit-8, CCK-8）、乳酸脱氢酶（Lactate dehydrogenase, LDH）释放试验、流式细胞术等检测细胞凋亡情况；血清谷丙转氨酶（Alanine aminotransferase, ALT）、谷草转氨酶（Aspartate aminotransferase, AST）水平及肝脏切片苏木精-伊红（Hematoxylin-eosin, H&E）染色评价肝脏的损伤情况。

结果：首先，阐明了随着 ERS 时间的延长，肝细胞中 DDX3X 表达增加并且由细胞质向细胞核转移；其次，明确了 DDX3X 在不同时间 ERS 介导的细胞结局中发挥双重作用；此外，揭示了磷酸化修饰是 DDX3X 发生质核迁移的关键调节机制。当细胞发生短期 ERS 时，DDX3X 主要在细胞质中表达，并与过氧化物酶体增殖物激活受体（Peroxisome proliferators-activated receptor alpha, PPARα）相互作用，促进转录因子 EB（Transcription factor EB, TFEB）的蛋白翻译，促进细胞生存。当细胞发生长期 ERS 时，磷酸化的 DDX3X 核转位增加，通过激活 CCAAT 增强子结合蛋白同源蛋白（CCAAT enhance-binding protein homologous protein, CHOP）促进细胞凋亡。此外，我们发现 DDX3X 水平在 HBV 相关 LF 患者血清和肝组织中显著升高；其次，DDX3X 血清水平的波动情况与 HBV-LF 患者的预后存在相关性：即在预后良好的 HBV-LF 患者中，血清 DDX3X 水平呈持续下降。

结论：ERS 的功能转换的 HBV-LF 的发生发展中发挥了关键作用。在细胞发生可逆的 ERS 时，DDX3X 主要在细胞质中表达，并与 PPARα 相互作用，DDX3X/PPARα 复合物的形成促进了细胞质内 TFEB 的翻译过程，进而促进了细胞的适应性反应，介导细胞恢复稳态。当细胞发生不可逆的 ERS 时，细胞内 DDX3X 表达水平显著增加并且发生核转位，上调 CHOP 启动子的转录活性，促进肝细胞死亡。此外，血清 DDX3X 水平可以被认为是 HBV-LF 患者病情恶化的早期预警标志物，有助于对患者的肝损伤情况早期识别；对 HBV-LF 患者血清中 DDX3X 水平进行连续监测将有助于判断患者的预后。本研究阐明了在 HBV-LF 疾病进展过程中，DDX3X 及其介导的信号通路通过调控 ERS 的功能转换促进疾病进展的分子机制，并且提供了以 DDX3X 为靶点干预 HBV-LF 疾病进展、改善肝损伤的理论基础。

关键词：内质网应激；DEAD-box 解螺旋酶 3X-连锁；细胞凋亡；肝衰竭

P10-16 聚乙烯微塑料通过引发鲤鱼鳃的氧化应激和激活 NLRP3 炎性小体来诱导细胞凋亡和炎症反应

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微塑料对水生生物造成不同程度的损害。鳃是继皮肤之后最先受到水中微塑料影响的组织之一。作为重要的免疫器官，微塑料的长期刺激会破坏鳃的免疫功能，继而破坏全身的免

疫功能，但其潜在机制尚不清楚。本研究将鱼养在聚乙烯（PE）微塑料污染的水源里，构建鳃损伤模型。H&E 染色显示接触聚乙烯微塑料的腮组织出现炎症、血管重塑和粘液细胞增多等病变。而胶原蛋白的增加表明腮组织损伤严重。此外，聚乙烯微塑料的暴露加剧了鳃组织的氧化应激，而 TUNEL 进一步证实了聚乙烯微塑料诱导细胞凋亡。RT-PCR 的结果显示，聚乙烯微塑料增加了核因子-κB （NF-κB）通路（NF-κB p65、IKKα、IKKß）和凋亡生物标志物（p53、caspase-3、caspase-9、Bax）的表达，作为先天免疫重要组成部分的核苷酸结合寡聚化结构域样受体蛋白 3 （NLRP3）炎性小体也过度活跃，引发免疫紊乱的促炎因子（TNF-α、IFN-γ、IL-2、IL-6、IL-8、IL-1β）也显著升高，但抗炎因子（IL-4、IL-10）显著降低。这些结果说明了聚乙烯微塑料引发腮组织氧化应激，从而激活 NF-κB 通路和 NLRP3 炎性小体，触发细胞凋亡，最终诱发炎症免疫应答。本研究探讨了聚乙烯微塑料诱发鳃损伤的机制，为预防微塑料的损害提供了重要靶点。

关键词：鱼鳃，聚乙烯微塑料，氧化应激，细胞凋亡，NLRP3 炎性小体

P10-17 Microglial NLRP3 inflammasome activation mediates diabetes-induced depression-like behavior via triggering neuroinflammation

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Background: Abundant evidence suggests that the prevalence and risk of depression in people with diabetes is high. However, the pathogenesis of diabetes-related depression remains unclear. Since neuroinflammation is associated with the pathophysiology of diabetic complications and depression, this study aims to elucidate the neuroimmune mechanism of diabetes-related depression. **Methods**: Male C57BL/6 mice were injected with streptozotocin to establish a diabetes model. After screening, diabetic mice were treated with the NLRP3 inhibitor MCC950. Then, metabolic indicators and depression-like behaviors were evaluated in these mice, as well as their central and peripheral inflammation. To explore the mechanism of high glucose-induced microglial NLRP3 inflammasome activation, we performed in vitro studies focusing on its canonical upstream signal I (TLR4/MyD88/NF-κB) and signal II (ROS/PKR/P2X7R/TXNIP). **Results:** Diabetic mice exhibited depression-like behaviors and activation of NLRP3 inflammasome in hippocampus. In vitro high-glucose (50 mM) environment primed microglial

NLRP3 inflammasome by promoting NF-κB phosphorylation in a TLR4/MyD88-independent manner. Subsequently, high glucose activated the NLRP3 inflammasome via enhancing intracellular ROS accumulation, upregulating P2X7R, as well as promoting PKR phosphorylation and TXNIP expression, thereby facilitating the production and secretion of IL-1β. Inhibition of NLRP3 with MCC950 significantly restored hyperglycemia-induced depression-like behavior and reversed the increase in IL-1β levels in the hippocampus and serum. **Conclusion**: The activation of NLRP3 inflammasome, probably mainly in hippocampal microglia, mediates the development of depression-like behaviors in STZ-induced diabetic mice. Targeting the microglial inflammasome is a feasible strategy for the treatment of diabetes-related depression.

Keywords: depression; diabetes; nlrp3 inflammasome; neuroinflammation; microglia

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P10-18 Role of the netrin-1/ DCC-Unc5 signaling pathway in inflammation-related depression

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Background: It has been found that the neural axon guidance factor (Netrin-1) and its receptor colorectal cancer deleted gene (DCC) and uncoordinated homologous gene 5 (Unc5) family have been confirmed to be significantly associated with depression, and the DCC-mediated Netrin-1 signaling alterations might be an important contributing factor in alter neuroplasticity. Inflammatory factors have been confirmed to enter the brain and participate in neurotransmitter metabolic processes, which affect neuroendocrine function and neuroplasticity, and they may disrupt the structure and function of neurons, leading to defects in neuroplasticity, but the specific mechanisms remain unknown. This study aimed to explore the role of regulation of neuroplasticity by immune inflammatory responses in the development and development of depression. **Methods：** Overexpression of Caspase-1 in hippocampus of C57BL/6J mice with subthreshold chronic unpredictable mild stress (CUMS) induced depressive and anxiety behavior in mice. Immunofluorescence（IF） staining were used to evaluate the expression of caspase-1 in hippocampal slices , and the RNA expression of Netrin-1, DCC, and Caspase-1 was detected by

Real-Time-PCR(RT-PCR) and Western-Blot(WB). **Results:** We found that AAV-caspase-1 mice showed a significant decrease in sucrose preference and increase in immobility time following subthreshold CUMS, pro-Caspase 1, Caspase 1-p20, and IL-1β were significantly up-regulated in the hippocampus of caspase-1-overexpressing mice, the expression of Netrin-1, DCC, and Unc5a and synaptic plasticity-related proteins were significantly downregulated. **Conclusions:** The results suggest that the activation of Caspase-1/IL-1β may be a key factor in the dysregulation of Netrin-1/DCC-Unc5 pathway, affecting synaptic plasticity and ultimately leading to depressive-like behavior.

Keywords: Depression, Caspase-1, Netrin-1, DCC, Neuroplasticity

P10-19 应激性认知功能障碍中 MALAT1 通过与 VCP 相互作用促进星形胶质细胞 A1 型活化

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目的 通过观察慢性应激下星形胶质细胞活化及其 MALAT1 的变化，探讨 MALAT1 在应激致认知功能障碍中对脑星形胶质细胞活化的影响及其可能机制。

方法 利用慢性不可预测的温和刺激（CUMS）来构建应激致认知障碍小鼠模型，利用旷场、水迷宫实验检测模型行为学指标，通过 ELISA 法检测应激应激激素糖皮质激素(GC)、去甲肾上腺素（NE）、星形胶质细胞 A1 型活化标志物（C3）、星形胶质细胞 A2 型活化标志物（S100A10）水平，Western 印迹,实时荧光定量 PCR(qRT-PCR)法检测海马 A1/A2 型活化标志物、MALAT1 的表达水平。体外小鼠星形胶质细胞系（C8-D1A）上采用调节 MALAT1 表达后检测其星形胶质细胞活化情况，通过 RNA-pulldown 及免疫共沉淀法检测 MALAT1 结合 VCP 后对星形胶质细胞活化的影响。

结果 与 Ctrl 组相比，CUMS 组小鼠血清 GC 水平显著增高（$P<0.05$），NE 无明显变化；海马组织 C3 显著增高（$P<0.05$），S100A10 无明显变化；旷场实验得分、水迷宫空间探索实验得分显著降低（$P<0.05$）;MALAT1 过表达通过激活 NF-κB 信号传导促进体内外星形胶质细胞 A1 型活化。MALAT1 增加了 VCP 与 iκBα 的相互作用，诱导了 iκBα 的降解和 NF-κB 的活化。这种诱导被 VCP 敲低所反转，表明 MALAT1 是 VCP/ i -κB α/NF-κB 信号通路的上游激活剂。此外，MALAT1 和 VCP 的高表达与认知功能障碍相关。

结论 综上所诉，MALAT1 通过与 VCP 相互作用，调节 iκBα/NF-κB 通路，在应激致认知功能障碍星形胶质细胞 A1 型活化中发挥重要作用。靶向 MALAT1/VCP/ iκBα/ NF-κB 信号通路可能是治疗应激致认知功能障碍的一种有前景的策略。

关键词:应激，星形胶质细胞活化，MALAT1, VCP, NF-κB，认知功能障碍

P10-20 应激诱导空间记忆损伤中海马乳酸变化及其作用机制研究

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应激是机体在面对生存环境中多种不利因素时所表现出的全身性非特异性反应。长时程高强度的应激对认知功能具有损伤作用。海马是空间学习记忆能力的关键调控脑区，也是应激易损伤的主要靶区。神经元动作电位的产生和突触间的信息传递都伴随着能量的产生和消耗，海马区神经元的正常代谢状态是维持空间记忆功能的基础。已有研究表明乳酸是神经元的重要能量底物，当脑处于活性状态时，所需能量增加，脑内乳酸产生增多，神经元会优先摄取乳酸作为底物进行供能，保持自身能量供应。但慢性应激时海马乳酸水平的变化及其作用仍不清楚。本研究采用慢性不可预见性温和应激（CUMS）方法建立应激小鼠模型，通过动物行为学实验，分子生物学实验及组织形态学实验等方法，研究应激诱导空间记忆损伤中海马乳酸变化情况及其作用机制。研究发现 6 周及 8 周 CUMS 处理可导致小鼠空间记忆功能损伤，并引起海马组织乳酸含量降低，小鼠海马注射乳酸可改善 CUMS 引起的空间记忆功能损伤，海马内乳酸可能参与慢性应激诱导空间记忆功能障碍的发生及调控。体外细胞实验结果表明乳酸促进海马神经元产生 ATP，提高突触相关蛋白 PSD95,SYP,GAP43 的表达水平。此外，慢性应激致小鼠海马单羧酸转运体 MCT2 表达水平降低，乳酸可提高小鼠海马组织及神经元 MCT2 表达水平，而拮抗 MCT2 的功能可抑制乳酸对神经元的调控作用。机制上，我们发现乳酸可促进海马神经元蛋白质合成，提高蛋白质总体乳酸化水平。综上所述，以上研究结果表明慢性应激条件下海马组织乳酸含量降低，MCT2 表达减少，通过改变神经元氧化磷酸化水平、调控蛋白质合成、蛋白乳酸化水平等抑制神经元功能，进而诱导空间记忆功能损伤的发生。研究结果有望为应激损伤的防护及治疗提供新靶点及新思路。

P10-21 缺硒通过氧化应激导致小鼠胃黏膜发生铁死亡和炎症损伤

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硒（Se）是维持生物体正常生理功能所必需的微量元素。氧化应激是指体内氧化作用和抗氧化作用不平衡的一种状态。缺硒会使机体更倾向于氧化，从而诱发相关疾病。本实验以小鼠胃黏膜组织为研究对象探讨缺硒通过氧化应激影响消化系统的作用机制。结果表明，缺硒处理导致胃黏膜中硒蛋白 GPX4 含量和抗氧化酶活性下降；ROS、MDA 和 LPO 水平升高，氧化应激反应被激活。ROS、Fe^{2+}和 LPO 的三重刺激诱导铁死亡。TLR4/NF-κB 信号通路

被激活，诱导炎症反应。BCL 家族和 Caspase（Cas）家族基因表达增加，导致细胞凋亡。同时，RIP3/MLKL 信号通路被激活，导致细胞坏死。综上所述，硒缺乏可通过氧化应激诱导铁死亡。同时，ROS 的大量产生激活了 TLR4/NF-κB 信号通路，导致胃黏膜细胞凋亡和坏死。

关键词：缺硒，胃黏膜，氧化应激，铁死亡，炎症损伤

P10-22 Hematopoietic stem cells reside in adult mouse steady state meninges

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Steady state extramedullary hematopoiesis during adulthood is an emerging field of great interest. The meninges contain both innate and adaptive immune cells which provide immunosurveillance of the central nervous system (CNS). Hematopoietic progenitors that give rise to meningeal immune cells remain elusive. Here we report that steady state meninges of adult mice host hematopoietic stem cells (HSCs), as defined by long term, efficient, multi-lineage reconstitution and self-renewal capacity in the meninges, blood, spleen, and bone marrow of sublethally irradiated adult recipients. HSCs lodge in the meninges after birth with local expression of pro-hematopoietic niche factors. Meningeal HSCs are locally maintained in homeostasis and get replenished from the blood only when the resident pool is reduced. With a tissue-specific expression profile, meningeal HSCs can provide the CNS with a constant supply of leukocytes more adapted to local microenvironment. The leukocytes change dramatically upon psychological stress.

Keywords: HSCs, meninges, extramedullary hematopoiesis, niche, transplantation

P11 血液生理

P11-1 Diverse effects of cryopreservation-induced mitochondrial dysregulation on cord blood cells

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Umbilical cord blood transplantation (UCBT) has been performed broadly in clinic by the specific biological and immunological characteristics of umbilical cord blood cells (UCB). UCB-based cell therapy and immune therapy also presents great application potential. UCB was usually cryopreserved for several years before using. Whether and how cryopreservation affects the function of divergent cell populations in UCB still remain to be illuminated.

Here, we firstly constructed a single-cell transcriptomic profile of Lineage$^-$ CD34$^+$ hematopoietic stem and progenitor cells (HSPCs) and mononuclear cells (MNCs) collected from fresh and cryopreserved UCB with 1, 5, 10 and 19 years. Subpopulations characterized by higher mitochondrial gene expression (Mito^{high}) were identified in all cell populations and found to be increased during cryopreservation. Compared with the fresh group, HSC/MPP cells after cryopreservation showed more active cell cycle and lower expression of HSC/MPP signature genes, especially in the Mito^{high} HSC/MPP cells. Consistently, colony-forming ability as well as long-term hematopoietic reconstitution of HSPCs derived from cryopreserved UCB gradually decreased within 5 years but remained stable thereafter. More importantly, we observed decreased megakaryocyte differentiation ability from cryopreserved HSPCs, which could be partially rescued by antioxidants treatment after cryopreservation. Mechanically, we revealed that the metabolic dysregulation of mitochondria including elevated mitochondrial reactive oxygen species (ROS), reduced adenosine triphosphate (ATP) synthesis and impaired mitochondrial membrane potential of cryopreserved HSPCs led to attenuated hematopoietic reconstitution. Although there was a mild increase of Mito^{high} subpopulations after cryopreservation, the cytokine production levels of T cells and NK cells were comparable to those of fresh samples. Additionally, NK cells exhibited almost same cytotoxic function with the fresh compartments.

Taken together, we elucidated the impact of cryopreservation on UCB HSPCs and provided the strategy for rescuing its functional impairment. The unaffected T and NK cells after cryopreservation also paved the way for UCB-based cell therapy and immune therapy. Our study provides important implements for the quality control of applicable UCB both in hematology and

immunotherapy.

Keywords: Cryopreserved umbilical cord blood, HSPC, recovery, engrafting, single-cell RNA-seq

P11-2 The hematopoietic ecosystem in acute myeloid leukemia

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The acute myeloid leukemia (AML) ecosystem comprises of normal hematopoietic stem and progenitor cells (HSPCs), AML cells, and niche cells. In this study, we utilized scRNA-seq to unravel the AML bone marrow (BM) ecosystem. Transcriptomic analysis revealed a downregulation of hematopoietic supportive factors and an upregulation of pro-inflammatory factors in BM stromal cells. HSPCs displayed dominant, but erythroid/megakaryocytic limited myeloid differentiation. Interestingly, we observed a new cell population called LSKlow ($Lin^{-}Sca1^{+}cKit^{low}$) in leukemia, which possessed five lineage reconstitution capacities. Cell-cell interaction analysis showed a reduced strength of Scf-Kit signaling between niche cells and HSPCs during AML development. Conditional knockout of Scf in BM stromal cells reduced the survival of AML mice, whereas tibia injection of AAV-Scf increased the survival, indicating SCF as a positive regulator for AML mice survival. In conclusion, our study constructed a single-cell atlas of the AML ecosystem and highlighted the crucial role of the Kitl (Scf)-Kit axis in leukemia development.

Keywords: Haematopoietic stem and progenitor cells; leukemia niche; single cell RNA-Sequencing; Cell ecosystem

P11-3 Blood transcriptomic disturbance and its clinical and immunology association in Alzheimer's disease

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Background The early diagnosis of Alzheimer's disease (AD) in large-scale high-risk populations is a major challenge. Blood-based biomarkers could enable widespread testing for AD. RNA-seq technology is becoming an effective method in investigating diagnostic biomarkers for diseases, but the blood transcriptomic profile of AD and its clinical association has not yet been revealed.platforms exploring RNA-seq data in AD blood are lacking.

Methods We collected blood the raw RNA-seq data (bulk RNA-seq, miRNA-seq, and scRNA-seq) in the blood of 246 AD patients, 282 mild cognitive impairment (MCI) individuals, and 859 normal people from the Gene Expression Omnibus (GEO) and Synapse databases. Data of AD mouse models and wild-type mouse were also collected. Differential gene expression, pathway enrichment analysis, clinical outcome association, and immune cell abundance estimation analyses were performed. with AD or mild cognitive impairment (MCI) or normal people and AD mouse models or wild-type mouse from the Gene Expression Omnibus (GEO) and Synapse databases. And the RNA-seq data was analyzed by the standard pipeline. We applied R/Shiny was applied to develop a the web server called site of RAD-Blood (RNA-seq analysis of AD blood, http://www.bioinform.cn/RAD-Blood/) to present plentiful analysis results.

Results RAD-Blood was designed for analyzing blood RNA-seq data sets (bulk mRNA-seq, miRNA-seq, and scRNA-seq) in AD/MCI/normal cases. It provides differential expression analysis, clinical association analysis, GSEA, immune abundance estimation, cell type annotation, T cell receptor (TCR) prediction, and cell communication analysis. We identified 270 consistently dysregulated protein-coding genes in AD/MCI, with four being erythroid cell biomarkers. Erythroid cell population decreased in AD, but their interactions with other cell types, mainly through the MHC-I signaling pathway, increased dramatically.

Conclusions RAD-Blood is a user-friendly web server for multi-level analysis and visualization of gene/miRNA expression, clinical association, and immune profile in AD blood. RAD-Blood allows broad utility in exploring potential AD blood biomarkers, testing hypotheses, guiding experiment design, investigating the peripheral pathogenic mechanisms and proposing

potential early diagnosis standards of AD.

Keywords: Alzheimer's disease; blood; mRNA; miRNA; single cell; biomarker

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P11-4 Single-cell transcriptomic atlas identified novel immunotherapeutic target for multiple myeloma

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Despite the evolving treatment landscape of multiple myeloma (MM), patient responses remain heterogeneous. Still, some patients experience rapid disease progression with short survival even in the context of active treatment. Underscoring the critical mechanisms leading to the aggressive disease progression is critical in providing novel therapeutic selection for these high-risk MM patients. Tumoral intrinsic factors involving genomic instability and immunosuppressive tumor microenvironment are especially highlighted in the MM progression. Therefore, we contributed to identify the potential therapeutic target which could both eliminate the tumor cells and improve the microenvironment.

We utilized single-cell transcriptomic sequencing to dissect the characteristic bone marrow niche of patients with survival less than two years. Notably, an enrichment of $CD38^{+}CD138^{low}LILRB4^{+}$ pre-matured malignant plasma cells was observed in patients with short survival compared with patients with durable remission. The pre-matured MM-cell cluster exhibited intensive aggressiveness at transcriptomic level. This minor but aggressive cluster was characterized by high expression of MM proliferating and drug-resistant genes, complex chromosomal abnormalities and high mutational burden.

For better distinguishing the high-risk patients, we combined the ISS staging system, high-risk CAs, and gene features extracting from the enriched pre-matured MM cluster, and constructed the RR2-ISS stratification model. To be noticed, the median OS of patients in the

high-risk group identified by RR2-ISS model was two years, which was in concordance with the high-risk definition.

We showed that *LILRB4* is specifically highly expressed in this aggressive pre-matured MM population. *LILRB4*, an immunoreceptor tyrosine-based inhibition motif-containing receptor, has been suggested to play critical roles in mediating T cell suppression, MDSC function, and tumor infiltration in multiple cancers. Therefore, we intended to explore the unique biological function of LILRB4 and the preclinical efficacy of targeting LILRB4 in MM. Importantly, high LILRB4 expression correlated with short survival (GSE2658; $P<0.0001$). We firstly detected the expression of LILRB4 in MM/plasma cells in patients by flow cytometry. We observed that the level of LILRB4 was significantly increased in precursor stage of plasma cells (pre-PC, $CD38^{+}CD138^{+}CD19^{+}CD56^{+}$) compared with mature malignant MM cells (MPC, $CD38^{+}CD138^{+}CD19^{-}$), which were both higher than normal PCs (NPC, $CD38^{+}CD138^{+}CD19^{+}CD56^{-}$). Gain-of-function studies in JJN3 and H929 MM cell lines demonstrated that overexpression of LILRB4 could promote the growth, clonogenicity and invasion ability of MM cells; the opposite effect occurred with LILRB4 deletion in ARP1, H929 MM cell lines. The tumor-promoting effects could also be observed in xenograft NOD/SCID mice model by injecting LILRB4-overexpressed MM cell lines subcutaneously. Deletion of LILRB4 significantly suppressed the tumor growth in vivo as well. Furthermore, we found a higher proportion of MDSCs in LILRBE-overexpressed tumor tissue by flow detection. Next we cocultured LILRB4-overexpressed and empty-vector transfected MM cell lines with peripheral blood mononuclear cells (PBMCs) from healthy donors in vitro. After 7-days coculture, *LILRB4*-overexpressed MM cells significantly induced more M-MDSCs ($CD14^{+}CD33^{+}HAL\text{-}DR^{low}$) from PBMCs compared with empty-vector transfected cells. Additionally, MDSCs in MM patients expressed high level of LILRB4. Hence, we postulated that LILRB4-targeted immunotherapy could be promising in MM.

Collectively, we constructed an RR2-ISS stratification model which could identify high-risk MM patients with survival less than two years. We demonstrated that LILRB4 played critical roles in promoting tumor growth and inducing the generation of immunosuppressive MDSCs. LILRB4-targeted immunotherapy might offer alternative promising options for the high-risk MM patients.

Keywords: single-cell RNA-sequencing; multiple myeloma; immunotherapy;

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P11-5 Landscape of bone marrow T cells in acquired aplastic anaemia reveals an activated state and a potential clonal expansion

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Background: Acquired aplastic anaemia (AA) is a typical example of human bone marrow (BM) failure syndromes and is characterized by peripheral blood cytopenia and empty bone marrow. Previous studies have identified AA as an autoimmune disease mediated by T-cells, which attack and destroy the hematopoietic stem cells in BM.

Aims: Our study aims to investigate the cellular heterogeneity, lineage and functional states of T cells that play a role in the development of AA, with the goal of shedding light on the underlying mechanisms of the disease.

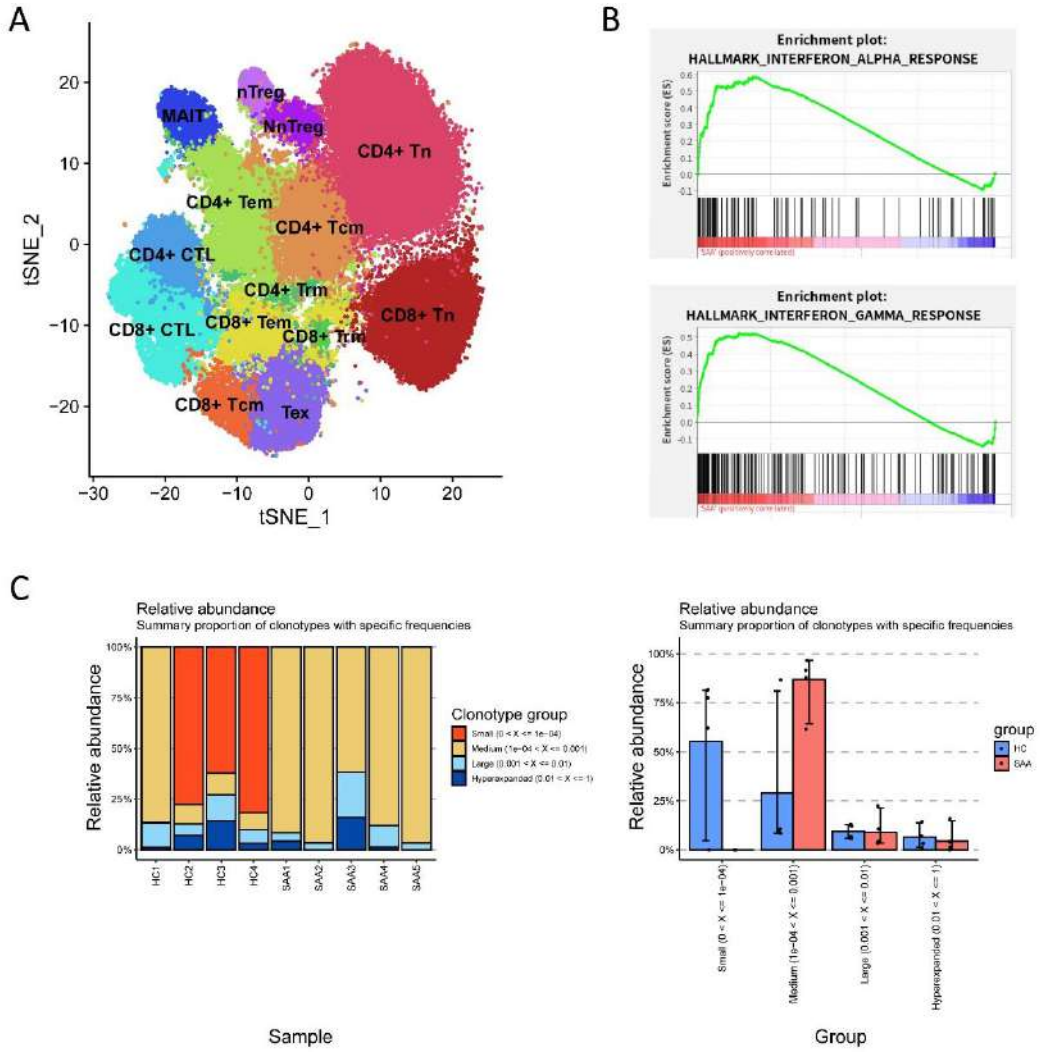
Methods: $CD3^+CD4^+$ and $CD3^+CD8^+$ mature T cells, isolated from BM of five newly diagnosed severe AA (SAA) patients and four healthy controls (HC) by fluorescence-activated cell sorter (FACS), were subjected to single-cell RNA sequencing (scRNA-seq) and T cell receptor (TCR) sequences using 10X Genomics Chromium Single Cell 5' and Single-Cell V(D)J protocols. Libraries were sequenced on Illumina NovaSeq platforms.

Results: Following a rigorous quality control process, 78,391 (SAA, n = 41,253; HC, n = 37,138) single-cell profiles were included in the downstream analyses. Bioinformatic analysis of the transcriptional profiles and TCR sequences revealed their molecular and functional properties and developmental trajectory. And a total of 14 stable clusters emerged, consisting of 7 clusters for $CD8^+$ and 7 clusters for $CD4^+$ cells (Figure 1A). We found that $CD8^+$ cytotoxic T lymphocytes (CTLs) in SAA exhibited stronger cytotoxicity and invasiveness compared to those in HC, and this abnormality may be involved in the destruction of bone marrow hematopoietic system in SAA. We observed an up-regulation of multiple chemokine genes and chemokine receptor genes, as well as an enhancement of IFN-α and IFN-γ response pathways in CTLs of SAA. These findings suggested that CTLs in SAA exhibited an activated state. We next assessed the TCR repertoire and clonal expansion. Sequencing and analysis of the TCR repertoire can yield valuable insights into adaptive immune responses, with significant implications for the investigation of autoimmune diseases. Although the majority of cells contained unique TCRs, we observed differing levels of repeat patterns in different samples, particularly in SAA patients. The relative abundance analysis

of TCR clones in all samples showed that the proportion of medium and above medium size clones was higher in SAA patients. The data supported the potential clonal expansion in SAA.

Conclusion: Our study provides a comprehensive reference map of human BM T cells in SAA patients. The unique characteristics of T cells observed in SAA patients suggest their potential critical role in the pathogenesis of this autoimmune disease.

Figure 1



Keywords: Acquired aplastic anaemia, scRNA-seq, TCR repertoire, clonal expansion

P11-6 TMEM56 通过调节自噬过程调控红细胞的生成

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红细胞的生成是一个极其复杂的过程，由多种调节因子，细胞内部信号以及细胞外部信

号交互作用控制。大量研究证明跨膜蛋白 (Transmembrane proteins, TMEMs) 是红细胞发育的关键调节因子，其功能涵盖了参与红细胞发育过程中血红素合成、离子转运和信号转导等多个方面。其中 TMEM56 是跨膜家族蛋白成员之一，并在红细胞发育过程中高表达，但其在红系发育中的功能尚不明确。因此，我们旨在深入探究 TMEM56 在红细胞发育中的具体作用及调控机制。

利用人脐带血来源的 $CD34^+$细胞的体外造血发育模型，可以研究红细胞不同发育阶段中 TMEM56 的功能。通过 shRNA 干扰技术对 TMEM56 进行敲降，我们发现 TMEM56 降低后红细胞的增殖和分化受到显著抑制，细胞周期阻滞于 G0 期。我们发现 TMEM56 敲降后红细胞中珠蛋白的表达水平显著降低，多核细胞的比例增加，说明 TMEM56 对于红系发育具有重要调控作用。为了进一步探究 TMEM56 调控红细胞分化发育的机制，我们对 TMEM56 敲降后的有核红细胞进行了 RNA-seq，分析结果表明 TMEM56 敲降后有核红细胞的溶酶体转运相关的通路显著富集，此外，我们还发现在 TMEM56 敲降后，巨自噬的关键蛋白 LC3 表达增高，这提示 TMEM56 可能是通过影响红细胞自噬过程调控红细胞的分化和发育。

总之，我们这项研究为 TMEMs 家族在红细胞发育中的调控机制研究提供了新的见解，鉴于 TMEM56 在红细胞增殖及分化中的重要作用，我们将进一步深入研究 TMEM56 的具体作用和调控机制，以便更好地理解其在疾病中的作用，未来有望将其作为治疗贫血和其他相关疾病的潜在靶点。

关键词：红细胞发育，自噬，TMEM56

P11-7 单细胞测序技术解析白血病微环境中单核细胞的异质性

Single-cell RNA sequencing reveals the heterogeneity of monocytes in the leukemia microenvironment

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目的：白血病微环境和肿瘤微环境相似，在白血病的发生、发展中发挥着至关重要的作用。单核细胞作为免疫微环境的一个重要组成成分，其在白血病微环境的研究还不充分。本文利用单细胞测序技术，分析白血病微环境中单核细胞的异质性改变，探讨白血病微环境对单核细胞免疫学功能的影响。

方法：收集临床淋巴细胞白血病标本及正常供者标本，分选骨髓样本中单核细胞，利用 10X Genomics Chromium 平台，进行了单细胞测序。Cellranger 进行质控及初步分析，tSNE

和 UMAP 降维分析展示细胞分群，研究不同微环境的单核细胞在分群上的差异。根据已知 Marker 和单细胞测序数据得到的每一亚群的特异基因对细胞亚群进行注释。KEGG 和 GO 分析各亚群富集的信号通路的差异。利用小鼠模型进一步分析白血病微环境影响单核细胞异质性的机制。

结果：单细胞测序结果显示白血病微环境中单核细胞亚群的组成比例发生改变，经典型单核细胞的比例降低，非经典型单核细胞的比例升高，免疫激活分子表达下降，且免疫活化信号被抑制。利用小鼠 T-ALL 模型研究发现这群增多的非经典单核细胞亚群明显抑制 T 细胞的活化，并且表达免疫抑制分子。这群免疫抑制性单核细胞亚群参与形成免疫抑制性白血病微环境。

结论：白血病微环境影响单核细胞亚群组成，其中非经典单核细胞亚群表达免疫抑制分子，免疫激活能力减弱，参与形成免疫抑制型微环境。本研究阐明了非经典单核细胞新的免疫调控机制，是微环境因素和白血病发生、发展关系研究的有益补充。

P11-8 白血病相关调节性树突状细胞的基因表达特征

Characteristics of gene expression in leukemia-associated regulatory dendritic cells

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目的：树突状细胞 (dendritic cells, DCs) 是一种专职的抗原呈递细胞，在先天性和适应性免疫系统中发挥不可或缺的作用。在一些免疫抑制物和肿瘤微环境的刺激下，诱导产生调节性树突状细胞 (DCreg)。DCreg 相关研究主要集中在实体肿瘤中，在白血病微环境中的性质和作用尚未阐明。我们利用 Notch1 诱导的小鼠 T-ALL 模型，研究白血病相关树突状细胞的基因表达特点。

方法：建立 T-ALL 模型，检测不同发病阶段 DCs 的比例。从正常及 T-ALL 小鼠中分选 Normal-CD11c$^+$MHC Ⅱ$^+$、T-ALL-CD11c$^+$MHC Ⅱ$^+$和 T-ALL-CD11c$^+$MHC Ⅱ^{lo} 三群细胞，RNA-Seq 和单细胞测序分析其基因表达谱。实时定量 PCR 检测免疫抑制性分子的表达水平。

结果：T-ALL 小鼠中出现了一群高表达 CD11c、低表达 MHC Ⅱ 的细胞。将 Normal-CD11c$^+$MHC Ⅱ$^+$，T-ALL-CD11c$^+$MHC Ⅱ^{lo}，T-ALL-CD11c$^+$MHC Ⅱ$^+$三组细胞进行 RNA 测序，主成分分析发现 T-ALL-CD11c$^+$MHC Ⅱ^{lo} 细胞与另外两组细胞的基因表达谱有显著差异：抗原呈递相关基因表达明显低于其他两组，负向调节免疫反应相关基因表达明显高于其他两组。单细胞测序分析发现 T-ALL-CD11c$^+$MHC Ⅱ^{lo} 细胞主要由 DC 细胞亚群组成。qPCR

发现 T-ALL-CD11c^{+}MHC Ⅱ^{lo} 细胞高表达 DCreg 的特征性分子 IL-10 以及 Nos2。流式细胞分析发现这群细胞比 T-ALL-CD11c^{+}MHC Ⅱ$^{+}$细胞表达更高水平的 PD-1。

结论：T-ALL 小鼠出现一群 CD11c^{+}MHC Ⅱ^{lo} 细胞。这群细胞主要由 DCs 细胞组成，其抗原呈递基因表达降低，负向调节免疫反应基因表达升高，提示这群细胞是白血病微环境中的 DCreg 细胞，可能通过高表达 IL-10 和 PD-1 发挥免疫抑制功能，促进 T-ALL 进展。

P11-9 白血病微环境通过调节 IRF7 相关信号通路激活 pDC

Activation of pDCs in leukemia microenvironment through the IRF7 associated signaling pathway

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目的：树突状细胞（DC）是一群重要免疫细胞，主要参与了抗肿瘤免疫和抗感染免疫。浆细胞样树突状细胞（pDC）一类主要产生 I 型干扰素的细胞，其在形态和功能上和经典树突状细胞（cDC）有区别。已有研究报导 pDC 在肿瘤免疫中的作用，然而，它们在白血病微环境中的特征尚未得到较为全面的探究。我们运用 MLL-AF9 诱导的小鼠急性髓系白血病（AML）模型，探索白血病微环境中 pDC 的表型、亚群和免疫调节潜能。

方法：检测构建小鼠 AML 模型，在疾病发展不同阶段分析 pDC 数量变化。RNA-Seq 分析 AML 微环境中 pDC 的基因表达谱。采用 IRF7 敲除（IRF7$^{-/-}$）小鼠构建 AML 模型，研究 pDC 中 CD80 和 CD86 等基因表达变化。在 DC 细胞系中过表达或敲降 IRF7 研究 CD80 和 CD86 等基因表达变化。

结果：通过流式分析结果显示，AML 小鼠脾脏中的 pDC 比例降低。进一步通过分析 AML 小鼠脾脏微环境中 pDC 的基因表达谱，发现 AML 微环境的 pDC 中高表达 IRF7，而 IRF7$^{-/-}$ AML 小鼠的 pDC 中 CD80 和 CD86 分子的表达下调。在 IRF7$^{-/-}$小鼠原代 pDC 中，CD80 和 CD86 的表达也下调。在过表达或敲降 IRF7 的 DC 细胞系中 CD80 和 CD86 的表达水平变化和 IRF7$^{-/-}$小鼠的变化趋势一致。

结论：白血病微环境中的 pDC 可能通过 IRF7 相关信号通路介导的 CD80 和 CD86 表达以及 T 细胞活化来发挥其免疫调节潜力。我们的研究结果揭示了在 AML 微环境中，IRF7 在 pDC 中介导产生 I 型干扰素之外的新作用，并为通过微环境的治疗策略来治疗 AML 提供了理论基础。

P11-10 Fbxw11 延缓 AML 疾病进展的分子机制研究

Molecular mechanism of Fbxw11 delaying the AML progression

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目的：泛素-蛋白酶体系统通过翻译后修饰调控细胞内信号转导通路，参与细胞的生长及分化、DNA 复制与修复、细胞代谢、免疫反应等多种生理病理过程。包含 F-盒/WD 重复序列蛋白 11（Fbxw11)是一种 E3 连接酶，通过靶向多种蛋白质参与许多重要的生物学过程。我们前期研究发现过表达 Fbxw11 能够延缓 AML 疾病进展，但其机制尚不清晰。本研究通过分析高表达 Fbxw11 的 AML 细胞与对照组 AML 细胞的差异蛋白并进行验证，探究 Fbxw11 延缓 AML 进展的机制。

方法：利用蛋白组学技术分析高表达 Fbxw11 的 AML 细胞与对照组 AML 细胞的差异蛋白并用 Western blot 进行验证。分选前期构建的高表达 Fbxw11 的白血病细胞，体外感染 Dpysl2 的慢病毒表达载体（pCDH-Dpysl2-EF1-RFP）及空载体对照病毒，构建同时高表达 Fbxw11 和 Dpysl2 的 AML 小鼠模型及对照模型（高表达 Fbxw11）。分选白血病细胞进行移植，观察小鼠生存期、发病进程中肝脾肿大情况。流式细胞分析白血病细胞 c-Kit（CD117）表达情况。研究白血病细胞凋亡情况。体外 Transwell 实验研究白血病细胞的迁移能力。

结果：对 Fbxw11 高表达的 AML 细胞与对照组 AML 细胞差异蛋白进行分析及 Western blot 实验发现，实验组中 Dpysl2 蛋白表达下降最显著。成功在高表达 Fbxw11 的基础上构建高表达 Dpysl2 的 AML 小鼠模型。与对照组相比，在移植后 12 天、16 天实验组小鼠外周血白血病细胞比例显著增高，并且生存期缩短，脾脏显著增大，肝脏差异不明显。通过对白血病细胞生物学性质的研究发现，与对照组相比，实验组 c-Kit$^+$比例增加，迁移能力增强，凋亡水平没有显著变化。

结论：我们的研究结果表明，Dpysl2 蛋白水平在高表达 Fbxw11 的 AML 细胞中与对照组相比显著降低，并且高表达 Dpysl2 逆转了高表达 Fbxw11 对 AML 进展的延缓作用。

P11-11 巨噬细胞训练免疫在白血病中的作用

The role of macrophage trained immunity on the progression of leukemia

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目的：经过刺激的固有免疫细胞， 在二次刺激下表现出增强或减弱的免疫反应, 这种现象被定义为“训练免疫”或“固有免疫记忆”。巨噬细胞作为重要的固有免疫细胞, 也具有免疫记忆性质。巨噬细胞固有免疫记忆在感染等疾病中已有一定的研究，在白血病中的作用尚未阐明。β-葡聚糖是目前常用诱导训练的分子，本研究利用 β-葡聚糖诱导巨噬细胞训练免疫，探究巨噬细胞固有免疫记忆在白血病中的作用。

方法：C57BL/6J 小鼠经腹腔给药 β-葡聚糖作为实验组，对照组不给药，通过流式细胞术对两组小鼠腹腔、骨髓、脾脏巨噬细胞比例和吞噬功能进行检测，通过 q-PCR 检测腹腔巨噬细胞极化相关基因的表达。β-葡聚糖预处理后移植 T-ALL 细胞构建小鼠急性 T 淋巴细胞白血病模型，对照组预处理不给药，流式细胞术检测发病早中晚期骨髓、脾脏、外周血中白血病细胞比例，病理切片 HE 染色对比上述组织中白血病细胞中的浸润情况。

结果：β-葡聚糖显著提高腹腔和骨髓巨噬细胞的比例；其中腹腔巨噬细胞中 SPM 亚群（$F4/80^{low}\,MHCII^{+}$）比例明显升高，LPM 亚群（$F4/80^{high}\,MHCII^{-}$）比例明显降低。β-葡聚糖引起腹腔巨噬细胞表型相关基因表达变化：M1 相关基因中 iNOS、IL-6、IL-1b、IL-12b 表达水平升高，其中 iNOS 基因表达升高尤其显著；M2 相关基因中 CSF-1、CCL-17、MMP9 的表达水平降低。通过巨噬细胞极化表型二维图对比，经 β-葡聚糖训练后腹腔巨噬细胞位于 M1 区域。T-ALL 模型早中期，β-葡聚糖处理显著延缓白血病细胞向骨髓、脾脏和肝脏等部位的浸润。

结论：β-葡聚糖显著提高腹腔和骨髓巨噬细胞比例，并促进腹腔巨噬细胞更偏向 M1 极化；T-ALL 中，β-葡聚糖预处理在疾病早中期表现出显著的抗白血病作用。

P11-12 The alternative splicing of LCK in Treg induction in immune thrombocytopenia

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Background: Immune intolerance, causing the production of autoantibodies, is thought to be one of the main pathogenesis of immune thrombocytopenia (ITP). As regulatory T cells (Tregs) are one of the most important cells to maintain immune tolerance and the phenotype, function, and importance of Tregs have been well defined over the past decade, extensive efforts have been devoted to unveiling the dysregulation of Tregs in ITP. It has been reported that the proportion of

Tregs in peripheral blood of ITP patients is reduced and the immunosuppressive function of Tregs is impaired, but the mechanism remains unclear. As peripheral Treg production can be induced from CD4+ naive T cells (NTC) with TCR-stimulated activation and TGF-β treatment, how peripheral Treg induction is impaired in patients with ITP remains to be further investigated.

Method: We isolated and performed high-throughput sequencing of the CD4+ NTC from the peripheral whole blood of ITP patients and healthy controls. After analyzing the differential expression and splicing pattern, we screened several genes of interest. In addition, a minigene plasmid of the target gene was constructed and RNA-chromatin immunoprecipitation (RNA-ChIP) was performed to explore the upstream splicing factor. PCR，Real-time quantitative PCR and Western Blot were used to validate the expression level and splicing pattern of various genes.

Results: Our results revealed the proportion of Tregs induced from CD4+ NTC of ITP patients was decreased in vitro, suggesting the abnormal Treg induction in ITP patients. The differentially expressed genes of the CD4+ NTC between ITP patients and healthy controls were significantly enriched in the alternative splicing pathway based on high-throughput RNA-seq data. Further exploration of the differentially spliced genes revealed significant differences in the exon 8 skipping in the LCK gene between healthy controls and ITP patients, as LCK plays a crucial role in TCR signaling and TCR signaling is essential for Treg induction. Overexpressing the exon 8 spliced LCK, other than overexpressing the exon 8 included LCK in T cells limited the TCR activation. Furthermore, we found splicing factor X could recognize the exon 8 of LCK and promote the inclusion of exon 8 of LCK. Splicing factor X was lowly expressed in the CD4+ NTC of ITP patients. Accordingly, we proposed the hypothesis that the lower expressed splicing factor X in the CD4+ NTC of ITP patients may limit peripheral Treg induction by regulating LCK alternative splicing in ITP. By using RNA-CHIP, we found splicing factor X specifically bound to the exon 8 of LCK. Moreover, the administration of antisense oligos, which could mask the binding site, suppressed the recognition of the exon 8 of LCK and enhanced the exon skipping events of LCK transcripts. As expected, ASO transfection inhibited the Treg induction in CD4+ NTCs from healthy controls, which may mimic the Treg induction in ITP patients.

Conclusion: Here we found splicing factor X was downregulated in the CD4+ NTC of ITP patients, which resulted in the exon 8 skipping in the LCK gene and a down-regulated TCR signaling, thereby limiting the induction of peripheral Tregs. This study will explore the pathogenesis of ITP from a novel perspective, and provide new ideas and targets for the clinical treatment of ITP.

Keywords: alternative splicing, LCK, Treg, ITP

P11-13 *SPI1-KLF1/LYL1* axis regulates lineage commitment during human endothelial-to-hematopoietic transition

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PU.1 (*SPI1*) is a crucial transcription factor in hematopoiesis, yet its role in human endothelial-to-hematopoietic transition (EHT) remains unclear. By comparing the human *in vivo* and *in vitro* EHT transcriptomes, we observed similarities in the transcriptional profiles of *SPI1*, suggesting its regulatory role in EHT. Knocking down *SPI1* in *in vitro*-generated hemogenic endothelial cells (HECs) led to a decrease in the generation of hematopoietic progenitor cells (HPCs) and their differentiation potential. Through multi-omic analysis, we identified *KLF1* and *LYL1* - transcription factors specific to erythroid/myeloid and lymphoid cells, respectively - as downstream targets of *SPI1*. Overexpressing KLF1 or LYL1 partially rescues the *SPI1* knockdown-induced reduction in HPC formation. Specifically, *KLF1* overexpression restores myeloid lineage potential, while *LYL1* overexpression re-establishes lymphoid lineage potential. We also observed a PU.1-*LYL1* axis in the regulatory network in *in vivo* EHT. Taken together, our

findings shed new light on the role of *SPI1* in regulating lineage commitment during EHT, potentially contributing to the heterogeneity of hematopoietic stem cells (HSCs).

Keywords: Hematopoietic stem cells；Endothelial-to-hematopoietic transition；Transcription factors；SPI1；In vitro hematopoietic differentiation；Single cell transcriptome

P11-14 骨髓巨噬细胞调控造血机理探索

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造血干细胞移植（HSCT）是治疗恶性血液系统疾病的有效手段。供者 HSC 成功植入是 HSCT 成功的基础，但有一部分临床 HSCT 患者造血恢复延迟或不完全，外周血血红蛋白、白细胞和血小板持续低下，为植入功能不良(PGF)。PGF 发生率虽然不高，但由于具体机制尚不完全清楚且无有效的临床干预措施，一旦发生，死亡率较高，是目前 HSCT 面临的临床新问题，也是 HSCT 的严重并发症之一。研究认为，PGF 与造血微环境关系密切，其中骨髓巨噬细胞是造血微环境的重要组成部分，与造血调控密切相关，但其具体机制尚不明确。为了探究巨噬细胞在移植后骨髓微环境中扮演的角色，本研究以骨髓巨噬细胞为研究对象，从造血组织损伤修复和造血重建入手进行了系列实验，阐明巨噬细胞调控造血组织损伤修复和造血重建的分子机理。首先建立小鼠 HSCT 模型并特异性清除受者体内的巨噬细胞，结果发现，特异性清除巨噬细胞可降低移植小鼠生存率，炎性因子虽降低，但骨髓损伤加重，初步提示，巨噬细胞能够促进损伤造血组织修复及造血重建。Clodronate-liposome 是多种疾病模型临床前研究的首选巨噬细胞清除药物。采用巨噬细胞清除剂在小鼠体内清除骨髓巨噬细胞后能够抑制亚致死照射小鼠的骨髓造血重建。归巢实验进一步证实 Clodronate-liposome 介导的骨髓巨噬细胞清除抑制造血干细胞的骨髓归巢过程。且体外实验验证巨噬细胞损伤后巨噬细胞对造血干细胞的直接支持作用减弱，且巨噬细胞对造血细胞的直接支持作用通过巨噬细胞与 HSC 的直接接触和细胞粘附来介导。本研究为全面评价 HSCT 后骨髓造血微环境的作用提供新的理论和实验依据。

关键词：骨髓巨噬细胞、造血调控、造血干细胞移植、植入功能不良

P11-15 Effects of the Aurora an inhibitor MZ-3B on the biological behaviors of AML cell lines via the JAK2-STAT3 pathway

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Acute myeloid leukemia (AML) is a complex in heterogeneous disease with many subtypes. Many AML patients still cannot cure with conventional chemotherapy, die from disease recurrence and drug resistance. Therefore, it is crucial to find the novel targeted therapy. Aurora kinases have shown great potential in treating malignant tumors, including acute myeloid leukemia (AML). However, weather it could reduce the drug resistance of AML is still unclear. In this study, AML cells were treated with MZ-3B followed by measuring cell viability, cell cycle, apoptosis, differentiation and the specific cell signaling pathways. We found that MZ-3B is a potential and selective Aurora-A inhibitor. Our results indicated that MZ-3B inhibited AML cell proliferation and arrested the cell cycle at the G0/G1 phase. It also activated the apoptosis signaling pathways in AML cells. Moreover, MZ-3B also reduced the number of the AML colonies and promoted cell differentiation. Mechanistically, MZ-3B inhibited STAT3 expression and regulated the JAK2-STAT3 signaling pathway. Additionally, the Co-administration of Daunorubicin (DNR) and Cytarabine (Ara-c) with Aurora-A inhibitor MZ-3B synergistically inhibited the viability of AML lines, with evidence of attenuated polyploidization, promoted the apoptosis and caused cycle arrest of AML cells. In conclusion, our results highlighted the potential role of Aurora kinases MZ-3B inhibited the progression of AML in vitro, hereby provided a theoretical basis for the selection of clinical chemotherapy options, especially for Daunorubicin-resistant and cytarabine AML.

Key words: Aurora; MZ-3B; JAK2-STAT3 pathway; Acute myeloid leukemia

P11-16 Assessment of intestinal status in MPL^{W515L} mutant myeloproliferative neoplasms mice model

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Abstract: The MPL^{W515L} mutation is a prevalent genetic mutation in patients with myeloproliferative neoplasms (MPN), and using this mutation can provide new insights into the disease. Although there is a close association between the state of intestinal homeostasis and the prognosis of MPN, the link between intestinal homeostasis and MPN mouse models remains unclear.

Here, we utilized a retroviral vector to transfect hematopoietic stem cells with the MPL^{W515L} mutation to develop mutated MPN mouse models and investigate their intestinal status.

Our findings revealed that the MPL^{W515L} mutation aggravated inflammation in the intestines, reduced the levels of tight junction proteins, and lowered the receptors for intestinal bacteria metabolites. Furthermore, the mutation increased the activation of the caspase1/IL1β signaling pathway while significantly reducing the phos-p38 level but increasing the phos-IKBα level in the intestinal tissue. The mutation also led to up-expression of anti-microbial genes and altered the bacterial composition, abundance, and differential analysis in the intestinal tract. Although the mutation did not affect the alpha diversity and dominant bacterial taxa, it did impact the rare bacterial taxa/sub-communities and thus intestinal homeostasis.

Our results underscored the significance of MPL^{W515L} mouse models for studying MPN disease and emphasized the impact of the MPL^{W515L} mutation on the intestinal homeostasis, particularly on inflammation, activation of the p38/IKBα signaling pathway, and the composition of gut microbial communities.

Keywords: MPL^{W515L}, myeloproliferative neoplasms, p38, IKBα, gut bacteria

P11-17 ROBO4 抑制照射损伤内皮间质转化促进造血重建

ROBO4 inhibits irradiation-induced endothelial-to-mesenchymal transition and improves hematopoietic reconstitution.

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研究目的：植入功能不良（PGF）是造血干细胞移植（HSCT）的严重并发症，移植后骨髓内皮损伤是导致 PGF 的重要原因但具体机理尚不清楚。ROBO4 是内皮细胞特有的跨膜蛋白，在维持血管完整性方面起着至关重要的作用，但其在骨髓内皮细胞损伤修复及造血重建中的作用及机理尚需探索。因此，本研究的目的主要是确定 ROBO4 在移植损伤内皮细胞完整性中的作用及机理，以及对 HSC 生物学功能的影响。

方法：将微血管内皮细胞进行 γ 辐射照射，建立内皮细胞损伤模型。利用慢病毒介导的 RNAi (shRNA)基因干扰和基因过表达技术改变小鼠微血管内皮细胞 ROBO4 的表达。采用 qPCR、免疫印迹等方法评价内皮细胞间充质转化，确定内皮细胞特异性分子和间充质特异性细胞标志物表达和分布的影响。采用 Transwell、迁移实验和 Matrigel 管形成实验等检测了 ROBO4 对照射后内皮细胞功能的影响。同时，建立 ROBO4 敲低或过表达内皮细胞与造血干细胞共培养模型，利用流式细胞术研究辐照内皮细胞中 ROBO4 表达水平对造血干细胞增殖、分化和细胞周期的影响。

结果：高剂量 γ 辐射损伤微血管内皮细胞发生明显的内皮间质转化，低表达 ROBO4 可增加 CD105 的表达，并通过激活 Smad 和 PI3K/NF-κb 信号通路促进内皮间质转化。内皮细胞 ROBO4 过表达显著降低 Endo-MT。同时，内皮细胞中 ROBO4 的下调可减少 HSPC 的增殖并增加 HSC 的静止，而 ROBO4 过表达减轻了受损内皮对 HSC 增殖的抑制作用。此外，ROBO4 的过表达能抑制内皮细胞辐射损伤后诱导的 HSC 分化。

结论：ROBO4 通过抑制损伤内皮细胞 Endo-MT，维持辐射预处理后微血管的完整性，保护内皮功能，减轻受损内皮对造血重建的抑制作用。

关键词：ROBO4; EndoMT;骨髓内皮；造血干细胞；造血重建

P11-18 AML-derived small extracellular vesicles promote leukemogenesis by transferring miR-221-3p

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Acute myeloid leukemia (AML) is a malignant disorder characterized by abnormal proliferation and differentiation of hematopoietic stem/progenitor cells (HSPCs). It has been elucidated that small extracellular vesicles (sEVs) can reprogram bone marrow microenvironment to suppress HSPC function via their contents. sEVs can transfer cargos between cells and participate in various physiological and pathological processes through their autocrine and paracrine effects. However, the pathological mechanisms of sEVs contained microRNAs involved in AML are still obscure. In this study, we investigated the effects of AML-derived sEVs (AML-sEVs) on AML cells and identified miR-221-3p prominently enriched in AML-sEVs by high-throughput sequencing. Our findings revealed that miR-221-3p promotes AML cell proliferation and leukemogenesis by accelerating cell cycle entry and inhibiting apoptosis. Furthermore, Gbp2 was confirmed as a target gene of miR-221-3p by dual luciferase reporter assays and rescue experiments. Additionally, AML-sEVs can impair the clonogenicity of HSPCs, particularly their erythroid differentiation ability. Taken together, our findings uncover a new mechanism for how leukemic cells protect themselves and provide a potential therapeutic target to suppress AML progression.

Keywords: Acute myeloid leukemia; Small extracellular vesicles; miR-221-3p; Gbp2.

P11-19 RNA 结合蛋白 PTBP1 对造血干细胞归巢和迁移以及红系发育的作用研究

RNA-binding protein PTBP1 is essential for hematopoietic stem cell function and erythroid development

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造血是造血干细胞（HSC）通过自我更新和谱系分化产生成熟血细胞的高度调控的生物过程，其功能受到多因素调控，目前对造血细胞转录调控的解析已十分详细，但对于转录后调节的解析仍十分有限，RNA 结合蛋白（RBP）作为一类重要的转录后调控因子，可参与转录，转录后，翻译等多个生命过程，且有研究证明其在一些血液疾病中发挥重要作用。PTBP1 做为 RBP 家族成员之一，可以参与到多种干细胞系统中指导谱系选择与分化，但在造血谱系中的研究很少。在此基础上我们想要探究 PTBP1 是否可以在造血系统中调节血细胞的发育。

为阐明 PTBP1 在造血系统中的功能，我们利用了 *Mx1*-Cre 小鼠构建了造血特异性敲除 PTBP1 的小鼠模型，发现小鼠骨髓中 HSC、MPP 的比例、数量显著增加，功能验证发现，$PTBP1^{-/-}$HSC 在连续移植实验中植入能力逐渐下降，重建功能降低，归巢实验及动员实验发现 $PTBP1^{-/-}$HSC 归巢能力受损，自发动员到外周及脾脏的细胞数量增加，表明 PTBP1 的缺失使造血干细胞的功能下降。对 HSC 进行 RNA-seq 发现 PTBP1 的缺失会使细胞迁移以及趋化的信号通路显著下调，提示 PTBP1 可能通过影响造血干细胞归巢而影响其对造血系统的重建能力。

此外，我们还发现 *Mx1*-Cre 介导的 PTBP1 的缺失还会导致小鼠外周中红细胞相关参数降低，骨髓中红细胞数量显著降低，对红系祖细胞 BFU-E，CFU-E 分析发现其数量、比例以及集落形成能力未发生明显变化，提示 BM 中的红细胞缺陷是由 PTBP1 细胞内在缺失引起的，为了验证 PTBP1 在红系中的特异性影响，我们利用 *Epor*-Cre 小鼠构建红细胞特异性敲除 PTBP1 的小鼠模型，可重现 *Mx1*-Cre 介导的 PTBP1 缺失的小鼠的表型，体现为外周中红细胞相关参数降低，骨髓中红细胞数量显著降低，表明 PTBP1 在红系发育的过程中发挥重要的生物学作用。

本研究证明 PTBP1 在维持 HSC 的归巢以及迁移能力方面有不可或缺的作用，且 PTBP1 对于红系发育是十分必要的。

关键词：造血干细胞 红系发育 PTBP1

P11-20 不同遗传特征的神经母细胞瘤因免疫状态的改变导致复发或进展

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神经母细胞瘤是一种儿童恶性肿瘤。临床表现具有异质性。神母的节段性染色体改变是很常见的，与预后不良有关，包括 1p 缺失、11q 缺失等。MYCN 变异是复发性体细胞突变，驱动神母发生。免疫细胞是肿瘤微环境中功能最多的参与者。相同肿瘤类型的患者可能有不同的免疫微环境变化，从而导致不同的疾病走向。在此，我们探索了具有不同遗传特征的神母与免疫表型、预后之间的相关性，以期更精准地对患者进行个性化治疗，改善疾病结果。

我们对 31 例神母患者的 MYCN、染色体臂 1p36 和 11q23 进行了 FISH 检测，调查了无事件生存率（EFS）及外周血免疫状态，分析了遗传特征、免疫状态和病情进展之间的关联。

在本队列中，MYCN 状态与是否复发或进展有关，1p 状态与诊断时 LDH 水平、是否进展或复发以及二次进展或复发有关，11q 状态与是否发生骨髓转移有关。MYCN 扩增组和相应正常组的 2 年 EFS 分别为 73.5%和 16.7%。1p 缺失组和正常组的分别为 75.2%和 31.7%。在 MYCN 正常的患者中，11q 缺失组和正常组的 2 年 EFS 分别为 55.7%和 100%。与相应正常组相比，MYCN 扩增组和 1p 缺失组的总 T 细胞百分比、CD4+T 细胞百分比和 CD8+T 细胞百分比均更低；MYCN 扩增组、1p 缺失组和 11q 缺失组的 Treg 百分比都更高；这三组的 IL-10 和 IL-6 也明显升高。

结果提示神母的遗传特征似乎与肿瘤浸润性淋巴细胞相关。IL-10 是免疫抑制细胞因子，来源是 Th2 细胞、Treg 细胞等。结果显示染色体异常组的 Treg 细胞是增多的，这与 IL-10 增多相一致。Th2 细胞表达高浓度的 IL-4、IL-6、IL-10 等，抑制 T 细胞介导的细胞毒作用。IL-6 和 IL-10 在肿瘤微环境中参与促肿瘤效应，还参与诱导 M2 样巨噬细胞极化。综合来看，在 MYCN 扩增、1p 缺失或 11q 缺失的患者中，Treg 等免疫抑制细胞上调，IL-6、IL-10 等相应增高。可能存在某种调节网络上调 Treg 细胞，下调肿瘤浸润性 T 细胞，并促进免疫抑制因子的分泌，形成免疫抑制的微环境，导致不良预后。

关键词：神经母细胞瘤，遗传特征，免疫状态

P11-21 lncRNA NEAT1 对红系发育的作用研究

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红细胞生成包含从红系祖细胞到终末红细胞的多个分化阶段，其中终末红细胞包括原始

红，早幼红，中幼红，晚幼红，网织红以及成熟红细胞。越来越多的证据表明 lncRNA 可以发挥重要的调控作用，但是这些研究都是基于细胞培养体系在体外进行的，lncRNA 在体内对红细胞的调控作用还没有被阐明。

为研究此问题，我们通过 CRISPR/Cas9 基因组编辑技术在 DBA/1JN 背景下构建 Neat1 基因敲除小鼠，对出生 8-10 周的成年小鼠进行解析，发现稳态下 Neat1 的缺失导致小鼠外周血象中红细胞数量增加，而不影响骨髓中红细胞的百分比、数量或形态，但是脾脏中 R1/R2 阶段红细胞的生成受到抑制。在成年小鼠中，脾脏是红细胞生成的重要器官，为了探索脾脏 R1/R2 阶段红细胞生成减少的原因，该研究采用 FACS 分选出脾脏 R1/R2 红细胞进行转录组测序(RNA-seq)，发现 Neat1 的缺乏损害了脾脏的血红素生物合成，导致脾脏 R1/R2 种群的减少。该研究建立了 CRISPR/Cas9 介导的 NEAT1 稳定敲除 K562 细胞株并检测其对珠蛋白表达的影响，发现 NEAT1 的敲降抑制了 b-globin 和 g-globin 的表达，为研究 NEAT1 在红系分化过程中的作用以及机制做了完善和补充。

综上，该研究揭示了对核斑组成必不可少的 lncRNA Neat1 的新的生物学功能，阐明血红素缺乏症相关的疾病的新的可能发病机制。

关键词：NEA1 红系发育

P11-22 高原红细胞增多症小鼠红细胞特征解析及干预措施

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缺氧的特点是组织含氧量不足，当个体上升到高海拔时，对高原相关缺氧的适应不良经常导致红细胞过度产生，从而导致血液粘度升高，最终导致严重的终末器官损伤、肺水肿、心血管功能障碍，甚至导致死亡。因此，我们想要解析高原红细胞增多症患者红细胞增多的可能原因并寻找干预靶点。

将小鼠连续 12 周暴露在模拟 6000 米海拔的低氧舱中，常氧条件下的同窝小鼠为对照组。监测发现低氧组小鼠红细胞计数、血红蛋白水平、红细胞比容等指标从缺氧第 2 周开始显著升高，而后持续升高至 6 周左右达到稳定水平。相反，其它谱系细胞（白细胞、血小板等）数量下降，表现出典型的高原红细胞增多症 (HAPC) 表型。使用流式表面标志物对红细胞分群进行分析发现骨髓和脾脏中有核红细胞的比例和数量均明显升高。

将来自骨髓和脾脏的红细胞与各自器官的单个核细胞混合后分别进行 10×转录组建库分析。与对照相比，低氧组小鼠红细胞上调的基因与红细胞分化、血红素相关代谢过程、细

胞周期、线粒体组织/运输和自噬呈正相关，并且更主要富集在脾细胞中。进一步进行实验验证发现高原缺氧条件下的红细胞具有代谢活性增强、自噬水平升高和增殖能力增强的特征。

鉴于红细胞能够与其它造血谱系细胞相互作用，检测红细胞与单个核细胞间相互作用，发现红细胞上 CD47 表达增加导致 SIRPα_CD47 或 LGALS9_CD47 相互作用在 HAPC 小鼠中更活跃。每天向低氧组小鼠腹腔注射 CD47 中和抗体，14 天时检测发现抗体阻断 CD47 表达并显著降低了低氧组小鼠红细胞计数与血红蛋白水平。总的来说，这意味着 CD47 可以作为低氧红细胞治疗的新靶点。

关键词：高原红细胞增多症 CD47 治疗

P11-23 O-GlcNAc 糖基化修饰转录因子 TWIST1 影响 MDS 克隆细胞耐药的分子机制

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骨髓增生异常综合症（Myelodysplastic syndromes，MDS）是由全能干细胞水平恶性变化导致的分化障碍的一组克隆性、异质性的造血干细胞病，具有极高风险转化为急性髓系白血病。近年来 MDS 的发病率不断升高，严重威胁着人类的生命健康。在本实验室的前期研究中发现转录因子 TWIST1 在对地西他滨耐受的 MDS 病人中表达异常升高，并且 TWIST1 能通过与甲基转移酶 3a 相互作用参与调控 DNA 甲基化过程，进而促进 MDS 克隆细胞对地西他滨耐受，然而 TWIST1 异常表达的机制还尚不明确。

糖基化修饰是蛋白质翻译后修饰的主要方式之一，其中 O-GlcNAc 糖基化是指发生在蛋白质丝氨酸、苏氨酸羟基末端连接的乙酰氨基葡萄糖上的单糖基修饰。近年来，O-GlcNAc 糖基化以其独特的细胞定位及连接方式被广泛研究。在本研究中，通过对临床样本的分析发现，相较于对地西他滨敏感的 MDS 病人，对地西他滨耐受的 MDS 病人中，O-GlcNAc 糖基转移酶（OGT）的表达显著升高，并且使用 OGT 抑制剂能够增强 MDS 克隆细胞对地西他滨的敏感性。与此同时，通过蛋白质谱发现，TWIST1 蛋白的 31 号丝氨酸上存在 O-GlcNAc 修饰，并且该修饰可以抑制 TWIST1 与 E3 泛素连接酶 CBLC 的结合，降低 TWIST1 的泛素化水平，抑制其通过蛋白酶体途径降解，增强 TWIST1 蛋白的稳定性，从而促进 MDS 克隆细胞对地西他滨耐受。通过染色质共沉淀与双荧光素酶报告基因检测发现，TWIST1 能够结合与 OGT 启动子区并且激活 OGT 转录。综上所述，从糖生物学角度理解 O-GlcNAc 糖基化对 TWIST1 功能的影响，能够更加系统地阐明 TWIST1 影响 MDS 去甲基化治疗的机制，以期为 MDS 的治疗提供新的思路。

关键词：MDS；TWIST1；O-GlcNAc 糖基化

P11-24 Gasdermin E dictates inflammatory responses by controlling the mode of neutrophil death

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Both lytic and apoptotic cell death remove senescent and damaged cells in living organisms. However, they elicit contrasting pro- and anti-inflammatory responses, respectively. The precise cellular mechanism that governs the choice between these two modes of death remains incompletely understood. Here we identified GSDME as a master switch for neutrophil lytic pyroptotic death. The tightly regulated GSDME cleavage and activation in aging neutrophils were mediated by proteinase-3 and caspase-3, leading to pyroptosis. GSDME deficiency did not alter neutrophil overall survival rate; instead, it abolished pyroptosis and skewed neutrophil death towards apoptosis, thereby attenuating inflammatory responses due to augmented efferocytosis of apoptotic neutrophils by macrophages. In a clinically relevant acid aspiration-induced lung injury model, neutrophil-specific deletion of GSDME reduced pulmonary inflammation, facilitated inflammation resolution, and alleviated lung injury. Thus, by controlling the mode of neutrophil death, GSDME dictated host inflammatory outcomes, providing a novel therapeutic target for infectious and inflammatory diseases.

Keywords: Programmed cell death (PCD), gasdermin, efferocytosis, apoptosis, pyroptosis, resolution of inflammation

P11-25 METTL3 和 METTL14 在幼年型粒单核细胞白血病中的作用及机制研究

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幼年型粒单核细胞白血病（JMML）是一种由生殖系或体细胞 RAS 激活突变引发的罕见的、严重的儿童早期骨髓异常增生综合征/骨髓增殖性肿瘤。2016 年世界卫生组织（WHO）将 JMML 归于骨髓增生异常综合征/骨髓增殖性肿瘤(MDS/MPN)范畴，其具有 MDS 和 MPN 的重叠特征并且是唯一的儿童发病实体，其主要的临床特征是单核细胞过度增殖，伴随脾脏、肝脏、肺等器官浸润。JMML 疾病进展迅速，目前尚无明确有效的靶向治疗药物，异基因造血干细胞移植是唯一有可能治愈 JMML 的治疗手段，但其排异和疾病复发使得患者 5 年生存率仍然很低，因此迫切需要寻找新的治疗靶点。表观遗传修饰是髓系恶性肿瘤发病的重要调控机制，m6A 修饰作为一种重要的表观调控机制，可以调控造血干祖细胞功能并参与多种髓系恶性肿瘤的发生发展。预实验结果显示，在小鼠 JMML 疾病模型中，敲除 m6A 甲基化转移酶 METTL3 或 METTL14 可以延长 JMML 小鼠存活时间，表明敲除 METTL3 或 METTL14 可以显著抑制 JMML 疾病进展。因此探索 METTL3 和 METTL14 在 JMML 中的作用及机制迫在眉睫。本研究通过引入不同基因敲除小鼠，利用流式细胞术分析发现在小鼠 JMML 疾病模型中敲除 METTL3 或 METTL14 后造血干细胞、多能祖细胞、髓系祖细胞以及分化过程中的多种细胞群发生改变，而且敲除 METTL3 与 METTL14 对造血干祖细胞的影响有显著差异，揭示 METTL3 或 METTL14 可能通过 m6A 修饰依赖及非 m6A 修饰依赖的功能作用于造血干祖细胞，进而参与 JMML 疾病进程；利用克隆形成试验等明确敲除 METTL3 或 METTL14 降低了 JMML 所引发的干祖细胞恶性程度；利用骨髓移植等明确 METTL3 和 METTL14 在 JMML 中的作用。以上研究结果表明 METTL3 或 METTL14 可促进 JMML 疾病进展，开展机制研究对造血干祖细胞进行 RNA 测序和 m6A RNA 测序等明确 METTL3 和 METTL14 的下游靶基因及信号通路，同时比较 METTL3 和 METTL14 的功能差异，明确其 m6A 依赖和非 m6A 依赖相关调控功能，旨在从 m6A 的角度探索 JMML 的发病机制并制定靶向治疗策略，为临床治疗提供理论指导。

P11-26 单细胞层面解析 allo-UCBT 和 allo-PBSCT 的造血重建规律差异

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临床研究表明，与异基因外周血干细胞移植相比，异基因脐血移植的造血重建明显延迟，提示脐带血的细胞成分和重建动力学过程与动员外周血干细胞存在显著差异。本研究旨在解析二者的造血重建差异及异基因脐血移植造血重建延迟的原因。

通过收集 4 例接受异基因脐血移植和 4 例异基因外周血干细胞移植的骨髓衰竭综合征患儿，分别在移植后不同时间点（d14, d21, d30, d60, d90, d180, d365）收取骨髓或外周血，同时收集脐血、动员外周血干细胞及正常儿童骨髓作为对照。用 FACS 分选出骨髓、动员外周

血干细胞和脐血中的 Lin-CD34+细胞进行 STRT-seq 测序；分离出所有样本的总有核细胞进行 10X 转录组测序。最后利用 Scanpy、Seurat 等方法对数据进行质控、过滤、整合等分析。

我们利用 276628 个造血细胞绘制了不同移植方式造血重建的单细胞转录组图谱，共注释 44 种细胞类型。与动员外周血干细胞相比，脐血来源的 Lin-CD34+细胞中，HSC/MPPs 比例升高且具有更强的淋系和红系分化偏向，但向髓系和巨核系分化能力降低；EBM、MEP 和 CMP 的比例降低；在总有核细胞中，T 细胞和 NK 细胞比例升高，其中 NK_CD56dim_CD16 具有更强的免疫功能。与异基因外周血干细胞移植相比，异基因脐血移植后早期 HSC/MPPs 和 CMP2 向中性粒细胞的分化趋势减弱；MEP 细胞比例降低，HSC/MPPs 向 MEP 的分化能力及 HSC/MPPs 和 MEP 向 MK 的分化能力减弱；但 HSC/MPPs 向 NK 的分化能力增强且 NKP 比例增高。

总之，我们发现异基因脐血移植患者中性粒细胞和血小板重建延迟与移植物自身的性质有关。移植后早期，异基因脐血移植的 MEP 细胞比例和 HSC/MPPs 向巨核系和髓系分化趋势均较弱是移植后重建延迟的原因之一，而 HSC/MPPs 向 NK 的分化能力增强及 NKP 细胞比例升高与促进 NK 细胞早期重建有关。

关键词：异基因脐带血移植；造血重建差异；单细胞 RNA 测序

P11-27 Molecular characteristics of MPN malignant hematopoietic stem cells across distinct driver mutations

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Abstract: Essential thrombocytosis (ET) includes the entities of JAK2-, CALR-, and MPL-mutant subtypes and the triple negative one. To date, it is still not completely understood the alterations of HSC cellularity and molecular similarities and disparities arising from distinct driver mutations, which underlies the phenotypic heterogeneity and varied prognosis of ETs. Here, we applied single-cell transcriptome sequencing paralleled with driver mutation detection on bone marrow-derived HSCs from ET patients across all subtypes. We found that MPL-mutated HSCs are marked with aberrant metabolism, CALR-mutated HSCs are characterized with active cell

cycling, while JAK2-mutated HSCs are pronounced with the Mk-priming and IFN responses. A mutant-like HSC subset was identified in TN ET with higher Mk-priming and active cell cycling. Importantly, a CXCR4+ HSC subset is commonly and significantly decreased or even disappeared across ET spectrum. Functional assays demonstrated that BFU-E, CFU-GM, and CFU-Mk generated from human CXCR4- HSCs were significantly higher than those from CXCR4+ HSCs. Competitive bone marrow transplantation showed that mice from CXCR4- LSK group yielded more megakaryocytes than those from transplanted CXCR4+ LSKs. These results suggest loss of CXCR4+ HSC subset might lead to the remaining HSCs obtain an enhanced proliferation and differentiation advantage toward myeloid and megakaryocyte lineage, which would be one of important contributors to MPN pathogenesis and progression.

Keywords: myeloproliferative neoplasms (MPN), essential thrombotythemia (ET), scRNA-seq, CALR, MPL, triple negative ET, CXCR4

P11-28 From integrin structures to explore: What does the future of structural biology look like?

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Integrins transmit signals between their extracellular ligands and the intracellular cytoskeleton through bidirectional signaling across cell membrane. At the ligand-binding βI domain, the α1/α1'-helix changes from a bent to a straightened α-helical conformation upon integrin headpiece opening. The binding of the cytosolic protein ligands to both the membrane-proximal (MP) and membrane-distal (MD) regions of the integrin cytoplasmic tail (CT) triggers the inside-out signaling. How conformational signals initiated from one end of the integrin are transmitted to the other end remains elusive for structural biology to explore.

We demonstrated that a conserved glycine at the α1/α1' junction is critical for maintaining the bent conformation of the α1/α1'-helix in the resting state. Mutations that facilitate α1/α1'-helix unbending rendered integrin constitutively active. However, mutations that block the α1/α1'-helix unbending abolished soluble ligand binding upon either outside or inside stimuli. Studies also showed that β-integrin CTs have common binding sites for regulatory proteins like talin and kindlin. In contrast, α-integrin CTs are only highly conserved at the MP regions, whereas the MD regions vary substantially both in sequence and length. We examined the role of αIIb, αV and αL integrin CT MD regions in the regulation of integrin activation. We report that the α-integrin CT

MD region helps maintain integrin in the resting state and is indispensable in talin- and kindlin-induced integrin conformational change and ligand binding. The proper length and proper amino acids are important for the α-integrin CT MD region to exert its effect on integrin activation.

X-ray, NMR, and EM are the traditional methods of structural biology. However, a deep-learning approach, AF2, brings a serious shock to this field recently. We will have to think about: What Does the Future of Structural Biology Look Like?

Key Words: integrin, structural biology, NMR, X-ray, EM, Af2

P11-29 IDF-11774 对弥漫大 B 细胞淋巴瘤的作用机制研究

The mechanism of IDF-11774 on diffuse large B-cell lymphoma

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目的 探究 HIF-1α 抑制剂 IDF-11774 对弥漫大 B 细胞淋巴瘤（DLBCL）细胞的作用及机制。

方法 运用 CCK-8 法检测 IDF-11774 对 DLBCL 细胞增殖的影响；流式细胞术检测 IDF-11774 对 DLBCL 细胞周期和凋亡的影响；Western Blot 和 RT-qPCR 检验 IDF-11774 对 DLBCL 细胞中 HIF-1α 表达、细胞周期、凋亡相关基因的影响；构建小鼠皮下 DLBCL 荷瘤模型，检测 IDF-11774 对成瘤的影响。

结果 IDF-11774 抑制 DLBCL 细胞中 HIF-1α 蛋白的表达。同时 IDF-11774 对 DLBCL 细胞增殖有抑制作用并诱导 DLBCL 细胞周期阻滞在 G_1 期，进一步我们发现 IDF-11774 通过内、外源性两条凋亡途径促使 DLBCL 细胞凋亡；IDF-11774 抑制 DLBCL 细胞中的 STAT3、ERK 以及 PI3K-AKT-mTOR 等信号通路的活化。另外实验表明 IDF-11774 联合 Doxorubicin 协同促进 DLBCL 细胞凋亡。体内实验表明 IDF-11774 显著抑制 DLBCL 荷瘤小鼠腋下皮下移植瘤的生长并促进 DLBCL 小鼠皮下移植瘤的坏死。

结论 IDF-11774 抑制 DLBCL 细胞的增殖，阻滞细胞周期在 G_1 期，同时促进 DLBCL 细胞凋亡。IDF-11774 抑制 ERK、STAT3 以及 PI3K-AKT-mTOR 等信号通路的活化，同时抑制 DLBCL 小鼠皮下移植瘤的生长。

关键词 弥漫大 B 细胞淋巴瘤；IDF-11774；HIF-1α；作用机制

P11-30 CARMA1 介导 Notch1 激活 NF-κB 信号影响 T-ALL 细胞增殖

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目的：分析 CARMA1 基因在 T-ALL 白血病中的表达及对患者预后的影响；研究其对 T-ALL 细胞增殖和 NF-κB 信号通路的影响。

方法：Western blot 分析 CARMA1 基因在不同类型白血病细胞系；基因芯片分析 CARMA1 的表达和对预后的影响。采用慢病毒 shRNA 沉默 CARMA1 基因，CCK-8 和 EdU 法分析对细胞增殖的影响；流式细胞术分析对细胞周期的影响；NSG 小鼠模型分析对体内增殖的影响；荧光素酶双报告基因法对 NF-κB 活性的影响。

结果：通过对 AML、B-ALL 和 T-ALL 细胞系检测，发现 CARMA1 蛋白在 T-ALL 细胞中特异性高表达，在原代 T-ALL 细胞中也高表达。通过对 GEO 数据库基因芯片分析，CARMA1 基因在 T-ALL 白血病中高表达，而且 CARMA1 高表达患者的预后显著好于低表达患者（*P*=0.0043）。CARMA1 基因沉默后，SIL-TIL1 阳性的 CCRF-CEM 细胞增殖未观察到显著变化。但是，MOLT-4 和 Jurkat 细胞的生长和增殖活性显著降低；细胞周期阻滞在 G1/S 期。将 CARMA1 基因沉默的 MOLT-4 细胞系通过尾静脉接种到 NSG 小鼠，小鼠的生存期显著延长（*P*<0.001）。CARMA1 基因沉默后，T-ALL 细胞的 NF-κB 的转录活性显著降低；抑制 CD3/CD28 刺激诱导的 IκBα 蛋白降解。

结论：在 T-ALL 细胞中，MALT1 和 BCL10 可能为组成型表达，CARMA1 为调节型表达。CARMA1 高表达患者的预后显著好于低表达患者。SIL-TIL1 融合基因阴性的 T-ALL 白血病细胞增殖依赖于 CARMA1 基因的表达。CARMA1 通过激活 NF-κB 信号途径调控 T-ALL 细胞增殖。

关键词：CARMA1，T-ALL，细胞增殖，预后分析，NF-κB 信号

P11-31 ACAT1 通过调控多发性骨髓瘤细胞代谢重编程促进疾病进展

ACAT1 promotes multiple myeloma progression by regulating metabolic reprogramming

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目的 多发性骨髓瘤至今仍不可治愈，因此深入了解骨髓瘤的发病机制是临床亟需解决的问题。代谢重编程在众多肿瘤进展中发挥重要。我们拟通过靶向乙酰转移酶 ACAT1，探索其影响的代谢重编程在多发性骨髓瘤恶性增殖中的作用及机制。

方法 1. 使用 shRNA 基因编辑技术敲低骨髓瘤细胞中 ACAT1 基因，获得基因稳定敲除细胞株；2. 应用 Western blot，CCK8，流式细胞术及克隆形成法检测敲除效果及基因敲低后对细胞增殖，细胞周期及克隆形成能力的影响；3. 使用 ACAT1 特异性抑制剂 Avasimibe 检测对骨髓瘤细胞增殖，细胞周期及克隆形成能力的检测；4. RNA-Seq 分析 ACAT1 抑制后转录组及细胞通路的变化；5. 应用 seahorse 实验基础 ACAT1 被抑制后糖酵解及氧化磷酸化水平的变化；6. 电镜检测 ACAT1 被抑制后线粒体结构的变化；7. 检测 ACAT1 介导能量调控相关通路及关键蛋白的变化。

结果 成功获得 ACAT1 敲低骨髓瘤细胞株，细胞周期阻滞，细胞增殖受到抑制，克隆形成能力减弱；Avasimibe 抑制骨髓瘤细胞增殖及克隆形成能力；RNA-seq 分析发现 ACAT1 被抑制后线粒体功能及糖酵解能力受损；Seahorse 结果提示糖酵解和氧化磷酸化水平受损；电镜结果显示线粒体损伤严重，膜破损，基质外溢；ACAT1 抑制后线粒体结构发生变化 ACAT1 抑制后发现 MYC 蛋白水平显著降低，MYC 下游糖酵解通路的 HK2 和 LDHA 水平显著降低。

结论 相比较正常人外周血单个核细胞，ACAT1 在骨髓瘤中的水平较高；靶向 ACAT1 不仅抑制了氧化磷酸化水平也下调了糖酵解的能力，提示 ACAT1 在调控多发性骨髓瘤细胞能量代谢及恶性增殖中挥着关键作用。

关键词：多发性骨髓瘤，ACAT1，糖酵解，氧化磷酸化

P11-32 AURKA 与 AURKB 异常活化调节 CALR 基因突变的 MARIMO 细胞的生长及代谢机制研究

The aberrant activation of AURKA and AURKB are associated with the regulation of growth or metabolism in MARIMO cells with CALR gene mutation

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目的：CALR 基因第 9 外显子的突变常见于 JAK2 或 MPL 突变阴性的 ET 或 PMF 患者中。目前，靶向 Aurora 激酶 A （AURKA）的小分子抑制剂 MLN 8237 在治疗 PMF 的临床实验中取得重要进展。探索 Aurora 激酶家族间的关系，尤其是其他成员对 AURKA 功能的

潜在补偿作用，对于提高 MLN 8237 的临床疗效尤为重要。**方法：**本研究分别通过蛋白免疫印迹，细胞增殖、细胞集落及细胞凋亡分析 Aurora 激酶抑制剂对 CALR 突变细胞生物学行为的影响；采用 RNA 测序进一步分析分别下调 AURKA 或 AURKB 在抑制 CALR 突变细胞存活机制上的异同性。**结果：**本研究中发现，在 CALR 突变患者的骨髓细胞中，Aurora 激酶 B（AURKB）与 AURKA 被共同激活，即磷酸化水平明显增加。应用 MLN 8237 选择性地抑制 AURKA 可明显抑制细胞生长和集落形成，诱导细胞成熟，最终凋亡。随着抑制剂浓度的增加，致使 AURKB 也被完全抑制，则会进一步增强 CALR 突变细胞生长受抑制的表型，提示，AURKA 与 AURKB 共同参与了 CALR 突变细胞的生长及发育过程。进一步，转录组分析结果显示，下调 AURKA 或 AURKB 可引起相似的基因表达水平变化，主要富集在代谢-氧化磷酸化、丝裂原激活蛋白激酶（MAPK）和凋亡信号通路上，这表明 AURKA 和 AURKB 在 CALR 突变细胞中的功能存在相似性。与预期相一致，敲低 AURKA 或 AURKB 都明显抑制了 CALR 突变细胞的生长，诱导细胞周期停滞在 G2-M 期，并诱导细胞凋亡。此外，下调 AURKB 促使 CALR 突变细胞的代谢能力增强，耗氧率（OCR）增加，并促进细胞表面 CD11b 的表达。同时，过表达 AURKA 或 AURKB 促进 CALR 突变细胞的生长，并致使突变细胞对 MLN 8237 处理更敏感。**结论：**以上研究结果表明，AURKA 和 AURKB 共同调节 CALR 突变细胞的生长或代谢，且 AURKB 可为突变细胞的成熟发育提供重要的能量支持，其作用在临床治疗 PMF 过程中不可忽视。

关键字：CALR 基因突变，AURKA 与 AURKB，细胞生长，代谢，凋亡

P11-33 IGF1-R 抑制剂 AEW541 对伊马替尼杀伤 SUP-B15 细胞的增效作用

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目的： 探讨伊马替尼处理 Ph^+ ALL 细胞株 SUP-B15 时是否出现细胞增殖受抑但不凋亡的耐受状态，探索 IGF1-R 抑制剂 AEW541 能否打破这种耐受状态并初探相关机制。**方法：** Deep Blue 试剂盒检测不同浓度的伊马替尼或 AEW541 对 SUP-B15 细胞增值率的影响；流式细胞术检测不同浓度的伊马替尼或 AEW541 对 SUP-B15 细胞生存率的影响；流式细胞术检测 AEW541 联合伊马替尼处理 SUP-B15 细胞后细胞生存率的影响；蛋白免疫印迹法（Western blot）检测 AEW5451 联合或不联合不同浓度伊马替尼凋亡相关标志 Caspase3 和 PARP1 蛋白切割情况及其 ABL 下游信号相关蛋白 STAT5、ERK1/2、AKT 及 p-STAT5、p-ERK1/2、p-AKT 的表达水平；流式细胞术检测 STAT5 抑制剂（AC-4-130）及 ERK1/2 抑制剂（曲美替尼）对 SUP-B15 细胞生存率的影响，进一步探索 AEW541 联合伊马替尼诱导 SUP-B15 细胞凋亡的关键机制。 **结果：** 伊马替尼单药处理虽然可以抑制 SUP-B15 细胞的

增殖，但杀伤作用不强，出现一种抑制而不杀伤的耐受状态；IGF1-R 抑制剂 AEW541 单药处理对 SUP-B15 细胞的增殖没有显著的抑制作用且杀伤作用不明显；流式细胞术检测结果显示 AEW541 联合伊马替尼时可以显著增加 SUP-B15 细胞的凋亡率；蛋白质印迹法检测结果显示 AEW541 联合伊马替尼处理 SUP-B15 细胞时凋亡相关标志 Caspase3 及 PARP1 蛋白有明显的切割活化； ABL 下游相关信号 STAT5、ERK1/2 磷酸化水平较 AEW541 或伊马替尼单药处理显著减弱，但对于 AKT 磷酸化水平及总蛋白 STAT5、ERK1/2、AKT 并无明显影响；STAT5 抑制剂（AC-4-130）可以显著增加 SUP-B15 细胞凋亡率；MEK-ERK1/2 抑制剂（曲美替尼）对 SUP-B15 细胞无明显杀伤作用； **结论：** SUP-B15 细胞对伊马替尼呈现抑而不杀，调而不亡的药物耐受状态；IGF1-R 抑制剂 AEW541 可进一步减少 ABL 下游信号 STAT5 的活化，继而显著增强经典 TKI 药物伊马替尼诱导 SUP-B15 细胞凋亡的作用，为增强 TKI 类药物疗效，开发新型治疗策略提供资料。

关键词: 药物耐受；细胞凋亡；Ph^+急性淋巴细胞白血病；伊马替尼；AEW541

P11-34 Novel c-Myc G4 stabilizer EP12 promotes myeloma cytotoxicity by disturbing NF-κB signaling

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Multiple myeloma (MM) is a B-cell malignancy characerized by the excessive proliferation of bone marrow plasma cells and the production of abnormal immunoglobulins, which, despite advances in therapeutic strategies, it is still incurable. Recently, the development and approval of innovative anticancer drugs have led to the improvement of MM therapy, but drug resistance remains a major problem leading to therapy failure. Therefore, novel agents need to be developed to achieve better therapeutic effects for relapsed/refractory MM patients. We previously identified a novel c-Myc G4 stabilizer, EP12, which could induce MM cell cytotoxicity *in vitro*. However, the *in vivo* anti-MM activity of EP12 and underlying molecular mechanisms need to be further elucidated. In this study, we found that compound EP12 inhibited primary myeloma growth *in vivo* by decreasing the stability of c-Myc and interfering with the canonical or classical nuclear factor-κB (NF-κB) signaling pathway. Taken together, the c-Myc inhibitor EP12 appears to be a promising therapeutic agent for MM.

Keywords: multiple myeloma, c-Myc G4, DNA damage, NF-κB signaling

P11-35 Impaired platelet function and thrombus formation in PDE5A-deficient mice

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In this study, we characterized the role of phosphodiesterase 5A (PDE5A) in platelet activation and function. Our results showed that PDE5A deficient mice presented significantly prolonged tail bleeding time, delayed arterial and venous thrombus formation. PDE5A deficiency significantly inhibited platelet aggregation, ATP release, P-selectin expression and integrin aIIbb3 activation. In addition, an impaired spreading on collagen or fibrinogen and clot retraction was observed in PDE5A-deficient platelets. Moreover, PDE5A deficiency reduced phosphatidylserine exposure, calcium mobilization, ROS production and increased intracellular cGMP level along with elevated VASP phosphorylation and reduced phosphorylation of ERK1/2, p38, JNK and AKT. In conclusion, PDE5A modulates platelet activation, function and thrombus formation, indicating that therapeutic targeting it might be beneficial for the treatment of thrombotic diseases.

Key words: PDE5A, cGMP, platelets, thrombosis, hemostasis.

P11-36 Thrombin receptor activating peptide-6 regulates T-cell mediated allogeneic reaction

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G protein coupled receptor 15 (GPR15) exerts immune regulatory functions. We previously showed knockout of GPR15 increased acute graft-versus-host disease (aGVHD). However, GPR15L, the natural ligand of GPR15, does not significantly decrease murine aGVHD. Small molecules that targeting GPR15 may help to suppress T-cell mediated alloreactivity. In this study, by using a GPR15/β-arrestin 2 reporter cell line, we found thrombin receptor activating peptide-6 (TRAP-6)

interacted with GPR15 through screening the G protein coupled receptor small molecule reservoir. TRAP-6 significantly decreased cell viability in the *in vitro* mixed lymphocyte reaction (MLR). We confirmed the anti-aGVHD effect of TRAP-6 in two murine allotransplant models. TRAP-6 reduced pathological scores and proportions of Th1 cells in liver and colon. Of note, the anti-aGVHD effect of TRAP-6 was not observed in recipients that transplanted with GPR15 knockout (GPR15 KO) donor T cells. Because TRAP-6 was originally identified as an agonist of coagulation factor II thrombin receptor (F2R), we also used F2R knockout (F2R KO) donor T cells to test the effect of TRAP-6. Interestingly, TRAP-6 still reduced aGVHD in the F2R KO allotransplant model. We confirmed binding of TRAP-6 and GPR15 *in vitro* by using pull-down assay and confocal microscope. In the *in vitro* MLR, TRAP-6 decreased percent of Th1 cells but increased percent of Treg cells. In a transwell culture assay, comparing with the strong chemotactic effect of GPR15L, TRAP-6 showed a weaker chemotactic effect on Treg cells. These effects all depended on expression of GPR15 but not F2R. In the *in vitro* cultured T cells, TRAP-6 increased protein levels of GRK5 and phosphorylated ERK1/2 which are downstream of the GPR15/β-arrestin 2 pathway. RNA-seq analysis indicated TRAP-6 down-regulated inflammatory pathways such as leukocyte activation and cytokine reactions in wild type T cells, an effect not seen in GPR15 KO T cells. The interaction between TRAP-6 and F2R could induce coagulation disorder and might have unfavorable impact on recipients because TRAP-6 treatment decreased blood platelet count. Since F2R is extensively expressed on different types of cells, using a mutated TRAP-6, which only interacts with GPR15, might help to avoid such defects. Through using alanine scanning on TRAP-6, we found the mutant peptide (L→A) exerted anti-alloreaction effect but significantly reduced the function in inducing platelet aggregation. In conclusion, we found TRAP-6 decreased murine aGVHD through interacting with GPR15.

Keyword: G protein coupled receptor 15; graft-versus-host disease; thrombin receptor activating peptide-6

P12 消化与营养

P12-1 黄连素改善 6-羟基多巴大鼠抑郁样行为和便秘症状

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帕金森病(PD)是一种常见的神经退行性疾病，除典型的躯体运动症状外，PD 患者还可

出现抑郁、焦虑、胃肠功能障碍等非运动症状。这些症状往往早于运动功能障碍出现，然而目前针对 PD 非运动症状治疗的方法相对有限。因此关注 PD 的非运动功能紊乱对于 PD 的早发现早治疗至关重要。黄连素是一种异喹啉类生物碱，最初用于治疗胃肠炎。最近的研究表明黄连素可以促进肠道微生物合成左旋多巴从而弥补中枢多巴胺的不足，并能改善帕金森病模型中的躯体运动功能障碍，但很少有研究关注黄连素对帕金森病模型中抑郁和便秘等非运动功能障碍的治疗作用。本研究采用消化道转运时间、粪便含水量、结肠动力学实验、转棒实验、糖水偏好实验、旷场实验、qPCR、Western Blot 和免疫组织化学等方法探讨了黄连素对双侧黑质注射 6-羟基多巴（6-OHDA）诱导的 PD 大鼠抑郁和便秘的影响。结果表明 6-OHDA 诱导的 PD 模型存在糖水偏好率下降，直立次数减少等抑郁表现和粪便含水量降低以及消化道转运时间延长等症状。同样该模型中枢存在多巴胺，食欲素和促肾上腺皮质激素释放激素等神经递质紊乱；结肠组织中多巴胺系统和胆碱能系统的异常；黄连素干预可以改善 6-OHDA 诱导的 PD 大鼠的糖水偏好率下降，直立次数减少等抑郁样表现，增加了粪便含水量并且缩短了肠道转运时间。同时也改善了中枢多巴胺，食欲素和促肾上腺皮质激素释放激素的紊乱以及结肠组织中多巴胺系统和胆碱能系统的异常。综上所述，黄连素可能通过影响多巴胺、食欲素和乙酰胆碱等中枢和外周神经递质，进一步改善 PD 的抑郁样表现和便秘症状。本研究为 PD 患者非运动功能紊乱提供了新的治疗方案。

关键词：帕金森病 抑郁 便秘 黄连素

P12-2 Based on the 5-HT2B receptor and PLCβ- IP_3R pathway to explore the intervening mechanisms of amitriptyline on gastrointestinal dysfunction in FD Rats

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Functional dyspepsia (FD) is a common functional gastrointestinal disease in clinical practice. Its pathogenesis is caused by a variety of pathogenic factors, which affect and interact with each other and eventually lead to gastrointestinal motility disorder. Clinical data show that the long-term recurrent symptoms of FD and the protracted course of the disease lead to different degrees of mental and psychological disorders in patients. Prokinetic drugs are often used for FD clinical treatment, but the single drug has a slow onset, long-term use has many adverse reactions,

and the recurrence rate is high. For FD patients with mental depression, appropriate combined antidepressant therapy will have a good therapeutic effect.

This project is based on the 5-HT2B receptor and PLC β- IP_3R pathway to explore the mechanism of antidepressant amitriptyline and prokinetic domperidone on gastrointestinal motility disorders in FD rats, to clarify the role of psychological factors in the gastrointestinal motility disorder of FD, and provide the theoretical basis for FD prevention and treatment from the perspective of clinical psychology.

In the present study, based on the previous research methods of our lab group, the FD rat model was established by feeding iodoacetamide, tail pinch stimulation, and fasting every other day. Compared with the control group, the rats in the model group had slower intestinal propulsion ($p<0.05$) and gastric emptying rate ($p<0.05$), and they were less excited and active, slow in response, withered, and moved stiffly. HE staining results of the stomach and duodenum showed that there was no obvious inflammation, indicating that the FD model was established successfully. Compared with the model group, the rats in the amitriptyline group had higher body weight and 3-hour food intake ($p<0.05$), and the activity, hair, and feces of the rat were similar to those of normal rats, indicating that amitriptyline improves FD rat symptoms. At the same time, the amitriptyline group had a higher preference for sugar water, and a higher number of shuttles in the light and dark shuttle box ($p<0.05$), and the time for floating in forced swimming and the time for latent feeding were shorter ($p<0.05$), indicating that amitriptyline can improve the depression and anxiety state of FD rats. The results of ELISA showed that the level of 5-HT in the gastric tissue of rats in the amitriptyline group was higher than that of the model group, but there was no significant difference. The results of real-time fluorescent quantitative PCR showed that compared with the blank group, the levels of 5-HT2B receptor, phospholipase C-β (PLCβ), inositol triphosphate receptor (IP3R), and calcium-activated chloride channel anoctamin 1 (ANO1) in the gastric and duodenal tissues of rats in the model group decreased significantly ($p<0.05$). Compared with the model group, the levels of IP3R and PLCβ in the stomach and duodenum tissue of rats in the amitriptyline group markedly increased ($p<0.05$), and the expression of ANO1, 5-HT2B receptor mRNA was slightly increased, but not significantly different.

We conclude that amitriptyline can improve FD symptoms in functional dyspepsia rats, and its mechanism may be related to serotonin regulating the downstream PLCβ-IP_3R-ANO1 pathway to promote FD gastrointestinal motility.

Keywords: functional dyspepsia, amitriptyline, gastrointestinal motility, 5-HT, PLCβ, IP_3R, ANO1

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P12-3 Neuroprotective effect of a compound comprising Taurine and L-serine on cerebral ischemia: An integrated basic and clinical investigation

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Background: The importance of Taurine and L-serine, both vital endogenous amino acids, in the protection of brain cells from injuries caused by ischemia has been previously documented. These amino acids provide a promising therapeutic opportunity that warrants further investigation. This study aims to explore the neuroprotective effects and mechanisms of a compound consisting of Taurine and L-serine in the context of cerebral ischemia injury, with a dual focus on basic research using animal models and clinical research involving stroke patients.

Methods: The methodology used in the study was two-pronged. Firstly, an experimental study was conducted using a mouse model of cerebral ischemia-reperfusion. Taurine and L-serine levels in the brain were evaluated using high-performance liquid chromatography (HPLC), allowing us to monitor the impact of cerebral ischemia and subsequent reperfusion on the concentration of these amino acids. We then compared the neuroprotective effects of the combined amino acid compound with those of Taurine and L-serine administered individually. Further investigations were carried out to evaluate the influence of Glycine and GABA receptor blockers on the therapeutic effects of the amino acid compound, as these receptors are known to play critical roles in neuronal function and response to injury. Secondly, a clinical trial was implemented involving 97 stroke patients from the Affiliated Hospital of Nantong University. This trial was designed to compare the effects of traditional feeding methods with those of a multidimensional nutrition drink containing the custom amino acid compound. This drink was introduced to the patients through nasal feeding in increasing quantities, beginning from a quarter of the total amount, and was escalated by a quarter each day.

Results: The experimental study demonstrated an initial increase in Taurine and L-serine levels following cerebral ischemia, followed by a continuous decrease. Remarkably, combined treatment with the compound at 2h and 12h post-ischemia significantly reduced the neuroethology score, brain water content, and cerebral infarction volume, exceeding the effects of Taurine or L-serine administered individually. It also significantly mitigated the degeneration and necrosis of hippocampal neurons. The compound's neuroprotective action seems to be linked to the activation

of Glycine and GABA receptors in the brain, leading to neuron membrane hyperpolarization and thereby inhibiting the excitotoxicity of glutamate on neurons.

The clinical trial showed that the amino acid compound could effectively enhance patients' immune function, reduce inflammatory responses, and promote neurological recovery. This indicates that the compound may offer additional benefits beyond its direct neuroprotective effects.

Conclusion: The compound consisting of Taurine and L-serine exhibits significant neuroprotective effects following cerebral ischemia. These effects may be driven by limiting the release of excitatory amino acids, inhibiting neuronal apoptosis, and reducing the inflammatory response. By offering new insights into the neuroprotective potential of this amino acid compound, this study paves the way for innovative therapeutic approaches in the treatment of cerebral ischemia.

Keywords: Taurine, L-serine, Neuroprotection, Cerebral Ischemia, Glycine receptor, GABA receptor, Stroke, Therapeutic methods.

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P12-4 葡聚糖硫酸钠诱导的结肠炎中热受体（TRPV1）和冷受体（TRPM8）的功能表达及相关性研究

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目的：研究热受体 TRPV1 和冷受体 TRPM8 在葡聚糖硫酸钠（DSS）诱导下的实验性结肠炎小鼠肠道和脊髓背根神经节（DRG）中的表达，进一步探讨 TRPV1 与 TRPM8 之间的联系及相关通路。方法：采用自由饮用 DSS 诱导的小鼠慢性结肠炎模型，将 C57BL/6 雄性小鼠 20 只随机分为正常对照组和慢性结肠炎组，正常对照组小鼠自由饮用无菌水 36 天；慢性结肠炎组小鼠自由饮用质量浓度为 20g/L 的 DSS 溶液 5 天，然后自由饮用无菌水 1 周，循环重复 3 次。每天观察各组小鼠的毛发、体重、粪便性状（颗粒状、稀便、血便等）、肛周情况（红肿、便血等），给予疾病活动指数（disease activity index，DAI）评分，采用 HE

染色进行组织病理学评分，Western blot 法检测结肠和 DRG 组织中 TRPV1、TRPM8、Gαq 蛋白的表达，实时荧光定量 PCR（RT-PCR）检测结肠组织中炎症因子（IL-1β、IL-6、IL-10 和 TNF-α）的 mRNA 表达水平。免疫荧光和 CO-IP 法检测结肠和 DRG 组织中 TRPV1、TRPM8 及 Gαq 的定位及表达。结果：与正常对照组相比，DSS 组结肠组织 DAI 评分上升(P＜0.05)。HE 染色显示，DSS 组肠道黏膜严重破坏，腺体排列紊乱甚至消失。Western blot 结果发现 TRPV1、Gαq 蛋白表达增高(P＜0.05)，TRPM8 表达降低(P＜0.05)。RT-PCR 发现 DSS 组促炎介质的 mRNA 表达上升(P＜0.05)。免疫荧光和 CO-IP 结果显示结肠和 DRG 组织中 TRPV1 与 TRPM8 和 Gαq 共表达，相较于正常对照组，DSS 组结肠和 DRG 组织 TRPV1 表达增加，TRPM8 表达减少。结论：实验性结肠炎小鼠结肠组织 TRPV1 表达升高，TRPM8 表达降低，TRPV1/TRPM8 可共表达于结肠和 DRG 组织，两者之间可能存在某种平衡机制以维持肠道功能稳定。

关键词：实验性结肠炎、瞬时受体电位通道、脊髓背根神经节、炎症性肠病

Functional expression and correlation of heat receptor (TRPV1) and cold receptor (TRPM8) in dextran sodium sulfate-induced colitis

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Objective: To study the expression of heat receptor TRPV1 and cold receptor TRPM8 in the intestines and dorsal root ganglion (DRG) of the spinal cord of mice with experimental colitis induced by dextran sulfate sodium (DSS), and to further explore the connection between TRPV1 and TRPM8 and related pathways. METHODS: The chronic colitis model induced by free drinking DSS was used in mice. 20 C57BL/6 male mice were randomly divided into normal control group and chronic colitis group, the mice in the normal control group were free to drink sterile water for 36 days; the mice in the chronic colitis group were free to drink DSS solution with mass concentration of 20 g/L for 5 days, then they were free to drink sterile water for 1 week, and the cycle was repeated 3 times. The mice in each group were observed daily for hair, body weight, faecal characteristics (granular, dilute, bloody stools, etc.), perianal conditions (redness, swelling, blood in stools, etc.), and given a disease activity index (DAI) score, and were scored histopathologically using HE staining. Western blot method was used to detect the expression of TRPV1, TRPM8 and Gαq proteins in colon and DRG tissues, and real-time fluorescence

quantitative PCR (RT-PCR) was used to detect the mRNA expression levels of inflammatory factors (IL-1β, IL-6, IL-10 and TNF-α) in colon tissues. Immunofluorescence and CO-IP methods were used to detect the localisation and expression of TRPV1, TRPM8 and Gαq in colon and DRG tissues. RESULTS: Compared with the normal control group, the DAI score of colon tissue in the DSS group increased ($P < 0.05$). HE staining showed that the intestinal mucosa in the DSS group was severely damaged, and the arrangement of glands was disorganised or even disappeared. Western blot results revealed that the protein expression of TRPV1 and Gαq increased ($P < 0.05$), and that the expression of TRPM8 decreased ($P < 0.05$). The mRNA expression of pro-inflammatory mediators was found to be elevated in the DSS group ($P < 0.05$). Immunofluorescence and CO-IP results showed that TRPV1 was co-expressed with TRPM8 and Gαq in colon and DRG tissues, and TRPV1 expression was increased and TRPM8 expression was decreased in colon and DRG tissues of the DSS group compared with the normal control group. CONCLUSION: TRPV1 expression was elevated and TRPM8 expression was decreased in colon tissues of experimental colitis mice, TRPV1/TRPM8 could be co-expressed in colon and DRG tissues, and there might be some balancing mechanism between the two in order to maintain the stability of intestinal function.

Keywords: experimental colitis, transient receptor potential channels, spinal dorsal root ganglia, inflammatory bowel disease

P12-5 急性肝损伤中巨噬细胞 β-catenin 信号通过外泌体/α-SNAP 通路调控肝脏 Treg 细胞的分子机制

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背景与目的：肝脏巨噬细胞与 Treg 细胞在维持肝脏免疫稳态中发挥重要作用，而急性肝损伤中肝脏巨噬细胞调控 Treg 细胞的分子机制尚不完全清楚。

方法：分别采用对乙酰氨基酚（APAP）和 D-氨基半乳糖（D-GalN）联合脂多糖（LPS）诱导小鼠急性肝损伤模型。使用流式细胞术检测肝脏内 Treg 细胞数量变化，并检测巨噬细胞 β-catenin 信号的表达变化。构建髓系特异性 β-catenin 敲除小鼠，检测其对肝脏内 Treg 细胞数量及肝损伤的影响。通过体外细胞共培养及外泌体蛋白质谱分析，探讨巨噬细胞 β-catenin 信号调控 Treg 细胞数量改变的分子机制。

结果：在两种小鼠急性肝损伤模型中，肝脏 Treg 细胞数量呈现代偿性增加，并且肝脏巨噬细胞 β-catenin 信号显著激活。有意思的是，β-catenin 信号只在浸润型的肝脏巨噬细胞

中表达上调，而在驻留的 kupffer 细胞中没有明显改变。髓系特异性 β-catenin 敲除明显降低了肝脏 Treg 细胞的数量，同时加重了炎性细胞的浸润及肝细胞凋亡。体外细胞共培养实验显示，巨噬细胞 β-catenin 信号可通过外泌体途径调控 Treg 细胞分化。巨噬细胞的外泌体蛋白质谱分析显示 β-catenin 信号通过改变外泌体中的 α-SNAP 表达变化从而调控 Treg 细胞数量发生改变。

结论：本研究揭示了急性肝损伤中巨噬细胞 β-catenin 信号通过改变外泌体的蛋白质表达谱，从而调控肝脏 Treg 细胞数量的分子机制，为急性肝损伤的治疗提供了新的潜在靶点。

关键词: β-catenin 信号；Treg 细胞；巨噬细胞；外泌体；急性肝损伤。

P12-6 黄连厚朴治疗慢性胃炎湿热证的疗效和分子机制

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研究背景：中医理论认为，清热祛湿是慢性胃炎的主要治疗方法之一。黄连具有清热、排毒、消炎的功效；厚朴可用于治疗腹痛、咳嗽和哮喘。黄连和厚朴可以调节肠道微生物群的平衡、抑制炎症反应。目的：本研究旨在验证黄连和厚朴对慢性胃炎的治疗效果，并通过转录组学的方法探索其机制。方法：首先建立大鼠慢性胃炎模型，观察建模前后大鼠肛门温度和体重变化情况。接下来，对大鼠胃粘膜组织进行 H&E 染色、TUNEL 凋亡染色和 ELISA 法测定炎症因子和胃肠激素。随后，采用高效液相色谱（HPLC）法检测黄连和厚朴的关键成分，通过构建 GES-1 细胞炎症模型，选择最优单体。最后，通过 RNA 测序探索黄连和厚朴的作用靶点。结果：与对照组相比，中药组大鼠病情较缓和，肛门温度较高，胃黏膜组织炎症反应减少，细胞凋亡减少。随后通过 HPLC 和 GES-1 细胞模型确定最优单体是黄连碱。RNA-seq 分析显示，DEG 在核糖体、NF-κB 信号通路等中显著富集，关键基因为重组人受翻译调节肿瘤蛋白 1（TPT1）和核糖体蛋白 L37（RPL37）。

关键词：慢性胃炎；黄连；厚朴；TPT1；RPL37

P12-7 Investigation of the L-Glu-NMDA receptor-H_2S-NMDA receptor pathway regulating gastric function in rats nucleus ambiguus

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Background: Studies have shown that either the release of the excitatory neurotransmitter L-Glu from brain neurons or electrical stimulation significantly increases the production of H_2S by CBS as a response to neuronal excitation. We previously investigated that both hydrogen sulfide (H_2S) and L-glutamate (L-Glu) injections in the nucleus ambiguus (NA) can regulate gastric function, and that both H_2S and L-Glu play a role in the physiological activities of the body, and that NA is an important nucleus for the reception of visceral sensation. The purpose of this study was to explore the potential pathway link between L-Glu and H_2S for the regulation of gastric function.

Methods: physiological saline (PS), L-glutamate (L-Glu) (2 nmol), NaHS (2 nmol), D-2-amino-5-phopho-novalerate (D-AP5, 2 nmol) + L-glutamate (L-Glu) (2 nmol), aminooxyacetic acid (AOAA, 2 nmol) + L-glutamate (L-Glu) (2 nmol), D-AP5 (2 nmol) + NaHS (2 nmol) were injected into the NA. The changes in gastric smooth muscle contraction curves were recorded using intragastric pressure measurements with a balloon inserted into the stomach, as well as changes in gastric fluid collection and observation of gastric fluid pH by esophageal perfusion.

Results: Injection of L-Glu or NaHS in NA was found to significantly inhibit gastric motility and promote gastric acid secretion in rats ($n = 6$, $P < 0.01$), while injection of PS and pre-injection N-methyl-D-aspartate (NMDA) receptor blocker D-AP5, and cystathionine beta-synthase (CBS) inhibitor AOAA followed by L-Glu or NaHS did not show significant changes ($n = 6$, $P > 0.05$).

Conclusion: These results indicate that both exogenous L-Glu and H_2S injected in NA regulate gastric motility and gastric acid secretion through NMDA receptors, suggesting the existence of an L-Glu-NMDA receptor-CBS-H_2S-NMDA receptor pathway in NA that regulates gastric function.

Keywords: nucleus ambiguus; hydrogen sulfide; L-glutamate; gastric motility; gastric acid secretion

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P12-8 PMCA4 抑制 NO 信号通路调节乳鼠结肠 ICC 的起搏电位

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背景：Cajal 间质细胞（ICC）是消化道起搏细胞，其产生的起搏电流可以引起消化道平滑肌生成慢波。在结肠 ICC 中观察到，给予一氧化氮（NO）信号通路抑制剂会使得 ICC 起搏活动增快，这说明 NO 参与 ICC 的正常起搏活动。然而，NO 浓度过高，会抑制肠道起搏活动。所以必然需要存在某种机制可以抑制 NO 过度产生。本研究旨在探讨质膜钙泵 4（PMCA4）是否可以抑制 NO 信号通路，限制 NO 过量生成，从而参与结肠 ICC 的正常起搏功能。

方法：取 ICR 小鼠的结肠进行原代 ICC 培养。通过全细胞膜片钳技术对 ICC 起搏电位进行记录。

结果：金精三羧酸（一种 PMCA4 特异性抑制剂）降低了结肠 ICC 中起搏电位的频率，表明 PMCA4 参与 ICC 起搏活动。PMCA4 被抑制后，可能激活了一些抑制性信号通路。金精三羧酸对结肠 ICC 的抑制作用被 Nω-硝基-L-精氨酸甲酯盐酸盐（L-NAME，NO 产生抑制剂）和 1H-[1,2,4]恶二唑并[4,3,-a]喹喔啉-1-酮（ODQ, 鸟苷酸环化酶抑制剂）所逆转。这表明当 PMCA4 活性受到抑制时，NO 信号通路被激活。另外，钾通道抑制剂（4-氨基吡啶，四乙基氯化铵，格列本脲）均抑制了 ATA 的作用，表明 PMCA4 的抑制引起了钾离子通道开放。

结论：这些结果表明 PMCA4 抑制 NO 信号通路及钾通道的过度激活，避免过多的 NO 产生并维持 ICC 的正常起搏活动。

关键词：Cajal 间质细胞；质膜钙泵；一氧化氮信号通路；钾通道

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P12-9 Maternal intermittent fasting deteriorates offspring metabolism via suppression of hepatic mTORC1 signaling

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The metabolic benefits of intermittent fasting (IF) have been well recognized. However, limited studies have examined the relationship between long-term maternal IF before pregnancy and offspring health. In this study, a C57BL/6J mouse model of long-term IF before pregnancy was established: 4-week-old female mice were subjected to alternate-day fasting for 12 weeks and resumed normal diet after mating. Female mice in the control group were fed ad libitum. Offspring mice were weaned at 6 weeks of age and fed a normal chow diet or a 60% high-fat diet. The effects of long-term pre-pregnancy IF on offspring metabolism and its underlying mechanism were examined. We found that neonatal IF offspring weighted significantly less relevant to control mice. This difference gradually disappeared as a result of catch-up growth. In the IF offspring, adipose tissue mass was significantly increased. This alteration was associated with a considerable deterioration in glucose tolerance. No significant difference in food intake was observed. Further, lipid deposition as well as triglyceride contents in the liver were greatly increased. Maternal IF significantly decreased levels of DNA methyltransferase in the liver of offspring. DNA methylation modifications of molecules associated with the mTORC1 signaling pathway were significantly altered, leading to the significant inhibition of mTORC1 signaling. Overexpression of S6K1 activated hepatic mTORC1 signaling and reversed the metabolic dysfunction in IF offspring. In conclusion, long-term pre-pregnancy IF increases hepatic steatosis and adiposity, as well as impairs glucose metabolism in adult offspring. This occurs through DNA methylation-dependent suppression of hepatic mTORC1 signaling activity.

Keywords: adiposity, DNA methylation, hepatic steatosis, intermittent fasting, maternal nutrition

P12-10 黄连素改善 6-OHDA 帕金森病大鼠胃底纤维化和氮能神经元受损

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帕金森病（Parkinson's disease, PD）是全球常见的神经退行性疾病，而 PD 患者经常伴有胃肠道功能障碍。我们之前的研究报道，大鼠双侧黑质经注射微量 6-羟基多巴胺（6-OHDA）会表现出典型的帕金森病胃轻瘫症状，包括胃排空延迟、胃体和幽门运动功能障碍。黄连素作为治疗肠道病症的特效药，其强大的功效备受关注，如治疗细菌性胃肠炎、痢疾等消化道疾病等。但关于黄连素是否能改善 PD 胃运动功能尚不清楚。本研究主要探究帕金森病大鼠胃底容受性舒张功能和黄连素对其治疗作用，采用离体胃底肌条动力实验、蛋白免疫印迹、

免疫荧光、qPCR、Sirius Red 染色等实验方法。6-OHDA 大鼠胃底肌条收缩和舒张功能减弱，与对照组相比由电场刺激引发的舒张幅度和外源给予 NO 供体硝普钠诱发的舒张幅度明显降低，109mmol 高钾溶液（KPSS）诱发的瞬时位相性收缩和紧张性收缩也显著下降，而经黄连素治疗 7 天后的 6-OHDA 大鼠胃底动力情况均明显改善。Sirius Red 染色显示 6-OHDA 大鼠胃底肌层及肌间神经丛中胶原纤维明显增多，同时胃底肌间神经丛中 nNOS 蛋白水平和 nNOS 阳性神经元数量减少，而经黄连素治疗后胶原纤维明显减少、nNOS 阳性神经元数量显著增加。进一步发现 6-OHDA 大鼠胃底肌层Ⅰ型和Ⅲ型胶原蛋白的 mRNA 和蛋白水平均显著上调，并且 CD68 和 CD206 双阳性的 2 型巨噬细胞细胞数量增多，转化生长因子β（TGFβ）mRNA 表达量增加，而黄连素治疗后其肌层炎症得到改善，2 型巨噬细胞数量下降。以上结果表明，6-OHDA 大鼠胃底容受性舒张障碍可能与肌层炎症导致的肌层纤维化和肌间神经丛 nNOS 阳性的神经元丢失有关，黄连素能很好的改善胃底容受性舒张功能障碍，并能缓解胃肌层纤维化和炎症，这为研究 PD 患者胃功能障碍的诊断和治疗提供了新的思路。

关键词：6-OHDA 大鼠；容受性舒张；纤维化；nNOS；黄连素

P12-11 慢性应激通过蓝斑-中缝神经环路抑制肝再生的机制研究

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背景：我国是肝病大国，慢性肝病患者基数庞大。慢性肝病患者常处于持续压力状态，一旦因病情恶化需要手术治疗，围术期诸多因素又往往加重患者原有的慢性应激状态。肝切和肝移植术仍是肝脏占位和终末期肝病的主要治疗手段，肝再生障碍是导致肝切或肝移植患者预后不良的重要因素。然而，肝病患者普遍存在的慢性应激状态对肝再生的影响却鲜有研究。因此，本课题的研究目标是：探究慢性应激对肝再生的影响，明确介导慢性应激影响肝再生的中枢和外周交互机制。

方法：①构建慢性睡眠剥夺、慢性束缚应激慢性应激模型，进行 90%肝切和 70%肝切，检测肝切后 48 小时肝脏的肝体比、KI67、PCNA 等分子的表达水平，评价慢性应激后小鼠再生功能水平变化。②将可逆行示踪的伪狂犬病毒注射肝脏，标记调控肝脏的神经核团。通过行为学实验、免疫荧光染色、脑片膜片钳等方法明确慢性应激状态下蓝斑（LC）、中缝（rMR）神经元的激活情况；在 *Th*-Cre 转基因小鼠，通过病毒标记，明确“LC-rMR”的投射关系，化学遗传学特异性调控“LC-rMR”神经环路，阐明该环路功能变化对肝再生的影响；化学灭活肝内交感神经末梢，明确交感神经是否介导慢性应激对肝再生的抑制效应。③利用流式细胞分析技术检测慢性应激状态肝再生起始阶段 B 细胞、T 细胞、中性粒细胞和巨噬细胞等免疫细胞变化；利用 RT-PCR、免疫荧光染色等方法阐明慢性应激状态肝再生过程肾上

腺素能受体基因转录水平变化和 β2-AR 在巨噬细胞表面表达情况。

结果：我们发现①慢性睡眠剥夺应激、慢性束缚应激均可显著抑制 70%肝切除术后肝再生，并且慢性应激后 90%肝切除术小鼠的总体生存率也显著更低。②LC、rMR 在支配肝脏的神经通路上，并且在慢性应激下被显著激活；LC 的去甲肾上腺素（NE）能神经元可投射至 rMR，且在慢性应激状态下投射至 rMR 的 LC TH 神经元兴奋性显著升高；化学遗传学抑制“LC-rMR”神经环路可逆转慢性应激对肝再生的抑制效应；化学遗传学激活“LC-rMR”神经环路可模拟慢性应激对肝再生产生抑制作用；灭活肝内交感神经可逆转慢性应激对肝再生的抑制作用。③流式细胞分析结果提示慢性应激状态下肝再生起始阶段 B 细胞、T 细胞和中性粒细胞的比例无明显改变，$Ly6C^{hi}$ 巨噬细胞的比例显著下调，$Ly6C^{lo}$ 巨噬细胞的比例上调。RT-PCR 和免疫荧光染色的结果提示慢性应激肝切后肝内肾上腺素能受体 β2（β2-AR）亚型表达显著上调，巨噬细胞表面高表达 β2-AR。

结论：慢性应激状态下，脑干“LC-rMR”神经环路过度激活，驱动肝内交感神经兴奋并持续释放 NE，促进巨噬细胞高表达 β2-AR，抑制促炎型巨噬细胞（$Ly6C^{hi}$）活化并减少 IL-6 等分泌，导致肝切后肝细胞增殖启动障碍，最终抑制肝再生进程。

关键词：肝再生，慢性应激，蓝斑核，交感神经，巨噬细胞

P12-12 QX-314 通过 TRPV1/VGSC 通道抑制食管高敏感的机制研究

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目的：探究食管高敏感的发生机制以及 QX-314 抑制食管高敏感的通道机制，从而为胃食管反流病（GERD）的治疗提供新思路。方法：建立胃食管反流豚鼠模型，对其使用不同浓度 QX-314（1mM、5mM、10mM）进行治疗。使用生理记录仪检测豚鼠造膜前后心率变异性结果，运用 qRT-PCR 检测各组食管黏膜 IL-1β、IL-6、IL-10、TNF-α 的表达，运用 qRT-PCR、Western blot 和免疫荧光检测各组食管黏膜、背根神经节（Dorsal Root Ganglion，DRG）、结状神经节（Nodose ganglia）和颈静脉神经节（Jugular ganglion）中 TRPV1 及 VGSC 的表达，观察不同浓度（1mM、5mM、10mM）治疗组、胃食管反流（GERD）组及正常组中 TRPV1 及 VGSC 的表达差异。结果：与正常组相比，治疗组及胃食管反流组中 IL-1β、IL-6、TNF-α 表达增加，IL-10 表达下降；造膜前各组心率变异性（LF/HF）无明显差异，造模后正常组 LF/HF 无明显变化，模型组 LF/HF 增高，其中 GERD 组 LF/HF 大于治疗组，10mM 治疗组 LF/HF 在治疗组中变化最小；模型组食管黏膜、DRG 及颈静脉神经节中 TRPV1 及 VGSC 表达较正常组增加，其中 GERD 组表达量大于治疗组，10mM 治疗组表达量在治疗组

中最低；结状神经节中 TRPV1 及 VGSC 表达量各组之间未见明显差异。

结论：胃食管反流（GERD）通过激活豚鼠食管黏膜、DRG、Jugular 中的 TRPV1/VGSC 通路介导食管高敏感，QX-314 可通过抑制 TRPV1/VGSC 通路，从而抑制食管高敏感的发生。

关键词：豚鼠模型；胃食管反流；TRPV1；VGSC

P12-13 胆汁酸受体 TGR5 对 DSS 诱导的小鼠结肠炎 NF-κB 通路的调节作用

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目的 探究胆汁酸受体 TGR5 对 DSS 诱导的小鼠结肠炎的影响及对 NF-κB 通路的调节作用。 **方法** 选择 24 只体质量相近的 C57BL/6 小鼠，随机分为 4 组，每组各 6 只：对照组（正常饮水）、DSS 模型组（2.5%DSS 饮水造模）、脱氧胆酸组（2.5%DSS 饮水+33.3mg/mlDCA150μl 灌肠）、TGR5 抑制剂组（2.5%DSS 饮水+33.3mg/mlDCA150μl 灌肠）+10 mM*20ul SBI-115 灌肠）。记录小鼠肠炎疾病活动指数（disease activity index，DAI）和结肠组织病理评分，qRT-PCR 检测小鼠结肠组织中的炎症因子 IL-1β、IL-6、IL-10、TNF-α，检测 p-CREB 和 NF-κB 通路中 NF-κB p65、p-CREB 的蛋白表达。 **结果** 与对照组相比，DSS 模型组及 TGR5 抑制剂组 DAI 评分和组织病理学评分更高（P<0.01），促炎因子 IL-1β、IL-6、IL-10、TNF-α 的表达升高（P<0.01），NF-κB p65 的表达水平上升（P<0.01）、p-CREB 的表达水平下降（P<0.01）；脱氧胆酸组对上述改变有缓解作用（P<0.01）。 结论 外源性脱氧胆酸可以激活胆汁酸受体 TGR5 抑制肠道炎症。

关键词：胆汁酸；TGR5；结肠炎；NF-κB 通路

P12-14 枳壳水煎剂对小鼠胃肠功能的影响

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目的：探讨中药枳壳对胃肠功能紊乱小鼠肠道中菌群的作用。**方法：**采用碘代乙酰胺联合蔗糖灌胃+隔日喂养方法建立胃肠动力紊乱小鼠模型。建模成功后给予枳壳水煎剂进行灌胃，7 天后收集小鼠新鲜粪便行细菌培养，尾静脉采血检测胃泌素水平，小肠平滑肌检测肠道活动能力。**结果：**与正常对照相比，模型组小鼠毛发稀疏散乱，活动减少，大便稀溏和干

燥交替，粪菌培养显示大肠杆菌数量减少，胃泌素水平降低，小鼠小肠平滑肌收缩张力增加。而枳壳处理组小鼠大便次数和性状无显著差异，粪菌数量减少，胃泌素水平下降，小肠肌张力下降，但均无显著性差异。与模型对照组相比，枳壳处理组小鼠活动量和食量有增加，外观变化不明显，细菌培养显示大肠杆菌数量增加，有显著差异，胃泌素水平升高，小肠平滑肌收缩张力降低，但无显著差异。**结论：**枳壳对胃肠功能紊乱小鼠肠道活动有改善性作用，其机制可能与影响肠道菌群有关。

关键词：枳壳 胃肠功能紊乱 肠道菌群

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P13 疼痛转化

P13-1 Development of multifunctional and orally active cyclic peptide agonists of opioid/neuropeptide FF receptors that produce potent, long-lasting peripherally restricted antinociception with diminished side effects

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We previously reported that a multifunctional opioid/neuropeptide FF receptor agonist, DN-9, achieved peripherally restricted analgesia with reduced side effects. To develop stable and orally bioavailable analogs of DN-9, eight lactam-bridged cyclic analogs of DN-9 between positions 2 and 5 were designed, synthesized and biologically evaluated. In vitro cAMP assays revealed that these analogs, except 7, were multifunctional ligands that activated opioid and neuropeptide FF receptors. Analog 1 exhibited improved potency for kappa-opioid and NPFF2 receptors. All analogs exhibited potent, long-lasting peripherally restricted antinociception in the tail-flick test without tolerance development after subcutaneous administration and produced oral analgesia. Oral administration of the optimized compound analog 1 exhibited powerful, peripherally restricted antinociceptive effects in mouse models of acute, inflammatory, and neuropathic pain. Remarkably, orally administered analog 1 had no significant side effects, such as tolerance, dependence, constipation or respiratory depression, at effective analgesic doses.

Keywords: Opioid, Neuropeptide FF, Multifunctional agonists, Cyclic peptide, Oral antinociception

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P13-2 Spinal interleukin-16 contributes to persistent inflammatory pain hypersensitivity

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Background: Chronic pain has a significant impact on patients' quality of life and has long been a challenging issue in clinical treatment. Interleukin-16 (IL-16), a proinflammatory cytokine, plays a pivotal role in inflammatory and autoimmune diseases, such as multiple sclerosis and experimental autoimmune neuritis. This study aims to examine the involvement of IL-16 in inflammatory pain.

Methods: CFA-induced inflammatory pain was established in mice. Mechanical allodynia and thermal hyperalgesia were assessed using the *von* Frey test and Hargreaves' test, respectively. We performed RNA sequencing and bioinformatics analysis to explore mRNA expression profiles in the spinal dorsal horn following normal saline or CFA injection. The expression and distribution of IL-16 mRNA and protein were examined using quantitative polymerase chain reaction (qPCR), immunofluorescence, and Western blotting. Intrathecal administration of IL-16 siRNA was used to block the CFA-induced increase of IL-16. Nociceptive responses including licking, flicking, and paw withdrawal were observed for 30 minutes after intrathecal administration of Pro-IL-16. Immunofluorescence was also utilized to examine c-fos, Iba-1, and GFAP.

Results: IL-16 in the spinal dorsal horn was screened in the CFA-induced inflammatory pain model using RNA sequencing and bioinformatics analysis. The increased IL-16 mRNA expression after CFA injection was further confirmed by qPCR and immunofluorescence, respectively. Western blotting demonstrated an elevation of IL-16 levels from 2 hours to 7 days post-CFA injection. Intrathecal injection of IL-16 siRNA not only significantly suppressed IL-16 expression in the bilateral spinal cord but also relieved CFA-induced mechanical and thermal pain

hypersensitivity. Meanwhile, intrathecal injection of Pro-IL-16 induced strong and long-lasting spontaneous and evoked nociceptive responses. Further data demonstrated that IL-16 siRNA suppressed glial activation, as indicated by Iba-1 and GFAP immunostaining, while Pro-IL-16 stimulated glial activation. Notably, IL-16, as well as CD4, the receptor of IL-16, were found to colocalize with F4/80 and Iba-1, which are markers for macrophages and microglia, respectively.

Conclusions: This study shows that peripheral injection of CFA induces the production of IL-16 by spinal macrophages and microglia, which can in turn promote CD4 receptor-mediated microglial activation, followed by astrocyte activation. The results of this study suggest that targeting IL-16 may provide a promising strategy to relieve inflammatory pain.

Keywords: Interleukin-16, Complete Freund's adjuvant, Spinal cord dorsal horn, Inflammatory pain.

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P13-3 Effect of aromatherapy on pain sensitization in pain empathy model rats

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Objective: To observe the effects of aromatherapy on pain sensitization induced by pain empathy in rats. **Methods:** The pain model was used as teaching rats, and the same caged rats without any treatment were used as observing rats and the changes of pain behavior of the observing rats were observed after social interactions. Thirty-four adult male Sprague-Dawle rats were taken, and a pain empathy model of paired observing rats (*n*=8, *modeling group*) was established by teaching rats (*n*=8) plantar injection of complete Freund's adjuvant. The teaching rats(*n*=3) and corresponding observation rats (*n*=3) were selected as the blank control group; Another group of teaching rats (*n*=3) were injected with normal saline on the sole, and the observation rats (*n*=3) were used as the normal saline control group; Another group of teaching rats (*n*=3) were selected and the corresponding observation rats (*n*=3) were given aromatherapy intervention as the blank aromatherapy control group. The paw withdraw mechanical threshold (PWMT) was measured with Von-Frey fiber before and after modeling. After modeling, the rats in

the modeling group were randomly divided into the pain empathy model group and the aromatherapy intervention group according to PWMT stratification. After modeling, 1% lavender essential oil was given for sniffing for 14 days. At the same time, PWMT was detected on the 1st, 3rd, 5th, 7th and 14th day after modeling. **Results:** (1) The PWMT of the pain empathy model group was not only decreased by 15.3g (P<0.01), but also lower than that of the blank control group by 15.3g (P<0.01). (2) The PWMT of the aromatherapy intervention group was decreased by 8.5g (P<0.05), lower than that of the blank control group by 8.5g (P<0.05), but higher than that of the pain empathy model group by 6.8g (P<0.01). (3) The PWMT of rats in the normal saline control group and the blank aromatherapy control group was similar to that in the blank control group. (4) Within 14 days after modeling, the average PWMT of rats in the pain empathy model group on day 7 was 7.5g, and that of rats in the aromatherapy intervention group was 10.8g, which were statistically different from those before modeling and the blank control group (P<0.01); On the 14th day, the mean PWMT of rats in the pain empathy model group was 7g, and that of rats in the aromatherapy intervention group was 13.8g, and the pain threshold increased and was significantly higher than that in the pain empathy model group (P<0.01). **Conclusion:** The long-term mechanical pain empathy model can be established by injection of complete Freund's adjuvant into the sole of rats, and the aromatherapy intervention can relieve the pain sensitization caused by mechanical pain empathy.

Key words: Pain empathy; Pain sensitization; Aromatherapy intervention; Rats

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P13-4 The central mechanism of trigeminal neuralgia mediated by HMGB1/TLR4 signaling pathway in rats

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High mobility protein 1 (HMGB1) is a damage associated molecular pattern (DAMP) which is released from damaged cells or tissues into the extracellular environment or bloodstream. Upon activation, HMGB1 can stimulate Toll-like receptors present on nociceptive neurons and modify the activity of two channels, TRPV1 and TRPA1. The objective of this study was to create a rat

model of chronic compression injury (IoN-CCI) and to research the potential central mechanism of trigeminal neuralgia mediated by HMGB1/TLR4. The orofacial mechanical pain threshold was evaluated using Von Frey fibers before and after the IoN-CCI on days -1, 3, 7, 11, 14 and 21. Notably, from day 7 onwards, the mechanical pain threshold of the rats in the operation group was notably reduced when compared to the sham operation group. The results of Real-time Fluorescence Quantitative PCR (qPCR) and Western blotting on the 21st day following a surgical procedure on the spinal trigeminal nucleus caudalis (Vc) revealed an increase in the mRNA and protein level of HMGB1 and TLR4. To investigate this further, stereotaxic equipment was used to administer AAV2/9-HMGB1 shRNA-EGFP and AAV2/9-EGFP NC to the bilateral Vc, and IoN-CCI was set up the same day. The rats were divided into four groups: HMGB1 shRNA+loN-CCI, HMGB1 shRNA+sham, NC+IoN-CCI and NC+sham. after euthanasia on the 21st day, green fluorescence protein was visible in the Vc under a fluorescent microscope. The qPCR data showed that HMGB1 had been knocked down after administering AAV2/9-HMGB1 shRNA-EGFP. The NC+IoN-CCI group had significantly lower mechanical pain thresholds, but HMGB1 knockout suppressed postsurgical orofacial mechanical hypersensitivity. In summary, this research thus demonstrated that the HMGB1/TLR4 signaling pathway is involved in the transmission of trigeminal neuralgia in the rat Vc.

Keywords: HMGB1; TLR4; Trigeminal Neuralgia; central sensitization; spinal trigeminal nucleus caudalis

P13-5 Thrombospondin 2 in peripheral sensory neurons regulates SNL-induced neuropathic pain

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Background: Neuropathic pain is one of the most refractory and painful diseases in clinic and is lack of effective drug therapy due to unclear mechanisms. Thrombospondin 2 (TSP2), belonging to TSP family, is extracellular protein involved in cell-cell and cell-matrix communication and play an important role in synapse formation and synaptic plasticity in nervous system. Polymorphisms in TSP2 gene has been found to affect the risk of developing chronic pain

in humans. However, it is not clear the expression and function of TSP2 in sensory neurons. The aim of this study is to examine the expression pattern of TSP2 in peripheral dorsal root ganglion (DRG) after nerve injury and whether TSP2 contributes to neuropathic pain.

Methods: In this study, the spinal nerve ligation (SNL) induced neuropathic pain model was used. Mechanical and thermal pain hypersensitivity were evaluated by von Frey test and Hargreaves' test, respectively, at days 0, 3, 7, 14 and 28 after surgery. The TSP2 expression and its relationship with Nav1.7 were examined by immunofluorescence, quantitative PCR, Western blotting and co-immunoprecipitation and mass spectrum analysis. TSP2 siRNA was administered by DRG microinjection.

Results: We observed that TSP2 was expressed in all sizes of DRG neurons and colocalized with calcitonin gene-related peptide (CGRP) and neurofilament-200 (NF200), the marker for small peptideric neuron and large neuron, respectively. SNL induced the increase of TSP2 mRNA and protein in injured DRGs examined by qPCR and Western blotting. Moreover, knocking down of TSP2 in DRGs by DRG microinjection of siRNA can alleviate SNL-induced pain hypersensitivity in the development period of neuropathic pain but not in the maintenance period. Furthermore, co-immunoprecipitation and mass spectrum analysis experiment showed that Nav1.7 binds with TSP2 in DRGs and dorsal root and the binding was significantly increased after SNL.

Conclusions: Our study demonstrated that TSP2 expressed in primary sensory neurons, promotes the nociceptive pain hypersensitivity and participates in nerve injury-induced neuropathic pain via regulating Nav1.7 trafficking in mice. Thus, TSP2 in DRGs may be a new potential target for neuropathic pain intervention.

Keywords: Neuropathic Pain; Spinal Nerve Ligation; Dorsal Root Ganglion; TSP2; Nav1.7

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P13-6 DNMT3a-triggered upregulation of $GABA_A$ receptor in mPFC contributes to paclitaxel-induced neuropathic pain and anxiety-like behavior

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Paclitaxel (PTX) is one of the most commonly used chemotherapeutic agents for various cancer diseases. However, PTX also causes behavioral deficits related to nervous-system dysfunction, such as neuropathic pain, anxiety and depression. The medial prefrontal cortex (mPFC) is one of the areas that is susceptible to adverse effects of chemotherapeutic agents. DNA methylation has adaptive changes in nervous diseases and represents promising neuromodulation targets. However, it is not clear whether DNA methylation and DNA methyltransferases in mPFC play a role in pain transmission during neuropathic pain development. Here, the present study was designed to examine the role of DNA methylation and DNMT3a expression in mPFC by using a PTX-induced neuropathic pain model. PTX (4 mg/kg) was injected intraperitoneally four times in mice every other day. Three weeks later, PTX-treated mice developed pain hypersensitivity and exhibited anxiety- and depression-like behaviors. Western blotting and RT-qPCR showed that PTX decreased the expression of DNMT3a and upregulated the expression of *Gabrb1* mRNA and its coding $GABA_AR\beta1$ protein in mPFC. Moreover, overexpression of DNMT3a in mPFC by stereotaxically injection of AAV-CMV-Dnmt3a into mPFC attenuated PTX-induced mechanical allodynia, heat and cold hyperalgesia, and anxiety-like behavior. DNMT3a overexpression also reversed the PTX-induced increase of mPFC $GABA_AR\beta1$. By immunostaining combined with an RNAscope technology, DNMT3a was widely distributed throughout the whole mPFC area and nonselectively expressed in either excitatory neurons or inhibitory neurons. Next, overexpression of DNMT3a in pyramidal neurons, but not in GABAergic inhibitory neurons by injecting AAV-DIO-Dnmt3a into mPFC of CaMKII-Cre mice or GAD-Cre mice, relieved PTX-induced neuropathic pain and anxiety-like behavior. Furthermore, a ChIP assay was carried out and found that PTX injection reduced the binding of DNMT3a to the *Gabrb1* gene promoter region and degraded the level of DNA methylation within this region using the pyrosequencing method in mPFC. DNMT3a overexpression reversed the decreased binding activity to the region and DNA methylation level with this region. In addition, long-term methyl donor diets were beneficial for PTX-induced pain hypersensitivity and anxiety-like behavior in mice. These results suggest that DNMT3a-triggered upregulation of mPFC $GABA_AR\beta1$ may contribute to PTX-induced neuropathic pain and anxiety-like behavior. DNA methylation-dependent epigenetic modulation can be served as the potential target for analgesia for chemotherapy-induced neuropathic pain.

Keywords: DNMT3a; $GABA_A$ receptor; medial prefrontal cortex; paclitaxel; neuropathic pain

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P13-7 YL-0919 对小脑浦肯野细胞自发性活动和运动行为的影响机制

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小脑浦肯野细胞（PCs）作为主要神经元，执行各种生理活动的核心神经元。PC 活动受多种神经传入调节，前期研究发现活化 5-HT 受体参与小脑皮层神经环路的功能。盐酸羟哌吡酮（YL-0919）是一种活性抗抑郁剂，具有部分激动 5-HT 受体和选择性抑制 5-HT 重摄取的双重作用，但 YL-0919 调控小脑 PC 自发性简单锋电位放电活动的机制仍不明确。**[目的]**实验采用在体电生理学及动物行为学等方法，探讨 YL-0919 对小鼠小脑皮层 Vermis PC 自发性简单锋电位放电活动的影响及其机制，探讨小脑皮层微量注射 YL-0919 对小鼠运动行为的影响。**[材料与方法]**选用昆明种小鼠将其麻醉气管插管后，行开颅手术。将小脑 Vermis 打开，细胞贴附式记录小脑 Vermis PC 的放电活动。行为学实验：对照组、YL 组和 WAY + YL 组，通过行走及恒速转棒实验观察各组小鼠的运动协调能力的改变，利用加速转棒实验检测各组小鼠在 5 天训练任务中的运动学习能力的变化。**[结果]**YL-0919 抑制小脑 PC 的简单性峰电位（SS）放电频率，其抑制作用具有浓度依赖性，IC_{50} 为 5.8μM。5-HT 再摄取抑制剂未消除 YL-0919 对 PC SS 放电频率的抑制；5-HT2B 或 5-HT7 受体阻断剂均未消除 YL-0919 对 PC SS 放电频率的抑制；5-HT1A 受体阻断剂(WAY)消除 YL-0919 对 PC SS 放电频率的抑制。行走障碍分析：小脑微量注射 YL-0919，小鼠在传感棒上四肢出错次数和错误持续时间较对照组显著增加，给予 WAY 和 YL-0919，四肢出错次数、错误持续时间较对照组无显著差异。在恒速转棒中，YL-0919 可显著减少小鼠跌落潜伏期；给予 WAY 和 YL-0919，小鼠在恒速转棒上的运动时间无显著减少。加速转棒中，YL-0919 可致小鼠从转棒仪掉落时转速和跌落潜伏期均显著降低。给予 WAY 和 YL-0919 使小鼠在加速转棒上的掉落时转速与潜伏期均无显著变化。**[结论]** YL-0919 通过 5-HT1A 受体降低小鼠小脑 PC 自发性活动。YL-0919 可以通过 5-HT1A 受体影响小鼠的运动协调和运动学习功能。本研究成果将为进一步揭示抗抑郁药对中枢的调节机制提供新的线索和思路。

P13-8 卫星胶质细胞在 A 纤维脱髓鞘诱导的神经病理痛中的作用机制研究

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背景：临床中一些神经病理性疼痛经常伴随着各种脱髓鞘疾病的发生。然而，由髓鞘损伤引发的疼痛机制尚未完全揭示。卫星胶质细胞（Satellite glial cells，SGCs）作为背根神经节（Dorsal root ganglion，DRG）中重要的外周胶质细胞，其围绕神经元并与之交互，影响神经元的兴奋性，参与疼痛的发生和发展。作为外周治疗的潜在靶点，可以有效预防中枢不良反应的发生。

目的：本研究旨在通过在大鼠胫神经干内注射眼镜蛇毒以特异性降解来自深部组织（肌肉）的 A 纤维髓鞘，以 L4DRG 中的 SGCs 作为治疗靶点，探索髓鞘在疼痛发生中的作用，并研究病理状态下 SGCs 与痛觉神经元之间的交互机制，以期为脱髓鞘所致的神经病理性疼痛患者提供一种有效的非阿片类镇痛方法。

方法：采用体内电生理技术，观察模型前后 C 类神经元及外周末梢感受器兴奋性和中枢痛觉信号传入的变化，并通过行为学和免疫荧光测评分别评估痛觉阈值与 SGCs 的活化程度。通过在 L4DRG 中局部应用激活剂与抑制剂调控 SGCs 活性，考察是否可以逆转上述变化。

结果：胫神经注射蛇毒后，大鼠表现出显著的自发痛，机械痛敏及热敏反应；A 纤维因脱髓鞘出现传导阻滞引起背根反射，导致 C 纤维外周末端出现炎症反应；中枢端痛觉信号传入增加；L4DRG 中 SGCs 活化；调控 SGCs 活性可以逆转上述变化。

结论：源于深部组织（如肌肉）的 A 纤维脱髓鞘通过背根反射激活 DRG 中的 SGCs，并驱动神经病理性疼痛的产生和发展，因此，SGCs 有望成为治疗神经病理性疼痛的重要靶点。

关键词：A 纤维脱髓鞘，神经病理性疼痛，卫星胶质细胞，背根神经节，C 类神经元

P13-9 Roles of transient receptor potential channels TRPV1 and TRPM8 in paclitaxel-induced neuropathy pain

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Thermosensitive transient receptor potential (TRP) channels have been reported to be involved in paclitaxel-induced neuropathy pain (PINP), but their exact functions remain controversial. Here, we tested the effects of transient receptor potential channel vanilloid subtype 1 (TRPV1, noxious heat sensor) and transient receptor potential melastatin 8 (TRPM8, cold sensor) in PINP. Behavioral assessments using the von Frey test, dynamic Brush test, hot plate test, and Hargreaves test showed that intraperitoneal administration of 8 mg/kg paclitaxel could induce obvious mechanical and thermal hyperalgesia after days 7 and 14. This paclitaxel-induced mechanical and thermal hyperalgesia were significantly inhibited by the TRPV1 antagonist capsazepine and its selective channel blocker JNJ17203212, indicating that TRPV1 played a key role in the development of PINP. Western blotting and Immunofluorescence staining showed that paclitaxel treatment increased the protein expression of TRPV1 in small and medium DRG neurons 14 days after treatment. Calcium imaging further indicated that TRPV1 channel activity was enhanced in DRG neurons of paclitaxel-treated rats. On the contrary, the expression of TRPM8 protein decreased and its channel activity was weakened in DRG neurons 14 days in PINP. Furthermore, activation of TRPM8 by topical treatment of menthol (TRPM8 agonist) attenuated the mechanical and heat pain in PINP, which was partially due to the over-activation of TRPV1. Mechanistically, we found that the activity of DRG neurons to capsaicin (TRPV1 agonist) was reduced after menthol application in both vehicle and paclitaxel rats, particularly in the paclitaxel group. Summarily, these results suggested that TRPV1 participated in the development of PINP and the activation of TRPM8 could inhibit TRPV1 function in DRG neurons. PINP mediated by up-regulation of TRPV1 function may be further aggravated by the down-regulation of TRPM8 function. Activation of TRPM8, might be a useful approach to alleviate pain associated with paclitaxel chemotherapy.

Keywords: TRPV1, TRPM8, paclitaxel-induced neuropathy pain, menthol analgesia

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P13-10 Sleep deprivation causes hyperalgesia via suppressing the activity of medial habenula cholinergic neurons

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It is becoming increasingly clear that there exists a vicious cycle between sleep disorders and pain. Although numerous studies have revealed how sleep and pain are regulated within the body, the precise process through which sleep disorders exert an influence on pain is still far to be elucidated. Here, we firstly confirmed that sleep deprivation would induce hyperalgesia and found that the activity of medial habenula (MHb) cholinergic neurons was reduced after sleep deprivation for 6 hours. Interestingly, although MHb cholinergic neurons did not directly respond to the stimulation of pain, their activation during sleep deprivation alleviated hyperalgesia, whereas solely inhibiting these neurons, to some extent, contributed to hyperalgesia. Furthermore, activating the projections of MHb cholinergic neurons to the paraventricular nucleus of thalamus (PVT) and the interpeduncular nucleus (IPN) resulted in alleviation of sleep-deprivation-induced hyperalgesia. Overall, our findings demonstrate that sleep deprivation may suppress the activity of MHb cholinergic neurons and affect their projections to PVT and IPN, leading to hyperalgesia. This novel neural mechanism sheds light on how short sleep can aggravate pain and opens the window to new therapeutic avenues to restrain the effects of short sleep on pain.

Keywords: sleep deprivation, hyperalgesia, medial habenula cholinergic neurons, paraventricular nucleus of thalamus, interpeduncular nucleus

P13-11 A study on the role of dopamine D2 receptors in the anterior cingulate cortex in participating in the regulation of pain aversion in rats

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Objective The present study aims to investigate the role of dopamine D2 receptors (DRD2) in the rostral anterior cingulate cortex (rACC) in the modulation of pain aversion in rats. Inflammatory pain was induced by subcutaneous injection of complete Freund's adjuvant (CFA) into the left hindpaw of rats, and behavioral test, multi-channel electrophysiological technology and immunofluorescence were employed. Activation of D2 receptors in certain areas of the brain

has been found to produce significant analgesic effects, while inhibition of D2 receptors could lead to nociceptive effects. The results of this study could provide insight into the potential of DRD2 in the rACC to regulate pain aversion in rats.

Methods 1) Establish an inflammatory pain model by injecting CFA into the left hindpaw of rats subcutaneously. 2) Measure the CFA-induced CPA behavior. 3) Inject DRD2 agonists or antagonists into the rACC of rats and assess the changes in CPA. 4) Utilize the OFT test to evaluate the effects of negative aversion and movement ability that activate or inhibit DRD2. 5) Select pyramidal neurons in the ACC based on their typical firing characteristics. 6) Utilize multi-channel electrophysiological technology to monitor the firings of pyramidal neurons in the ACC of rats. 7) Perform immunofluorescence.

Results 1) Pain and C-CPA model were successfully established. 2) Injection of DRD2 agonists or antagonist into the rACC could modulate the C-CPA behavior of CFA rats, but did not affect the CPA behavior of the NS rats. 3) Activating or inhibiting the DRD2 in the rACC altered the time spent in the center of the open field in rats with inflammatory pain, but did not alter the total movement distance in the OFT. 4) Multi-channel detection of the excitability of pyramidal neurons in the ACC of CFA rats on the "pain" side was increased. 5) Activating or inhibiting the D2 receptors could restore or further increase the discharge frequency of pyramidal neurons in the ACC of CFA rats on the "pain" side, but did not affect the excitability of NS rats. 6) Co-expression of DRD2 and NMDAR1 receptors was observed in the neurons of layer II/III of the rACC.

Conclusion Activation or inhibition of DRD2 in the rACC can reverse or amplify the C-CPA response and alter the discharge activities of pyramidal neurons on the "pain" side of rats. Thus, it is suggested that DRD2 in the rACC may be involved in the regulation of pain aversion during the inflammatory pain caused by CFA.

Key words: rostal anterior cingulate cortex (rACC); multi-channel electrophysiology; pain aversion; dopamine D2 receptor (DRD2); conditional position avoidance (CPA)

P13-12 Mechanism of pregabalin regulates complex spike activity of Purkinje Cells in mice

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Pregabalin (PGB), a clinical analgesic medicine is used for the treatment of a variety of

neuropathic pain. PGB can effectively influence the function of nervous system, by regulating the secretion of neurotransmitters through direct interactions on voltage-gated calcium channel. In cerebellar cortex, Purkinje cell receives excitatory inputs from climbing fiber, which exhibits a complex spike activity. Since climbing fiber (CF)-triggered complex spikes (CSs) are closely related to calcium channel activation, suggesting that PGB may modulate CSs activity. The present study investigated the mechanism of PGB modulated the CSs activity of PCs in mouse cerebellar cortex, by *in vivo* and *in vitro* electrophysiological recording. Under *in vivo* conditions, PGB significantly reduced the number of CS spikelets and the area under the curve (AUC) of CSs. Under *in vitro* conditions, PGB significantly reduced the amplitude of calcium-dependent component of CSs. Application of the BAPTA-containing internal solution increased rise and decay time of calcium current components, but failed to prevented the PGB-produced reduction of the number of spikelets and AUC of CSs. The effect of PGB on CSs activity was consisted in the presence of GABAA receptor blocker or NMDA receptor antagonist. Notably, the inhibitory effect of PGB on CS was abolished by application of a non-selected voltage-gated calcium channel (VGCC) blocker, $CdCl_2$. In addition, perfusion of a selective T-type VGCC antagonist, flunarizine significantly suppressed the inhibitory effect of PGB on the CSs activity of the mouse cerebellar PCs. These results indicate that pregabalin depress the CSs activity of mouse cerebellar PC by inhibiting the calcium influx from VGCC, at least partly through T-type VGCC, but not by modulating activities of NMDA receptor or GABAA receptor.

Key words: Pregabalin; Complex spikes; Cerebellar Purkinje cells; Electrophysiological recordings; Voltage-gated calcium channels;

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P13-13 Mechanism of noradrenaline enhances CF-PC LTD in mouse cerebellar cortex

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Noradrenaline (NA) is a monoamine neurotransmitter, which plays an important role in regulation of functional activities of the central nervous system. The climbing fiber (CF) originating from the inferior olivary nucleus which forms excitatory synaptic connection with

Purkinje cell (PC). NA involved in regulating the induction and maintenance of long-term plasticity of CF-PC synaptic transmission, but its mechanisms are still unclear. In the present study, we examined the effects of NA on long-term plasticity of CF-PC by whole-cell patch clamp recording technology combined with pharmacological methods. The results showed that CF stimulation with tetanic stimulation at 5 Hz (150 pulses) induced CF-PC long-term depression (LTD). In the presence of NA (500 nM), tetanic stimulation could induce a stronger CF-PC LTD than that under control conditions, which exhibited much more decrease in the amplitude of N1 accompanied with much more increase in PPR. Blockade of mGluR1 abolished CF-PC LTD, indicated that CF-PC LTD is mGluR1-dependent. Notably, In the presence of mGluR1 blocker, application of NA could rescue the tetanic stimulation to induce a CF-PC LTD. The NA-induced CF-PC LTD was not affected by blockade of β- or α1-AR with propranolol (Pro) and prazosin (Pra.). However, NA failed to rescue CF-PC LTD in the presence of α- or α2-AR antagonist, phentolamine (Phen) and yohimbine (Yoh). In addition, perfusion α2-AR agonist, UK14304, could also rescue the CF-PC LTD, and overwhelmed the NA to rescue CF-PC LTD. These results indicate that NA triggers tetanic stimulation to induce a presynaptic CF-PC LTD via α2-AR, and then enhances the expression of CF-PC LTD.

Key words: Noradrenaline (NA), Purkinje cells (PC), Adrenergic receptor (AR), Long term plasticity, Climbing fiber (CF)

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P13-14 Mechanism of noradrenaline suppresses the facial stimulation-evoked MLI-PC synaptic transmission in mouse cerebellar cortex *in vivo*

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The noradrenergic afferent from locus coeruleus (LC) modulates cerebellar neuronal circuit via

adrenergic receptors (ARs). However, the mechanism of noradrenaline (NA) modulates molecular interneuron-Purkinje cell (MLI-PC) synaptic transmission in mouse cerebellar cortex is unclear. In this study, we investigated the effect of NA on the facial stimulation-evoked MLI-PC synaptic transmission in urethane-anesthetized mice using in vivo cell-attached recording technique and pharmacological method. The MLI-PC synaptic transmission was induced by air-puff stimulation (duration: 60 ms) of ipsilateral whisker pad, which exhibited negative components (P1 and P2) accompanied with a pause of simple spike. Cerebellar molecular layer application of NA (15 μM) decreased the amplitude and area under the curve (AUC) of P1, and the pause of SS, but increased the P2/P1 ratio. The NA-induced decrease in P1 amplitude was concentration-dependent, and the half-inhibitory concentration (IC_{50}) was 10.94 μM. The NA-induced depression of the facial stimulation-evoked MLI-PC GABAergic synaptic transmission was completely abolished by blockade of α-ARs or α2-AR, but not by antagonist of α1-AR or β-AR. Bath application of α2-AR agonist inhibited the MLI-PC synaptic transmission, as well as occluded the effect of NA on the synaptic response. NA-induced depression of the MLI-PC synaptic transmission was completely blocked by a mixture of α2A- and 2B-AR antagonists, as well as abolished by inhibition of protein kinase A (PKA). In addition, electrical stimulation of molecular layer evoked MLI-PC GABAergic synaptic transmission in the presence of AMPA receptor antagonist, which was inhibited by NA through α2-AR. Our results indicate that NA inhibits MLI–PC GABAergic synaptic transmission by reduction of GABA release via an α2-AR/PKA signaling pathway.

Keywords: Cerebellum, adrenergic receptor; facial stimulation; molecular layer interneuron; Purkinje cell; synaptic transmission; in vivo cell-attached recording; protein kinase A

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P13-15 Mechanism of ganoderma lucidum polysaccharide improves learning and memory impairment in chronic stress rats

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The decline in learning and memory function caused by chronic stress (CS) is the main reason for depression and Alzheimer's disease, which is often overlooked in the early stages.

Ganoderma lucidum polysaccharides (GLP) are the main active ingredients of Ganoderma lucidum, with pharmacological effects such as anti-inflammatory, antioxidant, anti-tumor, and immune regulation. In this study, we investigated the effects and possible mechanism of Ganoderma lucidum polysaccharides on learning and memory function in chronic stress rats. Our results showed a significant decrease in spatial learning and memory abilities in CS rats. The CS-induced impairment of spatial learning and memory abilities was significantly improved by the oral administration of GLP (100mg/kg and 200mg/kg). CS significantly decreased in the expression of p-CREB, BDNF, and p-CAMK II in the DG region of hippocampus, which were significantly reduced by the oral administration of GLP (100mg/kg and 200mg/kg). CS significantly increased the levels of MDA and SOD in the serum, which were dose-dependently decreased by the oral administration of GLP. These results suggest that GLP may alleviate the CS-induced impairment of learning and memory function in rats by reducing free lipid peroxidation and inflammatory response through the CAMK II/CREB/BDNF pathway.

Keywords: Chronic stress, learning and memory, Ganoderma lucidum polysaccharides

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P13-16 Mechanism of ANP regulates CRF-mRNA expressing neuronal activity in mouse hypothalamic PVN *in vitro*

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Abstract: The paraventricular nucleus of hypothalamus (PVN) is an important center for the regulation of sympathetic nerve and cardiovascular functional activities. Atrial natriuretic peptide (ANP) and its receptors are widely distributed in PVN, and contribute to regulation of the various neuronal activity. In this study, we investigated the possible mechanism of ANP on modulation of the PVN CRF-mRNA expressing neuronal activity, by whole cell patch-clamp recording, single-cell reverse transcription-multiplex polymerase chain reaction, biocytin histochemistry and pharmacological methods. Our results showed that ANP significantly inhibited the membrane excitability of PVN CRF-mRNA expressing neurons, which was completely prevented by a ANP

receptor (NPR-A) antagonist, A71915. In addition， ANP significantly increased the amplitude of after-hyperpolarization potential and rectification current in CRF-mRNA expressing neurons. Under voltage-clamp conditions, ANP significantly suppressed hyperpolarization-activated cationic currents (I_H) of the CRF-mRNA expressing neuron, which was abolished by NPR-A receptor antagonist. Importantly, the ANP-induced inhibition of I_H in the CRF-mRNA expressing neuron was abolished by inhibition of protein kinase A (PKA) with KT5720. These results indicate that ANP combine with NPR-A receptor produces an inhibition of the PVN CRF-mRNA expressing neuronal activity through activation of IH channel through PKA signaling pathway.

Keywords: Atrial natriuretic peptide (ANP); Natriuretic peptide receptor A (NPR-A); Paraventricular nucleus of hypothalamus (PVN); Corticotropin releasing factor (CRF); Hyperpolarization-activated cation channels (IH)

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P13-17 混合型阿片类受体激动拮抗药：酒石酸布托啡诺的药理作用以及临床应用进展

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摘要 酒石酸布托啡诺是吗啡喃的衍生物，作为一种新型阿片类受体激动—拮抗药，其是一种高选择性 k 受体激动剂，部分拮抗 μ 受体，对 σ 受体几乎无作用。酒石酸布托啡诺对 k:μ:σ 受体的作用强度分别为 25: 4:1，镇痛效价是吗啡的 5～8 倍，而呼吸抑制仅为吗啡的 1/5。其镇痛效应强，可用于缓解中度至重度疼痛，镇痛时间久，由于布托啡诺主要激动的是 k 受体，对 μ 受体有部分拮抗作用，因此临床上基本不产生药物依赖，并有良好的镇静作用且呼吸抑制和烦躁焦虑情绪发生率较低。

关键词：酒石酸布托啡诺；镇痛；疼痛

P13-18 老年慢性疼痛患者抑郁症研究进展

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研究目的：疼痛是老年人感受最不舒适的疾病，疼痛会导致多种心理问题，如焦虑、抑

郁等。因此，本文旨在探讨老年慢性疼痛患者抑郁症研究进展，进而为慢性疼痛伴抑郁症的诊治提供理论依据。**研究方法：**本文运用文献资料法、逻辑分析法等研究方法，以“老年”、“慢性疼痛”、“抑郁”等作为关键词，收集老年慢性疼痛患者抑郁症研究进展，并对其进行整理分析。**研究结果：**1、症状：慢性疼痛的严重程度与老年抑郁症的发生呈正相关。老年人长期慢性疼痛会产生焦虑、抑郁等各种不良的情感反应，并在一定程度上影响老年人日常生活活动、生活质量。2、机制：慢性疼痛与抑郁之间的关系非常复杂，目前相关机制尚不明确，可能涉及大脑结构、神经递质和信号通路的改变。3、治疗：目前主要是药物治疗和物理治疗。研究发现，度洛西汀与舍曲林均具有较好效果，不良反应少，且度洛西汀起效快。由于药物治疗有副作用，进行 6 周低频调制中频干预可明显改善老年抑郁症状，并减轻其疼痛症状。**研究结论：**慢性疼痛和抑郁密切相关，其机制复杂尚不明确，临床已表明度洛西汀与舍曲林、低频调制中频等治疗均可改善此症状。

关键词：老年人；慢性疼痛；抑郁症

P13-19 经颅磁在缓解神经性疼痛康复中的应用现状

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研究目的：随着人类平均寿命的延长，围绕神经性疼痛的问题也越来越多。这一问题在发展中国家尤其严重，因此研究缓解神经性疼痛的方法具有重要意义。而许多研究发现经颅磁可以缓解神经性疼痛。经颅磁刺激技术（TMS）是一种无痛、无创的绿色治疗方法，它是通过磁信号可以无衰减的透过颅骨传送到大脑皮层，从而刺激大脑神经，提高或降低大脑皮层的兴奋性，从而治疗相应的疾病。因此总结与分析经颅磁在缓解疼痛康复中的应用具有很大的意义。**研究方法：**运用文献资料法、专家访谈法、实地调查法、逻辑分析法等研究方法对经颅磁在缓解疼痛康复中的应用现状进行深入剖析。**研究结果：**1)当 rTMS 作用靶点位于疼痛皮质区邻近区域时,镇痛效果明显优于刺激疼痛皮质区本身,运动皮质和前额叶皮质是 rTMS 治疗 NeP 推荐使用的两个主要刺激部位。2)高频 rT-MS(10 或 20 Hz)较低频 rTMS 镇痛效果好。3)“8”字形刺激器较环形和其他形状刺激器定位更准确,镇痛效果更好。3)rTMS 刺激强度不尽相同,但一般都为 80%~120%RMT,最佳刺激强度还有待进一步研究。**研究结论：**经颅磁在神经性康复中具有广阔的应用前景,但是效果是否具有持续性、其机制还有待进一步研究。

关键词：TMS；神经性疼痛；康复

P13-20 肱骨外上髁炎疼痛治疗的研究进展

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研究目的与方法：肱骨外上髁炎，也称为“网球肘”，其特征是握力下降及肘关节外侧疼痛，主要是由于在各种活动中反复握紧或伸展手腕造成的。本文通过搜索、梳理肱骨外上髁炎相关文献，旨在为肱骨外上髁炎疼痛的治疗提供更多思路。**研究结果：**1.临床诊断：(1)主诉：肱骨外上髁周围疼痛或灼烧，常沿前臂向下辐射，伴有抓握无力。(2)体格检查：通常在外上髁的桡骨短伸肌起源处有明显压痛。Cozen 测试、Mill 试验患者前臂内旋后疼痛加重。2.治疗：(1)动作调整。在抬起时将手掌向上转动并避免手掌向下运动，将力从外上髁转移到内上髁，有助于缓解疼痛。(2)物理治疗。如推拿，旨在通过拉伸腕伸肌来改善功能并减轻疼痛。(3)消炎药物。皮质类固醇注射可短期缓解疼痛。(4)反力支撑。使用反力支具压迫前臂伸肌，抑制和分散受累桡侧腕短伸肌起源处的压力可以显著缓解疼痛。(5)体外冲击波治疗。体外冲击波治疗对伤害感受器的直接抑制作用以及阻断门控制的过度刺激，从而缓解疼痛。(6)针灸。针刺在短期内对缓解肱骨外上髁炎疼痛非常有效。(7)富血小板血浆(PRP)注射液。有研究表明其可缓解疼痛、改善功能。**研究结论：**肱骨外上髁炎患者的主要治疗方法为非手术治疗，这些治疗对于缓解疼痛有明显效果。

关键词：肱骨外上髁炎；疼痛；消炎

P13-21 The Lysine-specific demethylase 1 in medial prefrontal cortex facilitates chronic stress–induced pain and emotional dysfunction in female mice

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Abstract ： Epigenetic modifications including DNA methylation, histone acetylation/methylation, and non-coding RNAs in the central nervous system (CNS) have been

convincingly implicated in the development of chronic pain and psychiatric disorders such as anxiety and depression. However, knowledge of the histone demethylation mechanisms underlying chronic pain and emotional dysfunction in the CNS is limited. Here, we investigated the role of lysine-specific demethylase 1 (LSD1, also known as KDM1A), a histone demethylase, in medial prefrontal cortex (mPFC) under chronic stress-induced pain and anxiety, depression.

Methods: Male and female KDM1A$^{fl/fl}$ mice were used for conditional knockout of LSD1, and female C57BL/6 wild-type mice were used in experiments for LSD1 overexpression and for chronic stress to build pain and anxiety, depression model. We established a female animal model of chronic widespread pain and anxiety, depression-like behavior via 21 days of chronic heterotypic stress. The chronic stress protocol included 3 randomly arranged stressors: forced swim stress (FSS), water avoidance stress (WAS), or restraint stress (RS). Paw withdrawal frequency and head withdrawal threshold to von Frey filaments were used to assess pain. Elevated plus maze (EPM) and open field tests (OFT), immobility time and sucrose preference tests (SPT) were used to evaluate the anxiety- and depression-like behaviors, respectively. Western blotting and qPCR were used to detect the expression levels of LSD1 in the mPFC.

Results: The results showed that conditional knockout of LSD1 in the mPFC exacerbated pain sensitivity both in the hindpaw and orofacial regions of female mice, while only facilitating hindpaw pain in male mice. The anxiety- and depression-like behaviors also occurred in the conditional knockout female but not male mice by showing decreased the distance and time spent in the open area of the OFT and in the open arms of the EPM, as well as reduced the sucrose preference in the SPT. In wild-type female mice, chronic stress significantly increased pain sensitivity in orofacial area and hindpaw, anxiety and depression-like behaviors, as well as reduced both mRNA and protein levels of LSD1 in the mPFC. Overexpression of LSD1 in the mPFC reversed the decrease of mRNA and protein levels of LSD1 induced by 21-day chronic stress, alleviated chronic stress-induced chronic pain, anxiety- and depression-like behaviors in female mice, but did not have any effects on basal pain and emotional conditions in naïve female mice.

Conclusion: Chronic stress leads to downregulation of LSD1 in the mPFC, thereby facilitating pain and emotional dysfunction with a sex-specific pattern. This study reveals LSD1 as a critical regulator of epigenetically modulating gene expression in chronic stress-induced chronic pain conditions and emotional dysfunction.

Keywords： Lysine-specific demethylase 1; Medial prefrontal cortex; Chronic pain; Stress; Anxiety; Depression.

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P13-22 Upregulation of KDM6B aggravates inflammatory pain through H3K27me3 demethylation-dependent production of TNF-α in the dorsal root ganglia and spinal dorsal horn in rats

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Aims: Lysine specific demethylase 6B (KDM6B) serves as a key mediator of gene transcription. It regulates expression of proinflammatory cytokines and chemokines in variety of diseases. Herein the role and the underlying mechanisms of KDM6B in the inflammatory pain were studied.

Methods: The inflammatory pain was determined by assessing paw withdrawal threshold (PWT) and paw withdrawal latency (PWL) following intraplantar injection of complete Freund's adjuvant (CFA) in rats. Immunohistochemistry, Western blotting, qRT-PCR, and chromatin immunoprecipitation (ChIP)-PCR assays were performed to investigate the underlying mechanisms.

Results: CFA caused a significant upregulation of KDM6B and decrease in the level of H3K27me3 in the dorsal root ganglia (DRG) and spinal dorsal horn. The mechanical allodynia and thermal hyperalgesia following CFA were alleviated by the treatment of intrathecal (i.t.) injection of GSK-J4. Microinjection of AAV2-EGFP-KDM6B shRNA in the sciatic nerve or in lumbar 5 spinal dorsal horn prevented the reductions of PWT and PWL following CFA. Moreover, CFA-induced increase in the production of tumor necrosis factor-α (TNF-α) in the DRGs and spinal dorsal horn was inhibited by these treatments. ChIP-PCR assay showed that CFA-induced increased binding of nuclear factor kappa-B (NF-κB) with TNF-α promoter was repressed by microinjection of AAV2-EGFP-KDM6B shRNA in the dorsal horn.

Conclusions: These results suggest that upregulated KDM6B via facilitating TNF-α expression in the DRG and spinal dorsal horn aggravates inflammatory pain.

Keywords: KDM6B, inflammatory pain, spinal cord, dorsal root ganglia, TNF-α, epigenetics

P13-23 Spinal cord injury enhances complex spike activity of cerebellar purkinje cells in mice *in vivo*

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Spinal cord connects with cerebellum via mossy fibers, which receives information from spinal cord and modulates motor coordination. Previous evidence indicated that spinal cord injury (SCI) could alter the structure and function of cerebellar neural circuits, suggesting that SCI may influence the complex spike (CS) of cerebellar Purkinje Cell (PC). We here employed in vivo cell-attached recording technique and neuropharmacological methods to investigate the effect of SCI on the spontaneous CS firing activity of PCs in mouse cerebellar cortex. Under current-clamp mode, the number of CS spikelets and pause in the SCI group was significantly different than that in the control (Sham) group. Administration of the mGluR1 blocker, JNJ16259685, and the NOS inhibitor, L-NNA, had no significant effect on the CS activity of the PCs in SCI mice. However, administration of the nonselective CRF receptor inhibitor a CRF receptor antagonist, alpha-helical significantly reduced the number of spikelets, area under the waveform, and pause of SS in the cerebellar PCs in SCI group but not in control group. Furthermore, the CS discharge activity of PCs in SCI mice was significantly inhibited by application of a specific CRF-R2 blocker, Antisauvagine-30, but not by a specific CRF-R1 blocker, BMS-763534. Moreover, administration of CRF significantly enhanced the CS discharge activity of PCs in Sham mice. These results indicate that CRF enhances CF-PC synaptic transmission in the cerebellar cortex of SCI mice via CRF-R2, which is independent of GABAA, NMDA, mGluR1, and NO.

Keywords: spinal cord injury, cerebellar Purkinje cells, complex spike, corticotropin-releasing factor, in vivo electrophysiological cell-attached recording

P13-24 Effects of different decibel noise exposure on pain sensitization in chronic migraine model rats

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Objective: To observe the effects of different decibel noise exposure on pain sensitization in

chronic migraine rats induced by nitroglycerin. **Methods:** Forty adult male SD rats were randomly divided into control, model, +5db, and +40db groups (n=10 each group). The control group and model group rats were naturally exposed to environmental noise of 50dB, while the +5dB and +40dB groups rats were exposed to increased noise of 5dB and 40dB. Except for the control group, the rats in each group were given 10 mg/kg nitroglycerin (s.c., qod, 9 days) in the neck back to prepare chronic migraine model, while the rats in the control group were injected with the same volume of normal saline. The paw withdrawal mechanical threshold (PWMT) and tail-flick latency (TFL) were measured in observing rats before and after modeling by using the Von Frey Filaments and rat tail light pain detector when the light intensity was set to 15, 23, 34, 51, 76 Focus value. After modeling, rats were exposed to noise for 3 days, 20 minutes per day. After exposure, PWMT and TFL were detected in all 4 groups of rats. **Results:** ①After the injection of nitroglycerin, the rats had red ears, frequent head scratching (P<0.01), and increased the number of turns (P<0.01). In the process of modeling (1-9 days), the number of head scratching decreased (P<0.01), and the activity decreased (P<0.01). ② The PWMT of rats in each group after modeling not only decreased compared to that before modeling (P<0.01), but also decreased compared to the control group (P<0.01). However, the PWMT of rats in the +5db group increased after exposure to +5db noise (P<0.01), and was higher than that of the model group (P<0.01). The PWMT of the +40db group rats was similar to that of the model group (P>0.05), and lower than that of the +5db group (P<0.01). ③The comparison of TFL before and after noise exposure showed that the TFL of the +5db group rats was prolonged after exposure at a light intensity of 34 Focus (P<0.05). The TFL of four groups of rats showed a timed dose-response relationship (TDRR, P<0.05) that shortened with the increase of light stimulation intensity before and after modeling and exposure. **Conclusions:** The rat model of chronic migraine can be established by injecting nitroglycerin every other day. Noise exposure of 5 decibels higher than ambient noise has some relief on pain sensitization caused by chronic migraine.

Keywords: Chronic migraine; Nitroglycerin; Pain sensitization; Noise exposure; rat

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P13-25 Activation of 5-HT_{1A} receptors alleviates the neuropathic pain-induced depression through GABAergic neurons in the ventrolateral orbital cortex

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The depression frequently occurs in patients with neuropathic pain, and the underlying mechanism is unclear. The ventrolateral orbital cortex (VLO) is involved in modulating neuropathic pain, anxiety, and depression. Serotonin (5-HT) influences the activity of VLO neurons through its different receptors to modulate pain. Among the seven classes of 5-HT receptors, 5-HT_{1A} receptors have emerged as a promising therapeutic target for treatment of depression. Previous studies in our lab have shown that activation of 5-HT_{1A} receptors in the VLO exhibits analgesia. However, the involvement of VLO 5-HT_{1A} receptors in the comorbidity of neuropathic pain and depression is unclear. Therefore, the present study is aimed at unveiling the role of 5-HT_{1A} receptors in the neuropathic pain-induced depression in the VLO. The depression-like behaviors in rats were detected in sucrose preference test (SPT) and forced swim test (FST). By using the rat spared nerve injury (SNI) pain model, the effect of 5-HT_{1A} receptors in the neuropathic pain-induced depression was identified by microinjection of selective 5-HT_{1A} receptor agonist 8-OH-DPAT and antagonist NAN-190 in the VLO. Microinjection of the 8-OH-DPAT into the contralateral VLO significantly alleviated the depression-like behaviors of SNI rats in SPT and FST, which were blocked by previous microinjection of the NAN-190. The antagonist applied alone had no effect on the depression-like behaviors. In addition, the expression level of 5-HT_{1A} receptor protein decreased in the contralateral VLO in SNI rats with depression. The overexpression of VLO 5-HT_{1A} receptors on the GABAergic neurons in SNI rats by using adeno-associated virus (AAV) reduced the depression-like behaviors, whereas the knockdown of VLO 5-HT_{1A} receptors on the GABAergic neurons in wild type rats acted depression-like behaviors. These results indicated that 5-HT_{1A} receptor activation-evoked antidepressant effects were mediated by GABAergic neurons in the VLO. We also found the 8-OH-DPAT-induced antidepressant effects were blocked by previous depression of the GABAergic neurons in the VLO through chemogenetics methods. Furthermore, the VLO application of the $GABA_A$ receptor antagonist bicuculline (100 ng) enhanced the 8-OH-DPAT-induced inhibition of depression-like behaviors, whereas the $GABA_A$ receptor agonist muscimol (250 ng) attenuated the 8-OH-DPAT-induced inhibition. These results further demonstrated the GABAergic disinhibitory mechanisms participate in the 5-HT_{1A} receptors-mediated effects on the neuropathic pain-induced depression. These findings provide support for the hypothesis that 5-HT_{1A} receptor activation may inhibit the inhibitory action of the GABAergic neurons in the VLO to produce attenuated effects on the neuropathic pain-induced depression.

Keywords: Neuropathic pain; depression; 5-HT_{1A} receptor; ventrolateral orbital cortex; GABAergic neurons

P13-26 Hemoglobin α derived peptides VD-hemopressin (α) and RVD-hemopressin (α) are involved in electroacupuncture inhibition of chronic pain

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Knee osteoarthritis (KOA) is a chronic degenerative bone metabolic disease that primarily affects elderly adults, leading to chronic pain and disability which affects patients' daily activities. Electroacupuncture (EA) is a commonly used method for the treatment of chronic pain in clinical, but the mechanism not fully understood. VD-hemopressin (α) and RVD-hemopressin (α) are endocannabinoid peptide ligands, which are derived from the hemoglobin α chain. In the present study, We used RNA-seq sequencing technology to obtain differentially expressed genes *Hba-a1* and *Hba-a2* involved in EA analgesia in the periaqueductal grey (PAG), which were translated into hemoglobin α chain. Further research found that EA can significantly increased the expression of hemoglobin α chain and the level of hemopressin (α) and RVD-hemopressin (α) in the PAG with KOA mice. We have also proved that vlPAG microinjection VD-hemopressin (α) and RVD-hemopressin (α) mimicked the analgesic effect of EA. Moreover, EA significantly increased the expression of 26S proteasome in the PAG. Microinjection of 26S proteasome inhibitor MG132 before EA, which prevented both anti-allodynic effect and up-regulation the concentration of RVD-hemopressin(α) by EA treatment, and up-regulated the expression of hemoglobin α chain. Our data suggest that EA up-regulated the concentration of VD-hemopressin(α) and RVD-hemopressin(α) through promoting the degradation of hemoglobin α chain by 26S proteasome in PAG, thereby exerting chronic pain inhibition in a mouse model of KOA.

Key words: Knee osteoarthritis (KOA); Electroacupuncture analgesia; hemopressin (α); 26S proteasome; Chronic pain

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P13-27 The RNA demethylase ALKBH5 in the spinal cord promotes neuropathic pain via NMDA receptor GluN2B

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Background: Neuropathic pain is clinically refractory pain. Drugs for neuropathic pain are limited and not adequately relieve pain. Alkylation repair homolog protein 5 (ALKBH5) has demethylation activity against N6-methyladenosine (m6A). ALKBH5 is known to alter the m6A level of mRNA associated with synaptic plasticity and affect synaptic plasticity. This study aims to explore the role of ALKBH5 in neuropathic pain and its regulatory mechanisms.

Methods: In this study, spinal nerve ligation (SNL)-induced neuropathic pain mice model was established. Different viruses were microinjected into spinal dorsal horn to knockdown or overexpress ALKBH5 in spinal cord. Pain behaviors were examined by von Frey test and Hargreaves' test. The ALKBH5 and GluN2B expression and regulatory mechanism was examined by immunofluorescence and Western blotting.

Results: ALKBH5 was upregulated in the ipsilateral L4 spinal cord on day 14 and day 28 after SNL surgery. GluN2B was also upregulated on day 28 after SNL surgery. The ALKBH5-positive signals were found in spinal cord neurons and colocalized with GluN2B in spinal cord dorsal horn neurons. Knockdown of ALKBH5 in spinal neurons by AAV-hSyn-cre reduced SNL-induced pain hypersensitivity and decreased expression of ALKBH5 and GluN2B in spinal cord. AAV-hSyn-cre also decreased synaptic ALKBH5 and GluN2B protein levels in spinal cord. Overexpression of ALKBH5 in spinal neurons induced pain hypersensitivity in naive mice and increased expression of ALKBH5 and GluN2B in spinal cord.

Conclusions: Our data indicates that SNL-induced upregulation of ALKBH5 expression in the spinal cord contributes to neuropathic pain via manipulating synaptic GluN2B expression. ALKBH5 may become a potential target for the treatment of neuropathic pain.

Keywords: Spinal cord dorsal horn, Neuropathic pain, ALKBH5, m6A demethylation

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P14 生殖生理

P14-1 生物钟在 PCOS 排卵障碍中的作用及机制研究

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多囊卵巢综合征（polycystic ovary syndrome, PCOS）是最常见的引起育龄期女性不孕的内分泌及代谢紊乱性疾病。其主要临床表现包括月经稀发、闭经，高雄激素，以及超声下卵巢多囊样表现。既往研究发现环境因素在 PCOS 发生发展过程中发挥重要作用。地球自转产生的昼夜节律通过生物体内的自主计时机制——生物钟——参与调节女性月经周期、排卵、胚胎着床及妊娠维持等一系列过程。生物钟紊乱与生育力降低密切相关。

本研究采用雌性 SD 大鼠，分别以正常昼夜节律或持续黑暗处理一段时间。研究结果表明，黑暗组大鼠动情周期异常，卵巢局部呈多囊样改变，且超促排卵后获卵数、M II 卵率显著降低，获得异常卵率与对照组相比呈上升趋势。这提示黑暗组大鼠存在排卵障碍等类 PCOS 表现。其次，通过收集两组大鼠卵巢颗粒细胞（GCs）并行 RNA-sequence 分析，结果显示黑暗组卵巢 GCs 中血管紧张素肽原（AGT）表达量明显高于对照组，q-RT PCR 分析验证了这一测序结果。进一步地，研究人员收集、分离 PCOS 患者与对照组女性优势卵泡液、GCs 后检测 AGT 表达水平，结果显示 PCOS 患者的 GCs 与卵泡液中 AGT 含量均显著高于正常对照组女性。此外，将 AGT 含量与入组女性临床指标作相关性分析，发现 AGT 水平与 LH、AMH 水平呈正相关联系。体外实验证实过表达 AGT 导致排卵相关基因表达量降低，而敲低 AGT 后出现相反现象。这提示 AGT 在生物钟异常引起的排卵障碍过程中存在重要作用。

综上所述，本项研究发现生物钟紊乱会引起排卵障碍等 PCOS 相关临床表现，与女性生育力降低密切相关。AGT 表达量升高在排卵障碍病理生理过程中发挥重要作用，其机制有待深入研究。靶向 AGT 及针对生物钟紊乱的干预手段探索将有益于提升 PCOS 临床诊疗效果，推动相关研究的临床转化。

关键词：多囊卵巢综合征，生物钟，排卵障碍，血管紧张素肽原

P14-2 Sertoli cell-only phenotype and scRNA-seq reveal hnRNPU as a regulator required for spermatogonial stem cell pool establishment in mice

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The continuous regeneration of spermatogonial stem cells (SSCs) underpins spermatogenesis and lifelong male fertility; however, little is known about the developmental origins of the SSC pool. Here, we document that heterogeneous nuclear ribonucleoprotein U (hnRNPU) is essential for establishing the SSC pool. In male mice, conditional loss of hnRNPU in prospermatogonia (ProSG) arrests spermatogenesis and results in sterility, characterized by complete loss of germ cells around postnatal day 10, which resembles the Sertoli cell-only phenotype in humans. hnRNPU-deficient ProSG fails to differentiate and migrate to the basement membrane to establish SSC pool in infancy. Moreover, we find that the deletion of hnRNPU leads to the accumulation of ProSG and the reduction of spermatogonia and further disrupts the process of T1-ProSG to T2-ProSG transition. hnRNPU-deficiency in ProSG deregulates the expression of spermatogenic-related genes and destroys the alternative splicing of genes related to cell cycles, and single-cell transcriptional analyses reveal germ cells are in a mitotically quiescent state and lost their unique identity upon hnRNPU deletion. We further show that hnRNPU could interact with DDX5, SRSF3, and TRIM28 proteins and bind to *Vrk1*, *Slx4*, and *Dazl* transcripts with identified to be suffered aberrant alternative splicing in hnRNPU-deficient testes. These observations give important insights into SSC pool establishment and may have translational implications for male fertility.

Keywords: hnRNPU, Prospermatogonia, Spermatogonial stem cells, Alternative splicing, Single-cell RNA-seq

P14-3 节律紊乱通过降低 SERPINE1 基因甲基化促进 PCOS 高雄激素血症

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目的：多囊卵巢综合征 (PCOS) 是女性不孕症的主要原因之一，长期威胁女性生殖健康。高雄激素血症作为 PCOS 的重要特征在该病发展中起关键作用，但机制未明。已有证据表明节律紊乱与 PCOS 的发生发展密切相关。课题组前期研究显示，持续黑暗造模 8 周造成大鼠昼夜节律紊乱，导致大鼠出现高雄激素血症表型。但其中的分子机制尚不清楚。因此，本课题拟从 DNA 甲基化层面探索节律紊乱造成高雄激素血症的发病机制，并针对表观遗传学修饰寻找 PCOS 有效的干预及治疗新方法。

方法：利用雌性 SD（Sprague-Dawley）大鼠构建持续黑暗的节律紊乱大鼠模型，每两周处死黑暗组及对照组并留取卵巢颗粒细胞，进行大鼠靶向序列 DNA 甲基化捕获测序及转录组测序并进行联合多组学分析。在体外试验中，利用大鼠原代颗粒细胞、人颗粒细胞系 KGN 及大鼠正常肝细胞细胞系 BRL-3A，采用焦磷酸盐测序、CRISPR-dCas9、基因敲低、基因过表达、相关酶抑制剂和 ELISA 等技术进行深入的机制研究。在体内实验中，通过构建 SERPINE1 抑制剂干预模型，探究其对改善 PCOS 高雄激素血症的作用。

结果：持续黑暗可以致大鼠出现类 PCOS 的高雄激素血症。甲基化捕获测序及 RNA 测序结果显示黑暗造模引起的变化主要集中在神经、代谢和炎症途径上。联合分析四个候选基因 Serpine1、Il2、Agt、Lep。其中，Serpine1 与血清睾酮高度相关。焦磷酸测序证实黑暗造模的大鼠卵巢颗粒细胞 Serpine1 启动子区存在低甲基化，甲基化抑制剂及 CRISPR-dCas9 证实该低甲基化可造成 Serpine1 基因高表达。细胞实验发现 SERPINE1 通过 PI3K/AKT 途径抑制芳香化酶的表达并促进雄激素的积累。动物实验发现 SERPINE1 抑制剂 Tiplaxtinin 能有效改善 DHEA 大鼠及持续黑暗大鼠的高雄激素血症。

结论：研究首次解析了 SERPINE1 及其 DNA 甲基化在高雄激素血症中的作用机制，发现 SERPINE1 启动子区低 DNA 甲基化造成基因高表达。而高水平的 Serpine1 通过 PI3K/AKT 通路抑制芳香化酶的表达，雄激素向雌激素转化受阻，造成外周血雄激素水平升高，最终导致持续黑暗大鼠的高雄激素血症。SERPINE1 抑制剂可以作为 PCOS 治疗高雄激素血症的潜在药物。

关键词：多囊卵巢综合征；高雄激素血症；颗粒细胞；DNA 甲基化

P14-4 Effects of genistein combined with mifepristone on uterine leiomyoma model rats

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Objective: To investigate the effects of genistein combined with mifepristone on uterine leiomyoma model rats. **Methods:** Fifty-five female SD rats were randomly divided into normal

group (*n=11*) and modeling group (*n=44*). The rats in the modeling group were induced by estrogen and progesterone to prepare the uterine leiomyoma model rats.After modeling, 44 modeling rats were randomly divided into model, genistein, mifepristone, and combined groups (*n=11*). The rats were treated with genistein (20mg/kg) and mifepristone (2.24mg/kg) for 25 days respectively.The behavioral changes were observed and the bilateral uteri were taken to observe the gross morphological changes, calculate the uterine coefficient, and observe the histopathological changes. **Results:** ① After modeling, compared with normal group, the rats in model group had abnormal behavioral changes, increased uterus coefficient, and tumor-like changes. Compared with model group, the rats in drug intervention groups showed the improved behavior, the decreased trend of uterine coefficient, which was even lower than that of the normal group, especially in the combined group. ② Compared with the normal group, the uterine wall thickness was significantly increased, the tumor hyperplasia was obvious, and the thickness of the uterine smooth muscle layer was increased in model group (*P<0.05*). Compared with model group, the drug intervention could improve the pathological morphology of the uterine tissue, reduce the thickness of the uterine wall and the thickness of the uterine smooth muscle layer, especially in the combined group *(P<0.05*). ③ Compared with normal group, the uterine smooth muscle of the model group was significantly hyperplasia, hypertrophy, and disordered arrangement (*P<0.01*). Compared with model group, the smooth muscle of the drug intervention group was significantly thinner, and the hyperplasia and hypertrophy of muscle fibers and disorder of arrangement were alleviated (*P<0.01*), and the improvement in the combined group was the most significant. **Conclusion:** Genistein combined with mifepristone can improve the behavioral activities and inhibit the proliferation of uterine leiomyoma induced by estrogen and progesterone in rats.

Key words: Genistein; Mifepristone; Uterine leiomyoma; Behaviors; Histomorphology

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P14-5 TNFα-GSDME mediated pyroptosis in placental trophoblast contributes to systemic inflammation in EOPE patients

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Early onset preeclampsia (EOPE) is often considered to be associated with placental pathology, but direct evidence for this is currently lacking. In this study, we utilized a highly sensitive and specific proximity extension assay technology to measure the expression of 1536 proteins in the plasma/serum of pregnant women between gestation weeks 12-16 who were subsequently diagnosed with EOPE (n=7) and normal pregnant controls (n=7). We identified 158 differentially expressed protein markers between the EOPE and control groups, with a significant increase observed in apoptotic pathway proteins such as Bax, Caspase 3, and Caspase 8, as well as inflammatory-related proteins such as IL8, IL18, and TNFα in the EOPE group. These findings were further reflected in the placenta of PE subjects through Luminex assay. To determine the contribution of the maternal or fetal part of the placenta to the systemic inflammation, we utilized an apoptotic inducer, TNFα plus SM164, to trigger apoptosis in either stromal or trophoblast cells. Interestingly, we found that TNFα induced classical apoptosis in stromal cells through the bax-caspase3-cleaved caspase 3 cascade, while in trophoblast cell lines, it induced pyroptosis by cleaving GSDME, leading to cell swelling, rupture, death, and increased LDH release. Flow cytometry using the LEGENDplex™ inflammation panel confirmed that the increased inflammation was dependent on GSDME, as knockdown of this protein reversed the expression levels of inflammation-related proteins. Interestingly, targeting GSDME by GUTE or GLP-1 reduces inflammation in trophoblast cell lines and EOPE placenta derived organoids. Our findings provide genetic evidence supporting the role of trophoblasts in mediating systemic inflammation and highlight the potential of targeting the Caspase3-GSDME pathway as a therapeutic strategy for EOPE patients.

P14-6 A gonadal gap junction/notch signaling axis suppresses gut defense through an intestinal lysosome pathway

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Gap junctions mediate intercellular communications across cellular networks in the nervous

and immune systems. Yet their roles in intestinal innate immunity are poorly understood. Here, we show that the gap junction/innexin subunit *inx-14* acts in the *C. elegans* gonad to attenuate intestinal defenses to *Pseudomonas aeruginosa* PA14 infection through the PMK-1/p38 pathway. RNA-Seq analyses revealed that germline-specific *inx-14* RNAi downregulated GLP-1/Notch signaling, while lysosome and PMK-1/p38 pathways were upregulated. Consistently, disruption of *inx-14* or *glp-1* in the germline enhanced resistance to PA14 infection and upregulated lysosome and PMK-1/p38 activity. We show that lysosome signaling functions downstream of the INX-14/GLP-1 signaling axis and upstream of PMK-1/p38 pathway to facilitate intestinal defense. Our findings expand the understanding of the links between the reproductive system and intestinal defense, which may be evolutionarily conserved in higher organism.

Keywords: Reproductive tract, Gap junction, Gut defense, Notch signaling, Lysosome pathway

P14-7 HnRNPK regulates the spermatogonia differentiation and meiosis initiation by interact with DAZL and MILI in male mice

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Sequential mitotic and meiotic cycles are essential prerequisites for germline development and male fertility. Nevertheless, our comprehension of the mechanisms governing spermatogonial differentiation and meiotic initiation in mammals is still insufficient. Here, we employ a specialized knockout mouse model to elucidate the crucial role of heterogeneous nuclear ribonucleoprotein K (hnRNPK) in spermatogenesis and male fertility. Specifically, adult mice with germline-specific *Hnrnpk* deletion exhibit a complete infertility, characterized by the absence of sperm within epididymis and the presence of some Sertoli cell-only seminiferous tubules. Subsequent

investigations demonstrate that hnRNPK knockout impedes spermatogonia differentiation and meiosis initiation. Blockage of spermatogonia differentiation leads to increased number of undifferentiated spermatogonia in pubertal mice and decreased number in adult mice. Meiosis initiation is disrupted, as c-KIT positive cells are unable to enter meiotic process normally. Consequently, within the seminiferous tubules, an almost complete absence of spermatocytes is evident, with only a few pre-leptotene spermatocytes. By means of mass spectrometry and RIP-seq analysis, we prove hnRNPK can interact with DAZL and MILI to promote spermatogenesis. These proteins are recognized as facilitators of the progression of spermatogonial differentiation and meiosis initiation. Further analysis shows that hnRNPK establishes extensive bindings with RNA of numerous genes within c-KIT^{+} germ cells, orchestrating RNA functionality and actively participating in the process of germ cell development. This study effectively highlights the critical role of hnRNPK, binding with DAZL and MILI, collectively exerting a central regulatory role in the differentiation of mammalian spermatogonia and the initiation of meiosis.

Keywords: hnRNPK, spermatogonia differentiation, meiosis initiation, male fertility

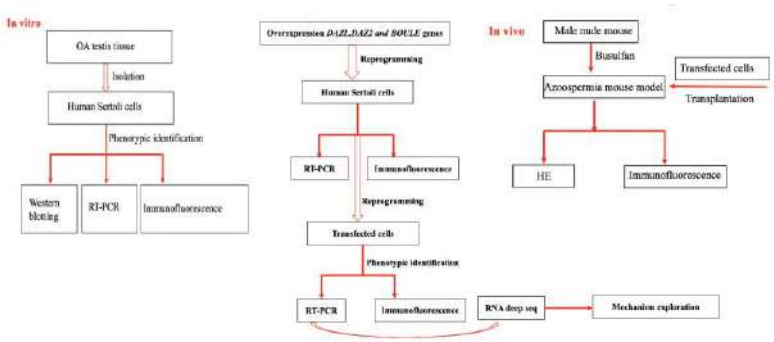
P14-8 RAD21L1 调控过表达 *DAZ* 家族基因重编程人支持细胞为精原干细胞的分子机制研究

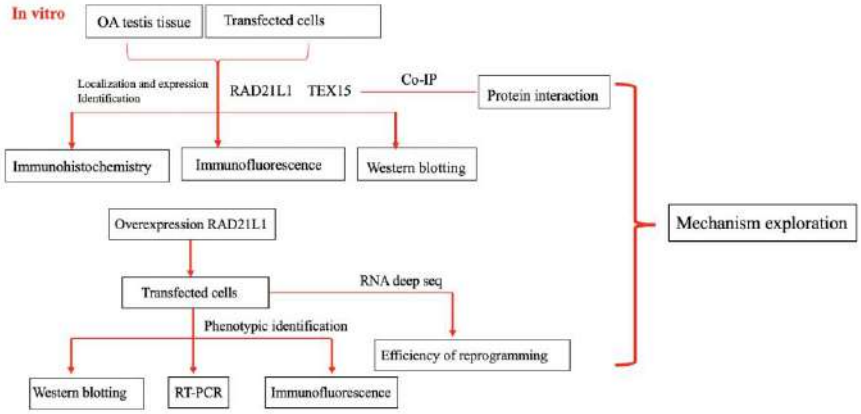
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目的：由于环境因素、不良生活方式、感染、遗传因素等交互影响，不育症已经成为严重影响人类生殖与人口健康的重大疾病。因此，如何获得有功能的男性配子是解决男性不育的一个重大科学问题。我们将揭示跨越体细胞如何通过重编程为生殖细胞的桥梁，阐明人类支持细胞重编程为有功能的精子细胞的基因调控重编程的分子机制，为无精子症患者提供单倍体配子精子细胞提供科学依据,为体细胞重编程为生殖细胞和男性不育患者单倍体配子解决科学问题。为体细胞重编程成为生殖细胞、男性精子发生提供新的遗传与表观遗传调控机理。

材料与方法：





结果：体内外实验证实过表达 *DAZ* 家族基因的质粒重编程 Sertoli cells 为人精原干细胞（SSCs）：（1）体外实验通过 WB,RT-PCR,IF 等实验技术检测 DAZL-gene transfected cells 表达 SSCs 标记分子 GFRA1、GPR125、UCHL1、PLZF、MAGEA4、RET、SV40；体内实验 WB,RT-PCR,IF 发现 DAZL-gene transfected cells 具有增殖和分化的能力；**（2）**通过 RNA-seq 测序发现 DAZL-gene transfected cells 与 Sertoli cells 转录组水平完全不同，差异上调基因 901 个，并且发现 DAZL-gene transfected cells 与 SSCs 转录组水平共表达 GFRA1、GPR125、UCHL1、PLZF、MAGEA4、RET、SV40；同时发现在睾丸组织和 SSCs 高表达的 *RAD21L1* 基因。将 RAD21L1 过表达后重编程 Sertoli cells 为 RAD21L1-gene transfected cells：（1）首先体外实验通过 WB,RT-PCR,IF 等实验技术检测 RAD21L1-gene transfected cells 表达 SSCs 标记分子 GFRA1、GPR125、UCHL1、PLZF、MAGEA4、RET、SV40；**（2）**然后 RNA-seq 测序 RAD21L1-gene transfected cells 与 Sertoli cells 转录组水平不同，并且上调的差异基因有干性维持相关基因 *OCT4* 和 *LIN28A* ，重编程标记分子基因 *ESRRB*，DNA 甲基化相关基因 *DNMT1* 等重要基因。下一步 WGBS 测序发现 RAD21L1-gene transfected cells 组中发生 DNA 甲基化显著高于 Sertoli cells。

结论：RAD21L1 通过调控 DNMT1 发生 DNA 甲基化提高重编程的效率，将体细胞重编程为人精原干细胞。

P14-9 Single-cell transcriptome characteristics of testicular terminal epithelium lineages during aging in the *Drosophila*

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Aging is a complex biological process leading to impaired functions, with a variety of hallmarks. In the testis of *Drosophila*, the terminal epithelium region is involved in spermatid release and maturation, while its functional diversity and regulatory mechanism remain poorly understood. Herein, we conducted single-cell RNA-sequencing analysis on testes at 2, 10, and 40 Days. Terminal epithelium populations were identified using the *MtnA* gene, and a series of marker genes were identified based on their expressions in novel sub-cell clusters (EP0–EP5). The data revealed the functional characteristics of terminal epithelium populations, such as tight junction, focal adhesion, bacterial invasion, oxidative stress, mitochondrial function, proteasome, and apoptosis. Importantly, we also discovered a series of age-biased genes via expression trend analysis and identified many state-biased genes via pseudotime trajectory analysis during terminal epithelium aging. Several common signatures (e.g., mitochondria-related events, protein synthesis and degradation-related processes, and metabolic processes) were revealed by analysis of differentially expressed genes for the majority of terminal epithelium populations during aging. Surprisingly, we noted that genes biased in all the sub-cell clusters of young TE populations had higher ratio of non-synonymous to synonymous substitutions than those in old TE populations, indicating that young age-biased genes in epithelial cells evolved rapidly and were endowed with greater evolutionary advantages. Single-cell RNA-sequencing analysis revealed the diversity of testicular TE populations, providing a gene target resource for further systematic research of their functions during aging.

Keywords: Aging; Terminal epithelium; Single-cell RNA-sequencing; *Drosophila*; Testis

P14-10 CBS-线粒体转位介导 Miro2 硫巯基化修饰调控滋养细胞侵袭及其机制研究

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子宫螺旋动脉重铸不足（Insufficient Spiral Artery Remodeling）是自发性流产、子痫前期、胎儿宫内发育迟缓等妊娠相关疾病的共同病理表现，是导致胎盘缺血缺氧的重要病理因素。绒毛外滋养细胞（Extravillous Cytotrophoblast，EVT）是介导妊娠期子宫螺旋动脉重铸的主要效应细胞，子痫前期中 EVT 细胞向母体子宫肌层的侵袭显著减少。但是 EVT 侵袭的分子机制尚不明确。所以，阐明 EVT 向子宫侵袭的分子机制及其调控机理，为临床子痫前期等疾病提供新的干预靶点和治疗策略，这对降低母婴死亡率、减轻社会医疗负担具有重要意义。

材料及研究方法：本研究通过正常妊娠和子痫前期胎盘组织标本及体外细胞模型实验，通过免疫荧光，活细胞线粒体成像及追踪，蛋白质谱分析及蛋白修饰位点质谱分析，小干扰 RNA 技术，透射电镜，transwell，H2S 探针标记等技术，针对性验证 H2S 促进 CBS-线粒体转位及滋养细胞侵袭；线粒体 CBS/H2S 介导 Miro2 硫巯基化，后者调控线粒体结构和功能并促进滋养细胞侵袭。

研究结果：子痫前期（PE）患者血浆 H2S 含量较正常妊娠女性显著降低；同时胎盘组织及 EVT 中 CBS 特异性表达显著降低。而 si-RNA 敲减滋养细胞系 HTR-8/SVneo 中 CBS，抑制该细胞侵袭和迁移；外源性 H2S 供体 GYY4137 逆转上述 si-CBS 所致的细胞迁移和侵袭的降低作用，并促进 CBS 在线粒体聚集。Si-CBS 同时导致线粒体数量增加，长度变短及碎片化增加;GYY4137 可以改善 si-CBS 所致的线粒体形态变化。蛋白修饰位点质谱分析发现，GYY4137 促进 HTR-8/SVneo 细胞线粒体 Rho GTP 酶 2（Mitochondrial Rho GTPase，Miro2）第 185 位半胱氨酸（C185）硫巯基化修饰，点突变 Miro2C185 后，CBS/H2S 促进线粒体形态、功能及滋养细胞侵袭的作用消失。

结论：以上结果提示，H2S 通过促进 CBS 向线粒体转位，CBS 局部释放 H2S 并促进 Miro2 C185 硫巯基化，增强滋养细胞侵袭及迁移功能。因此，CBS-线粒体转位介导 Miro2 硫巯基化修饰调控滋养细胞侵袭及迁移，该机制为揭示滋养细胞侵袭和迁移提供新的理论支持，为临床防治子痫前期等疾病提供新的作用靶点。

关键字：子痫前期 线粒体转位 CBS H2S Miro2

P14-11 The Rose26 locus is inactive in the spermatogenesis of C57BL/6 mice

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Background and Objective: The mouse *Rosa26* locus demonstrates ubiquitous transcriptional activity while encoding LncRNAs of no functional significance in various types of tissue and cell, therefore, is widely used for targeting transgene knock-in studies. However, the expression pattern of *Rosa26* locus remains elusive in testis. In this investigation, we performed a detailed transcriptional analysis of the *Rosa26* locus in mouse spermatogenesis. **Materials and Methods**: The transcriptional activity of *Rosa26* locus in the testes was detected by immunohistochemistry or direct fluorescence observation in two *Rosa26* locus-targeting knock-in mouse lines Rosa26-Flag-Cas9 and Rosa26-mT/mG with C57BL/6 background, in which the Flag-tagged Cas9 and red fluorescent mTomato (membrane-tethered tdTomato) proteins are presumed to be constitutively expressed. **Results**: In Rosa26-Flag-Cas9 mice, immunostaining of the testis sections revealed robust expression of the Flag-Cas9 transgene in the spermatogonia adjacent to the basement membrane but was absent in germ cells undergoing spermatogenesis in seminiferous tubules and also absent in maturing spermatids in the epididymis. The transgene was also observed in the inter-tubular Leydig cells and epididymal epithelia but was lacking in Sertoli cells. Similarly, in Rosa26-mT/mG mice, fluorescent microscopic observation found a completely absent of mTomato expression in the entire spermatogonial lineage and Sertoli cells. However, robust mTomato was perceived in inter-tubular Leydig cells in seminiferous tubules and epididymal epithelia. **Conclusions**: Findings in this study suggest the *Rosa26* locus is inactive during spermatogenesis, implying that gene functional studies in the spermatogonial lineage by targeting knock-in transgene in the *Rosa26* locus may not be applicable in C57BL/6 mice.

Keywords: Spermatogenesis, Rosa26, C57BL/6 mice, transcriptional inactivation

P14-12 胚胎 SGLT1 在早期胚胎发育和着床中的作用

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背景：成功的着床与子宫内膜容受性、胚胎质量、胚胎与子宫内膜的同步发育密切相关。胚胎发育到囊胚期进入宫腔后，葡萄糖就会优先成为能量来源，葡萄糖消耗量与胚胎发育第4、5 天的存活率呈正相关。SGLT1 是唯一一种高亲和力的钠耦联葡萄糖协同转运蛋白，允许细胞逆浓度梯度摄取葡萄糖，在缺血和过度利用葡萄糖的条件下，对细胞的生存尤为重要。目前尚未有关于胚胎上 SGLT1 的作用及机制的文献报道。基于 SGLT1 的功能特性，我们推断：小鼠胚胎上可能存在 SGLT1，在胚胎早期发育和着床过程中转运葡萄糖，满足孕 3 天囊胚进入宫腔后的胚胎基因组的激活、细胞增殖、以及膜合成所需的三酰甘油和磷脂需要的葡萄糖消耗，使之能够成功着床。

方法：本研究拟选 ICR 小鼠，运用 PCR 和免疫荧光技术检测 SGLT1 在胚胎各个时期的表达强弱及位置。我们将收集小鼠孕 1、2、3 天胚胎，分为正常对照组和 phlorizin 组（在培养基中加入 SGLT1 抑制剂 phlorizin），分别体外培养 24h 后，观察早期胚胎不同时期的发育情况，同时用免疫荧光技术检测两组胚胎对葡萄糖类似物 2-NBDG 的摄取情况。我们进行异体胚胎移植将两组体外培养的胚胎植入到正常假孕小鼠不同侧子宫内，随后检测胚胎着床情况。

结果：我们发现小鼠胚胎植入前各个时期均有 SGLT1 的表达， phlorizin 组的囊胚形成率低于正常对照组，同时异体胚胎移植结果表示 phlorizin 组胚胎的着床率显著低于正常对照组，并且 phlorizin 组胚胎对 2-NBDG 的摄取明显低于正常对照组。

结论：小鼠 SGLT1 在早期胚胎发育和胚胎着床中起着重要作用，抑制其表达导致胚胎发育迟缓以及胚胎植入失败，而这种作用是小鼠胚胎 SGLT1 通过对葡萄糖的摄取发挥的。接下来我们将通过单基因测序实验继续探索 SGLT1 通过摄取葡萄糖在胚胎发育及着床中的通路以及更深层的机制。

关键词：SGLT1、早期胚胎发育、胚胎着床

P14-13 Redox homeostasis in the uterine epithelium is critical to embryo implantation

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The uterine epithelium undergoes a dramatic spatiotemporal transformation to enter a receptive state, involving a complex interaction between ovarian hormones and signals from stromal and epithelial cells. Redox homeostasis is critical for cellular physiological steady state; emerging evidence reveals that excessive lipid peroxides derail redox homeostasis, causing various diseases. However, the role of redox homeostasis in early pregnancy remains largely unknown. We found that uterine deletion of Glutathione peroxidase 4 (GPX4), a key factor in repairing oxidative damage to lipids, confers aberrant receptivity and defective implantation, leading to infertility. To further pinpoint Gpx4's role in different cell types, uterine epithelial-specific Gpx4 was deleted by a Ltf-Cre driver; the resultant females were infertile, suggesting unbalanced redox homeostasis in the uterine epithelium compromises receptivity and implantation. Our study reveals the pernicious impact of unbalanced redox signaling on embryo implantation and suggests the obliteration of lipid peroxides as a possible therapeutic approach to prevent implantation defects.

Keywords: Uterine epithelium, Redox homeostasis, Lipid peroxidation, Infertility

P15 体适能研究

P15-1 基于 CiteSpace 的运动干预抑郁症研究热点及趋势的可视化分析

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目的：基于 CiteSpace 对运动抗抑郁近十年的研究热点和趋势进行可视化分析，为未来研究提供参考。

方法：检索中国知网（CNKI）和 Web of Science（WOS）数据库中主题为运动对抑郁

症影响的文献，检索时间为 2010 年 1 月—2023 年 7 月。使用 CiteSpace 6.1.R6 软件在作者、机构、高频关键词、突现性被引关键词等方面对文献进行可视化分析。

结果：（1）纳入文献 4927 篇，其中中文文献 790 篇，英文文献 4137 篇。中文发文最多为华东师范大学刘微娜。英文发文最多为伦敦大学 Stubbs Brendon。（2）中文频次前 5 位的关键词依次为抑郁、帕金森病、抑郁症、焦虑、运动；英文为 depression、quality of life、exercise、physical activity、anxiety。（3）中文关键词聚类分析显示，帕金森病、心理健康、有氧运动，涉及疾病、运动干预方式、抑郁类型等方面；英文关键词聚类分析显示，physical activity、Parkinson's disease、pulmonary rehabilitation、depression-like behavior，涉及康复、心理健康、抑郁症状等方面。（4）关键词突现：英文文献中 2012-2016 年研究主要针对 depression scale 和 myocardial infarction；2017-2020 年研究主要针对 psychological distress、hippocampal neurogenesis 和 rating scale；2021-2023 年研究主要针对 generalized anxiety disorder、college student 和 mental health。中文文献中突现关键词为应激（2010-2015 年）、运动干预（2015-2020 年）、认知功能（2020-2023 年）和青少年（2021-2023 年）。（5）研究热点集中于：①运动与心理健康/帕金森病之间的关系；不同强度/方式锻炼对抑郁的影响；②运动对脑结构的重塑，如运动调节抑郁症患者海马结构重塑，运动对事件相关电位（ERP）和脑电图（EEG）的影响等；③运动改善抑郁症的神经生物学机制，包括影响单胺类递质的代谢、调节突触可塑性、调节神经炎症和神经免疫、调控脑-肠轴等。

结论：未来的研究应着眼于运动对不同人群特别是青少年人群精神卫生的影响；探索不同方式/强度运动对抑郁症认知功能/认知障碍的影响；使用新的神经科学技术探究运动抗抑郁的生物机制，形成防治抑郁的个性化、精准化运动方案和客观评价方法。

关键词：运动，抑郁，CiteSpace

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P15-2 老年人体力活动水平对肺功能的影响：肌肉适能的中介效应

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背景与目的：老年人增龄性机能衰退表现为机体各器官、系统及组织呈明显退化趋势，其中肺功能退化是老年人机能衰退的典型表现。体力活动水平对维持老年晚年生命质量，对抗机能衰退具有一定的积极效用。然而，目前多数研究聚焦体力活动或肌肉适能对肺功能的单向影响，忽略三者间可能存在的中介效应。皆在探究老年人体力活动水平对肺功能的影响，及肌肉适能在此影响中的中介效应。

方法：采用横向研究设计（伦理审查编号：NNU202206009），于 2021 年在南京市五个行政区域共计 10 个社区招募到 200 名（男性=82 人）具备独立行走能力的老年人（65-79

岁）。采用三维加速度计测量老年人日常体力活动水平（一周），采用肺功能训练仪（Power Brethe K5）测量呼吸肌适能（力量与耐力），使用肺功能检查仪（AS-507，美能，日本）测量肺功能水平，采用手握力、5 次坐站起、30 秒坐站测试收集四肢肌肉适能。运用 AMOS 24.0 分析老年人体力活动水平对肺功能的影响与肌肉适能在对其的中介效应。

结果：影响路径中老年人体力活动水平积极作用于肺功能水平（$\beta = 0.187$，$p < 0.001$）的用力肺活量（r=0.29）、1 秒钟用力呼气容积（r=0.299）、肺活量（r=0.206）指标，尤其中高强度体力活动水平（1.61）对肺功能贡献更高。中高强度体力活动水平对四肢肌肉适能（$\beta = 0.415$，r=0.198~0.299，$p < 0.001$）与呼吸肌适能（$\beta = 0.234$，r=0.083~0.159，$p < 0.05$）均有促进作用，且呼吸肌适能（0.71）对肺功能的贡献更大。以肌肉适能为中介的老年人体力活动水平对肺功能水平的直接效应为 0.17，四肢肌肉适能的间接效应为 0.065 且对 5 次坐立测试（0.92）影响最为显著，呼吸肌适能的间接效应为 0.102，总效应值为 0.337。

结论：中高强度体力活动水平对老年人肺功能具有更加正向的影响，肌肉适能是老年人体力活动对肺功能产生影响的中介因素，且呼吸肌适能在体力活动影响肺功能中的中介效应更为显著。

关键词：老年人、肺功能、呼吸肌、中介、体力活动水平、骨骼肌

P16 基质生物

P16-1 Cyclic substrates softening strengthens cell mechanoresponse by accumulating force signaling molecules

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Considering that cells usually experience dynamic mechanical stimuli in vivo, many efforts have been devoted to studying the influence of dynamic mechanical signals on cell mechanotransduction by cyclic stretching of the extracellular matrix. The extra force applied in this way is considered to directly enhance the myosin-based intracellular force. Here, we applied cyclic stimuli in an opposite way by reversibly softening the cell adhesive substrates at appropriate frequencies, which is supposed to decrease the cell adhesive force but, surprisingly, still increases cell mechanotransduction. Thus, a previously unknown mechanism was unmasked to explain the cellular mechanoresponse to cyclic mechanical stimulation. The loss and recovery of the matrix

stiffness causes the cyclic disassembly-assembly of the molecular clutches (i.e, actomyosin-integrin linkage), which periodically activates mechanotransduction signaling molecules (e.g, FAK-ROCK-Myosin signaling). When the re-activation rate of these signaling molecules is faster than the dephosphorylation rate, these molecules accumulate to enhance the robustness of the molecular clutchesto promote the intracellular force. This new finding can be beneficial for understanding and regulating cell-matrix interactions.

Keywords: cell, mechanotransduction, cyclic mechanical stimulation, switchable hydrogel, photo-active yellow protein

P17 整合生理

P17-1 High-altitude hypoxia exposure inhibits erythrophagocytosis by inducing macrophage ferroptosis in the spleen

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This study investigates the role of the spleen and splenic macrophages in the development of high-altitude polycythemia (HAPC), a condition characterized by an imbalance between erythropoiesis and eryptosis, typically observed in high-altitude (HA) environments. We employed a mouse model subjected to hypobaric hypoxia (HH) to simulate the conditions of a 6000 m HA exposure. For in vitro examination, primary splenic macrophages were treated with 1% hypoxia. Our findings revealed that the HH treatment enhanced erythropoiesis, resulting in erythrocytosis, with marked splenic contraction evident, later progressing to splenomegaly over a 14-day period. HH exposure also impaired the ability of the spleen to process red blood cells (RBCs), predominantly due to a decrease in splenic macrophages within the red pulp. Furthermore, the application of HH treatment over 7 and 14-day intervals resulted in increased iron mobilization and onset of ferroptosis within the spleen, as corroborated by the expression of iron metabolism-related and ferroptosis-related proteins. The expression levels of these proteins mirrored gene expression levels in human peripheral blood mononuclear cells. Subsequent single-cell sequencing of the spleen demonstrated a substantial decrease in macrophages 7 days post-HH exposure. In vitro investigations confirmed the decline in primary splenic macrophages and induction of ferroptosis following hypoxic treatment, which were reversed by pre-treatment

with the ferroptosis inhibitor ferrostatin-1. In summary, the data suggested that HH exposure instigates splenic ferroptosis, predominantly in the red pulp, thereby hampering the RBCs clearance in the spleen. This leads to increased RBCs retention within the spleen, triggering splenomegaly, which may potentially foster continuous RBCs production and accelerate HAPC progression. The major conclusion from this study elucidates the critical role of spleen and splenic macrophages in the pathogenesis of HAPC.

Keywords High altitude, Hypobaric hypoxia, High-altitude polycythemia, Spleen, 51 Eryptosis, Ferroptosis

P17-2 肝 X 受体对肾缺血再灌注损伤的保护作用及机制探讨

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研究目的 急性肾损伤（Acute Kidney Injury，AKI）是由各种病因引起的肾功能快速下降而出现的临床综合征。肾缺血再灌注损伤（Renal Ischemia Reperfusion Injury，RIRI）是导致 AKI 的主要原因之一。目前，RIRI 的发生机制尚未完全阐明，临床上也缺乏针对性的治疗方法或药物。肝 X 受体(Liver X Receptor，LXR)是核受体超家族成员，有两种亚型即 LXRα 和 LXRβ。LXRα 高表达于肝脏和肠道等，而 LXRβ 在全身广泛表达。以往研究提示 LXR 激活可以减轻心肌或脑缺血再灌注损伤，我们推测其可能也参与了 RIRI 的病生理过程。本研究将揭示 LXR 在 RIRI 中发挥的作用及机制，为疾病的治疗提供理论依据和潜在靶点。

方法 体内实验:手术构建小鼠 RIRI 模型，给予 LXR 激动剂 GW3965 处理。两批动物实验（1）对照组、RIRI 组、RIRI+GW3965 治疗组；（2）LXRα-WT 对照组、LXRα-KO 对照组、LXRα-WT+RIRI 组、LXRα-KO+RIRI 组。体外实验：缺氧复氧处理 HK2 细胞模拟 RIRI 模型，给予 GW3965 处理。

结果 体内实验：（1）GW3965 显著抑制 RIRI 导致的血肌酐、尿素氮水平升高；病理学染色结果显示 GW3965 明显缓解 RIRI 导致的肾组织形态损伤；免疫组化染色结果显示 GW3965 明显缓解 RIRI 导致的氧化应激以及内质网应激；TUNEL 染色表明 GW3965 减少肾脏细胞凋亡；qPCR 和 WB 结果显示 GW3965 减轻 RIRI 导致的细胞凋亡和炎症反应。（2）LXRα-WT+RIRI 组和 LXRα-KO+RIRI 组的肾组织形态、细胞凋亡、氧化应激、内质网应激和炎症反应等没有明显差别。

体外研究：镜下观察结果显示 GW3965 可以降低缺氧复氧后的细胞死亡；CCK8 结果显示 GW3965 可以缓解缺氧复氧导致的细胞活力降低；超氧化物歧化酶（SOD）试剂盒结果

显示 GW3965 可以缓解细胞缺氧复氧后的 SOD 水平。

结论 本研究证实 LXR 激动剂 GW3965 显著改善小鼠 RIRI，机制可能与减轻细胞凋亡、氧化应激、内质网应激及炎症反应相关；同时，我们的结果初步证实 LXR 激动剂的治疗作用不依赖 LXRα，而极有可能是通过另一种亚型 LXRβ 实现的。

关键词：肾损伤 缺血再灌注 肝 X 受体激动剂

P17-3 db/db 小鼠肝脏脂质沉积与脂滴代谢机制研究

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目的：对比研究正常 BKS 小鼠与 2 型糖尿病模型 BKS-db/db 小鼠肝脏脂质沉积水平，从脂解与脂噬两方面探究 2 型糖尿病小鼠肝脏脂滴的代谢特征。**方法：**选取 8 只 SPF 级 7 周龄 BKS 小鼠和 8 只 BKS-db/db 小鼠。16 周末测量小鼠体重、空腹血糖后处死，取新鲜血液检测血脂四项表达水平，取新鲜肝脏组织切除部分装入冻存管，放入液氮速冻后转-80℃冰箱保存，用以免疫印迹检测脂滴代谢相关蛋白（Plin2、LC3、Lamp 2A、ATGL）表达水平。部分肝组织用 4%多聚甲醛固定，制作冰冻切片用以油红 O 和免疫荧光染色，观察肝脏脂质沉积程度和脂解水平。其余新鲜肝组织研磨离心后提取上层一部分与游离线粒体动态结合和锚定结合的脂滴为 FL_1（Fat layer 1），其余部分经高速离心后提取与线粒体锚定结合的 FL_2（Fat layer 2），观察其形态。并提取原代肝细胞观察肝脏脂噬水平。所得数据用 IBM SPSS 20 进行单因素方差分析。免疫荧光结果用 Image J 分析，Western blotting 采用 ImageLab 分析，GraphPad Prism8.0.2 作图，显著性水平选择 $P<0.05$ 和 $P<0.01$。**结果：**1）与 WT 组相比，16 周龄 db/db 组小鼠体重、肝重、肝指数显著增加（$P<0.05$），伴随空腹血糖和血脂四项水平显著升高（$P<0.01$）；2）WT 组小鼠脂滴含量极低，而 db/db 小鼠肝脏脂质沉积显著，油红染色、肝脏 TG 含量均显著增多。肝细胞内脂滴数量、脂滴所占面积显著增加（$P<0.01$），且脂滴形态偏大，呈橘红色聚集样分布。3）与 WT 组相比，db/db 小鼠肝组织中脂滴含量丰富，肝组织中提取的 FL1 形态偏大，且脂滴周围富集 ATGL 红色阳性信号及较高蛋白表达，而 FL2 形态偏小，脂滴周围富集溶酶体，LC3 及 Lamp2A 等脂噬蛋白表达水平显著增高（$P<0.01$）。**结论：**与正常 BKS 小鼠相比，2 型糖尿病小鼠出现血脂异常、肝脏脂质沉积显著，肝组织中脂滴代谢方式与脂滴大小相关，大脂滴可能优先通过 ATGL 发生脂解后变为小脂滴，小脂滴通过脂噬作用进一步降解代谢。

关键字：2 型糖尿病、肝脏、脂质沉积、脂解、脂噬

P17-4 棕榈酸处理不同时长对肝细胞线粒体功能及 LONP1 表达的影响

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目的：探讨棕榈酸（PA）干预不同时长对 AML12 细胞线粒体功能及线粒体蛋白酶 1（LONP1）表达的影响。**方法：**AML12 细胞培养于含 10%FBS、40ng/ml 地塞米松及 1%液体培养基补充剂（ITS）的 DMEM/F12 培养基中，置于 37℃，5%CO2 饱和湿度培养箱常规培养，适时更换培养基。根据实验需要，将 AML12 分为以下处理组：空白对照组（Con），400uM PA 干预 6h 组（6h PA）、12h 组（12h PA）、18h 组（18h PA）和 24h 组（24h PA）。检测细胞中脂质沉积情况、细胞 ROS 水平及线粒体膜电位、线粒体稳态相关基因 LONP1 表达。**结果：**（1）油红染色显示，与 Con 组相比，PA 干预 12 小时后 AML12 细胞脂质沉积含量显著增加（P<0.01），并且 18h PA 干预组脂质含量显著高于 6h PA 干预组（P<0.01），24h PA 干预组细胞脂质沉积水平较 6h 和 18h PA 干预组显著增加（P<0.01）。（2）DCFH-DA 探针标记发现，与 Con 组相比，PA 处理后的细胞 ROS 含量显著增加（P<0.01），且 PA 处理 12h 组 ROS 水平显著高于 PA 处理 6h 组（P<0.05），与 6h 和 12h 组相比，24 小时 PA 处理显著增加肝脏细胞 ROS 含量（P<0.01）。JC-1 染色显示，与 Con 组相比，PA 处理 12 小时后，AML12 细胞线粒体聚合物含量显著显著降低，单体含量显著增加，线粒体高膜电位增加，低膜电位降低（P<0.05）。24h PA 处理组细胞线粒体低膜电位显著高于 6h 和 12h PA 处理组（P<0.05）。（3）Western Blotting 检测结果显示，棕榈酸处理可增加细胞内线粒体质量控制蛋白 LONP1 表达。分析结果显示，与 Con 组相比，12h 和 24h PA 处理后细胞中 LONP1 表达量显著增加，且 18h 和 24h PA 处理显著高于 6h PA 处理组（P<0.05）。**结论：**棕榈酸可诱导肝细胞发生脂质沉积，且脂质沉积程度随棕榈酸处理时长逐渐增加。脂质沉积加剧伴随肝细胞线粒体功能受损，线粒体蛋白酶 LONP1 表达增高，其可能在参与水解线粒体蛋白、维持线粒体稳态中发挥重要作用。

关键词：棕榈酸；线粒体功能；LONP1

P17-5 大电导钙激活钾通道（BK）在嗜血细胞现象中的新作用

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研究背景：噬血细胞现象是指在脾、骨髓、淋巴结等组织发现巨噬细胞吞噬以红细胞为主的血细胞的现象，是噬血细胞性淋巴组织细胞增多症（HLH）的关键性诊断指标之一。当

伴有噬血细胞现象时，HLH 的病情更为凶险，会出现更差的预后和更高的死亡率，但其发生机理至今仍不完全清楚。本团队前期在构建大电导钙激活钾通道全敲（$BK^{-/-}$）大鼠时意外发现，$BK^{-/-}$大鼠多脏器中出现噬血细胞现象。同时在 HLH 患者中发现了 BK 表达下降的现象，提示 BK 可能与 HLH 和嗜血细胞现象有关，但 BK 通道在嗜血细胞现象中的作用如何目前尚无报道。

方法与结果：本研究运用免疫组织化学、免疫荧光染色、Western blot、普鲁士蓝染色等方法检测显示，巨噬细胞上表达有 BK 通道。在体水平上，$BK^{-/-}$大鼠脾、肺、肝脏中巨噬细胞数目增多，且吞噬自身红细胞情况多于同期野生型（WT）大鼠。离体水平上，BK 通道表达和活性的减少均使分离培养的原代巨噬细胞吞噬中性红染料增加，提示吞噬能力增强。对于红细胞，利用免疫荧光染色、瑞士-姬姆萨染色、红细胞渗透脆性实验等检测显示，红细胞上同样表达有 BK 通道；且与正常人相比，HLH 患者红细胞 BK 通道表达降低，棘形红细胞数目增多，细胞膜渗透脆性增加，提示膜稳定性下降。与患者类似，$BK^{-/-}$大鼠全血细胞数目减少，红细胞形态异常，膜渗透脆性增加。进一步开展吞噬实验发现，离体情况下，同种类型巨噬细胞吞噬 $BK^{-/-}$红细胞数多于吞噬 WT 红细胞，而对同种类型红细胞的吞噬在 $BK^{-/-}$巨噬细胞和 WT 巨噬细胞间无显著性差异。

结论：综上提示，BK 通道下调可增强巨噬细胞吞噬能力，同时破坏红细胞膜结构，使得巨噬细胞对异常红细胞吞噬增加，诱发嗜血细胞现象，且在启动嗜血细胞现象中 BK 通道不足引起的红细胞异常可能发挥着更为重要的作用。提示增加 BK 通道有可能成为治疗噬血细胞现象相关疾病的新策略。

关键词：大电导钙激活钾离子通道，巨噬细胞，红细胞，嗜血细胞现象

P17-6 The ubiquitin ligase UBR-1 regulates the synaptic strength between the GABAergic and glutamatergic signaling

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Excitation/Inhibition (E/I) balance is carefully maintained by the nervous system.

Neurotransmitter GABA has been reported to be co-released with its sole precursor, another neurotransmitter glutamate. The genetic and circuitry mechanisms to establish the balance between GABAergic and Glutamatergic signaling have not fully elucidated. *C. elegans* DVB is a classically defined excitatory GABAergic motoneuron that drives the expulsion step in defecation motor program. We show that in addition to UNC-47, the vesicular GABA transporter, DVB also expresses EAT-4, a vesicular glutamate transporter. UBR-1, a conserved ubiquitin ligase, regulates the DVB activity by suppressing a bidirectional inhibitory glutamate signaling. Loss of UBR-1 impairs the DVB Ca^{2+} activity and the expulsion frequency. These impairments are fully compensated by the knock-down of EAT-4 in DVB. Further, glutamate-gated chloride channels GLC-3 and GLC-2/4 receive DVB's glutamate signals to inhibit DVB and enteric muscle, respectively. These results implicate an intrinsic cellular mechanism that promotes the inherent asymmetric neural activity. We propose that the elevated glutamate in *ubr-1* being the cause of the E/I shift, potentially contributes to the Johanson Blizzard Syndrome.

Keywords: E/I balance; *ubr-1*; glutamate metabolism; defecation; co-release

P17-7 非酒精性脂肪性肝炎中 CHCHD2 表达的增加促进肝纤维化的发生

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非酒精性脂肪性肝炎（NASH）是由包括代谢、基因、环境和肠道微生态等多种机制调控的复杂疾病，会进一步发展为肝纤维化。CHCHD2 在 NASH 疾病发展中所扮演的角色尚未可知。CHCHD2 是一种细胞核与线粒体双定位的蛋白质，目前对于其作为转录因子进行的研究较为缺乏。因此，我们通过 CHIP-seq 技术探讨其作为转录因子所发挥的功能并发现其靶基因可富集于非酒精性脂肪性肝病（NAFLD）。接下来我们发现，NASH 小鼠的肝脏组织中，CHCHD2 蛋白表达水平明显增高。紧接着，给予 CHCHD2 全身性敲除小鼠 NASH 饮食喂养或硫代乙酰胺注射以诱导肝纤维化模型，发现敲除小鼠的肝纤维化程度明显改善。进一步，我们通过尾静脉注射腺相关病毒的方式在肝细胞中特异性过表达 CHCHD2，发现过表达 CHCHD2 以后能通过激活 Notch 信号通路进而加重 NASH 小鼠的肝纤维化程度。在肝细胞中过表达 CHCHD2 后，骨桥蛋白（OPN）表达上调，进而激活邻近的肝星形细胞。同时，体内和体外实验均证明使用 Notch 信号通路抑制剂后能改善 CHCHD2 过表达所导致的肝纤维化。综上所述，CHCHD2 通过激活 Notch 信号通路和增加骨桥蛋白的产生来促进肝纤维化的发生。

关键词：CHCHD2、NASH、肝纤维化、肝星形细胞激活

P17-8 不同体力活动水平的超重肥胖老年人群血清脂联素水平与静息能量代谢、糖脂代谢的相关关系研究

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目的：本研究拟探讨日常身体活动在超重肥胖老年人群脂联素，静息代谢（RMR）和糖脂代谢之间相关关系中的调节作用。

方法：本研究招募并采纳符合条件的 120 名超重肥胖老年人群作为受试对象，其中 73 名肥胖女性（年龄 = 64.1 ±6.1 岁；BMI = 26.1 ±2.4 kg/m^2）和 37 名肥胖男性（年龄 = 66.3 ±5.6 岁；BMI = 26.9 ±2.2 kg/m^2）。采用间接测热法（Cortex Metamax 3B-R2，德国）进行 RMR 测量；采用双能 X 线吸收测定法（GE Lunar Prodigy，美国）对进行身体成分测量；通过放射免疫测定法测定血清脂联素和糖脂代谢相关指标；通过三轴加速度计（Actigraph GT3X-BT，美国）采集受试者 7 天的身体活动数据，根据所有受试者体力活动时间的平均分钟数（180 分钟/周）将受试者分为低体力活动水平组和中高体力活动水平组。

结果：1）女性的体脂百分比，高密度胆固醇水平高于男性（39.1 ±4.8 VS 29.7 ±4.7%；1.3 ±0.2 VS 1.1 ±0.2 mmol/L；均 $p < 0.01$），而男性的 RMR 高于女性（1423.3 ±264.1 VS 1368.4 ±287.5 Kcal/day， $p < 0.01$）。

2）低 MVPA 组的脂联素、胰岛素、HOMA-IR、体脂百分比均高于高 MVPA 组（20.76 ± 14.2 μg/mL VS 15.7 ± 12.1 μg/mL；8.6 ± 4.2 VS 7.1 ± 3.1 μU/mL；2.2 ±1.4 VS 1.7 ±0.9；37.1 ±7.0 VS 34.2 ±6.4%；均 $p < 0.05$），然而两组之间的 RMR 和其他糖脂代谢指标均无显著性差异（均 $p > 0.05$）。

3）低 MVPA 组中，血清脂联素水平与胰岛素呈负相关（$r = -0.284$，$p = 0.045$）；血清脂联素水平与低密度胆固醇呈正相关（$r = 0.331$，$p = 0.019$），与 RMR 和其他糖脂代谢指标未发现显著相关关系（均 $p > 0.05$）。高 MVPA 组中发现血清脂联素与甘油三酯及单位体重 RMR 呈负相关（$r = -0.310$，$p = 0.021$，$r = -0.275$，$p = 0.040$），与其他糖脂代谢指标均未发现显著相关关系。

结论：脂联素可能在超重肥胖的老年人中参与能量代谢和糖脂代谢。脂联素与能量代谢和胰岛素抵抗的关系可以通过日常体力活动的改变来调节。

关键词：脂联素，超重与肥胖，体力活动水平，静息能量代谢，糖脂代谢

P17-9 Heart-enriched long noncoding RNA NPPA-AS1 regulates pathological cardiac hypertrophy by initiating the EP300-GATA4 axis

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Aims: Over time, physiology cardiac hypertrophy transforms into a maladaptive reaction to alterations in hemodynamics that are essential for sustaining cardiac output, ultimately culminating in heart failure even sudden death. Nevertheless, the intricate regulatory mechanisms that instigate cardiac hypertrophy have yet to be fully comprehended. Recent investigations have underscored the significance of long non-coding RNAs (lncRNAs) in a multitude of biological processes and diseases. Despite this, our understanding of the involvement of lncRNAs in cardiac ailments remains somewhat limited.

Methods and Results: We identified the role of NPPA-AS1 in cardiac hypertrophy and remodeling. Notably, NPPA-AS1 emerges as a heart-specific and evolutionarily conserved long non-coding RNA, situated on the antisense strand of the atrial natriuretic peptide (NPPA) gene. The cardiac expression of NPPA-AS1 was markedly up-regulated early and sustained in response to stress caused by transverse aortic constriction (TAC) procedure in mice. Furthermore, elevated levels of NPPA-AS1 were also detected in the failing human hearts, underscoring its clinical relevance. To determine the functional role of NPPA-AS1 in the heart in vivo, we use three distinct animal models, including CRISPR-Cas9 mediated NPPA-AS1 inactivation, AAV9-shRNA-mediated and GapmeR-mediated NPPA-AS1 silencing, to determine cardiac and global phenotype. No apparent body or cardiac morphological abnormality or dysfunction in mice was seen under basal conditions. However, inactivation or down-regulation of NPPA-AS1 minimized the TAC-induced cardiac

hypertrophy and fibrosis, indicated by cardiac size, weight, and functional test, in all models which reveals the clinical translation potential. The beneficial cardiac effects of NPPA-AS1 inhibition were related to reducing the recruitment EP300 binding with GATA4, which promotes GATA4 acetylation, and consequently inhibits the transcription of pro-hypertrophic gene expression.

Conclusions: Our current study has unveiled the cardiac-enriched lncRNA NPPA-AS1, which orchestrates the intricate process of cardiac remodeling by initiating the EP300-GATA4 axis. Consequently, disrupting this EP300-GATA4 axis through targeted inhibition of NPPA-AS1 offers a promising therapeutic approach for addressing maladaptive cardiac hypertrophy and remodeling.

Keywords: long noncoding RNA; cardiac hypertrophy; NPPA-AS1; EP300; GATA4; CRISPR–Cas9; GapmeR

P17-10 Mechanosensitive channels mediate transcranial ultrasound-induced neuronal electrophysiological activity

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Objective: Ultrasound as a promising tool for neuromodulation has been applied in pre-clinical research which focused on brain function enhancement and behavior improvement. These higher brain activities rely on the electrophysiological activities of the neurons which are controlled by the ion channels' dynamic actions. However, the current ultrasound strategy lacks specificity and precision. To reach these goals, a direct functional component must be found to mediate the ultrasound effectively. We raised a hypothesis that the mechanosensitive (MS) ion channels play a leading role. **Methods:** Targeted mechanosensitive ion channels were overexpression via packaged AAV virus to the rat primary visual cortex (V1) and hippocampus (HP). The local field potentials and spikes of V1 and HP were recorded when transcranial ultrasound stimulation was applied in the anesthetized state. **Results:** Overexpressed MS channels in the targeted brain region didn’t induce any behavior change. By recording LFPs and spikes from V1 and HP during an anesthetized state when specific ultrasound was applied, we found that the evoked-related potential (ERP) existed in the experimental group compared with the control group. With the mediation of MS channels, the characteristics of the ERP waveforms in V1 were different from HP. In detail, the first negative peak amplitude in HP was larger than in V1 but the first positive peak was lower. Furthermore, stimulus-parameter-dependent variability in LFP

responses was shown in the ERP character values evaluation. **Conclusion:** MS channels could mediate the ultrasound to affect the neuron activity, the responses model was different in the superficial brain area compared with the deep brain area.

Keywords: Ultrasound stimulations; visual cortex; hippocampus; local field potential; evoked-related potential

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P17-11 有氧运动改善卵巢切除联合慢性束缚应激大鼠焦虑抑郁样行为的雌激素受体机制研究

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研究目的：抑郁症是一种常见的神经精神障碍疾病。持续的压力性应激与女性绝经期碰撞会严重影响中年女性的情绪处理。前人在运动抗抑郁研究方面未对有氧运动是否可以通过激活雌激素受体抵抗抑郁发生发展进行深层次的了解，因此，本研究旨在探究雌激素受体介导的有氧运动抗抑郁的作用机制。

研究方法：本研究以 13 周龄雌性 SD 大鼠为研究对象。实验分为假手术（Sham）组、慢性束缚应激联合卵巢切除（OVX+CS+Sedentary)组、雌激素治疗(OVX+CS+E2)组、跑台运动（OVX+CS+EX）组、跑台运动加拮抗剂（OVX+CS+EX+ICI）组，共 5 个组。运动为中等强度跑台运动，18 m / min，0 °，50 min/天，6 天/周，共 6 周。行为学测试包括糖水偏好测试、强迫游泳试验等六项。上述实验样品的病理学检测包括①不同信号通路中关键信号转导分子的基因表达，即 AMPK、PGC-1α、FNDC5 等 12 种 mRNA 的表达。②不同信号通路中关键蛋白及磷酸化蛋白的表达，包含 AMPK、p-AMPK、PGC-1α 等 17 种蛋白的表达。统计方法采用易流算法。

研究结果：Sham、OVX+CS+Sedentary、OVX+CS+E2、OVX+CS+EX、OVX+CS+EX+ICI 各组所有行为学参数的健康标尺(GCYY)分别为 10.92、4.74、8.82、9.02、3.74 以及所有分子参数的 GCYY 分别为 21.30、12.85、26.20、29.60 和 12.39。其中，OVX+CS+EX 组和 OVX+CS+EX+ICI 组之间行为学参数和分子参数 GCYY 的定量差异（QD）分别为 1.83 和 1.81，这表明 ICI 给药显著性逆转了有氧运动的改善作用。此外，数据易流数据模型处理后发现，在分子参数网络空间中，PI3K、Akt、ERK、CREB、CaMKⅡ和 GSK-3β 的相对 mRNA 表达水平以及 SIRT1 和 mTOR 的相对蛋白表达水平表现出参数洞。有趣的是，PI3K、Akt 和 GSK-3β 位于 PI3K-Akt-GSK-3β 信号通路上。因此在信号通路的参数网络空间中，PI3K-Akt-GSK-3β 信号通路可能是雌激素受体介导有氧运动改善卵巢切除联合慢性束缚应激大鼠焦虑抑郁样行为的重要信号通路。

研究结论：定位于质膜上的 ER 与非受体酪氨酸激酶（如：GSK-3β、PI3K）形成的大分子复合物介导有氧运动对 PI3K-Akt-GSK-3β 蛋白激酶途径的激活。

关键词：有氧运动；膜雌激素受体；海马体；卵巢切除术；慢性束缚应激；抗抑郁

P17-12 心脏老化与纤维化的机制及其代谢干预策略

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老化（aging）是心脏纤维化发生发展的独立因素，但其发生机制尚不明了。我们前期发现琥珀酸在老年人的心脏，特别是心肌纤维化和心衰患者明显增多，提示琥珀酸可能与心脏纤维化的发生发展有关，有望成为心脏纤维化的潜在干预靶标。本研究围绕“老化过程中，心肌细胞琥珀酸堆积与心脏纤维化发生发展的分子机制” 开展研究，初步结果表明心肌细胞产生的琥珀酸通过三种方式活化成纤维细胞：（1）琥珀酸直接激活成纤维细胞膜 SUCNR1 受体，通过调控 PKM2 琥珀酰化和二聚体形成，二聚体 PKM2 转移至细胞核，与转录因子 HIF-1α 相互作用，驱动纤维化相关基因表达；（2）琥珀酸经有机阴离子转运蛋白 SLC13A5/3 进入成纤维细胞，通过抑制脯氨酰羟化酶减轻 HIF-1α 水解，增加 HIF-1α 的入核，进一步加剧纤维化进程；（3）琥珀酰化的 PKM2 发生构象变化，转移至线粒体，与 VDAC1 互作并磷酸化 VDAC1，促进其与 SYVN1 泛素连接酶结合，促进 VDAC1 泛素化降解，抑制细胞凋亡、维持成纤维细胞的活化状态。综上，本研究初步明确老年人心肌细胞产生琥珀酸增多，通过受体依赖和非依赖方式活化成纤维细胞：琥珀酸-SUCNR1-PKM2-HIF1α 信号轴和 PKM2 琥珀酰化修饰促进心脏纤维化的新机制。上述结果为有助于寻找延缓老年人群心脏纤维化与心衰干预的新靶点、新方法，具有潜在应用价值。

关键词：老化，心脏纤维化，琥珀酸，琥珀酰化

P18 中医药与脑稳态调控

P18-1 生脉地黄汤调控突触微环境改善 CIH 诱导认知障碍的作用机制

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慢性间歇性低氧（chronic intermittent hypoxia, CIH）导致突触可塑性损伤是阻塞性睡眠呼吸暂停（obstructive sleep apnea, OSA）患者认知障碍的核心病理因素。CIH 可诱发氧化应激、炎症和细胞凋亡，导致神经元突触可塑性损伤，引起学习和记忆能力以及注意力下降等认知障碍表现，目前尚不确定 CIH 影响突触可塑性的确切分子机制。研究认为，促红细胞生成素（EPO）发挥神经保护作用可能是“肾精通于脑”的生物学机制。我们前期研究基于益气滋阴补肾法发现生脉地黄汤可有效改善 CIH 暴露小鼠气阴两虚认知障碍表现，上调海马 EPO 水平，减轻神经元炎症反应和氧化应激损伤。本研究拟进一步明确突触微环境调控在生脉地黄汤改善 CIH 诱导认知障碍中的作用机制。建立 CIH 暴露小鼠模型，应用 CD31 染色观测海马微血管密度，免疫荧光和 Western Blot 检测血管内皮生长因子 VEGF，BDNF 表达情况，应用 ELISA 检测 NO 和 ET-1 分泌水平；应用 Iba-1/CD206，Iba-1/CD68 检测海马小胶质细胞活化情况，应用 ELISA 检测 TNF- ，IL-1 ，IL-6 分泌水平；应用 GFAP 染色观测海马星形胶质细胞情况，应用 ELISA 检测 GFAP 分泌水平。研究结果发现，生脉地黄汤干预可增加 CIH 暴露小鼠微血管密度，促进 VEGF，BDNF 表达，促进 GFAP 分泌水平，抑制小胶质细胞活化，下调 TNF- ，IL-1 ，IL-6 分泌水平。本研究明确了生脉地黄汤通过调控突触微环境发挥神经元保护作用进而改善 CIH 诱导认知障碍的作用机制，基于中医治法为 OSA 合并认知障碍提供针对性中医药防治策略。

关键词：慢性间歇性低氧；突触微环境；生脉地黄汤；中医治则治法

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P18-2 以溶酶体为靶点探索槲皮素改善脑缺血损伤的机理研究

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血管性痴呆（Vascular Dementia, VaD）是仅次于阿尔兹海默症的第二大常见的痴呆症，罹患此症会出现严重的记忆和学习障碍。由于目前相关研究较少，缺乏统一标准，我们通常将其更广泛地称为血管性认知功能障碍(Vascular Cognitive Impairment, VCI)。脑慢性低灌注（Chronic Cerebral Hypoperfusin， CCH）被认为是造成 VCI 的主要病因之一。前期研究发

现槲皮素（Quercetin, Qu）具有抗炎和抗氧化效应，并可发挥神经保护作用。但此单体对CCH 诱导的神经损伤是否有治疗作用，潜在机制是什么，尚不清楚。本研究发现，SD 大鼠经双侧颈总动脉结扎术来模拟 CCH 病理状态后，模型组大鼠学习和记忆能力下降，脑皮质区和海马区可见神经元细胞核碎裂，细胞质萎缩，尼氏小体(Nissl's Body)数量增多，给予 Qu 可以改善 CCH 大鼠的学习和记忆能力，并缓解神经细胞的损伤；通过进行细胞活性检测，可见 Qu 可以保护 HT22 细胞免受氧糖剥夺（OGD）术导致的死亡。机理研究发现，Qu 在动物体内和细胞体外模型中均可抑制 NF-κB 通路，同时降低神经细胞内促炎因子如 IL-6、TNF-α 的水平，提示 Qu 可以通过抑制 NF-κB 改善 CCH 导致的炎症反应。更重要的是，Qu 对神经细胞内溶酶体具有显著激活效果，如联合溶酶体抑制剂（Bafilomycin A1, Baf 和 Chloroquine, CQ）可反转 Qu 对 NF-κB 通路和炎症因子的抑制作用，并且阻断 Qu 发挥的神经保护作用。综上所述，Qu 可以通过激活溶酶体功能，进而阻断 NF-κB 通路介导的炎症因子上升、抑制 CCH 导致的神经炎症反应，从而发挥神经保护作用。本研究为探索开发 Qu 神经保护潜力，并应用于改善血管性认知功能障碍药物提供了实验室依据。

关键词：槲皮素；脑慢性低灌注；溶酶体；NF-κB；炎症反应

P18-3 Naotaifang Formula ameliorates cerebral ischemia-reperfusion injury by attenuating ferroptosis and m6A demethylases via FTO/ALKBH5/GPX4 signaling pathway

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Background and Aims: Cerebral ischemia-reperfusion injury (CIRI) is a complex pathophysiological process involving multiple factors such as N6-methyladenosine (m6A) which becomes the footstone of rehabilitation after ischemic stroke. As a novel Chinese medicine formula, Naotaifang (NTF) was proven to exhibit a neuroprotective effect against CIRI by alleviating ferroptosis. This study aims to explore the physiological and pathological roles of NTF-targeted m6A and ferroptosis after CIRI.

Methods: The pharmacodynamics of the formula was evaluated by establishing rat model of

middle cerebral artery occlusion/reperfusion. *In vivo* experiments, the therapeutic effect of NTF was performed using TTC, HE and Nissl staining. Regional cerebral blood flow (rCBF) was measured the brain blood flow and the morris water maze test was used to investigate rats' learning and memory ability. Dot blot analysis for measuring global m6A modification of RNA. And *in vitro* experiments, we also used Perls staining and colorimetric assay kit to quantify the iron content of cortex. Immunohistochemistry, immunofluorescence and western blot were used to detect the corresponding protein.

Results: Our research showed that pretreatment with NTF improved neurological function and inhibited CIRI. *In vivo* experiments, we confirmed that NTF increased cerebral blood flow, improved neural function, and reduced iron content and level of m6A demethylation via up-regulating the expression of fat mass and obesity-associated protein (FTO) and glutathione peroxidase 4 (GPX4), down-regulating ALKB homolog 5 RNA demethylase (ALKBH5) levels in CIRI rats. The *in vitro* experimental results revealed that NTF alleviated OGD/R-induced SH-SY5Y cell injury. Further experiments demonstrated that the protective role of NTF was achieved by regulating m6A demethylation to reduce ferroptosis in OGD/R.

Conclusions: Taken together, our study systematically revealed the potential therapeutic effects of NTF against CIRI via the FTO/ALKBH5/GPX4 signaling pathway.

Keywords: Naotaifang, cerebral ischemia-reperfusion injury, m6A demethylation, ferroptosis

P18-4 蒙药珍宝丸治疗对大鼠脑缺血再灌注后血脑屏障的影响

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血脑屏障（BBB）是脑组织与血液之间进行选择性物质交换的屏障。珍宝丸是一种著名的蒙成药制剂，在治疗脑卒中方面有着悠久的历史。在本研究中，探究蒙药珍宝丸治疗对大鼠脑缺血再灌注后 BBB 通透性和紧密连接蛋白 occludin、ZO-1 表达量的影响。采用线栓法对大鼠进行大脑中动脉阻塞再灌注（MCAO/R）模型，造模成功后将存活大鼠随机分为假手术组、模型组、尼莫地平组（10mg/kg）、珍宝丸低剂量组（0.25g/kg）、珍宝丸中剂量组（0.5g/kg）、珍宝丸高剂量组（1g/kg）。在治疗 7 天后对各组大鼠进行神经功能学评分，随后取脑进行 2,3,5-氯化三苯基四氮唑(TTC)染色测量脑梗塞体积；伊文思蓝(EB)染色检测大鼠 BBB 的通透性；蛋白免疫印迹分析大鼠脑组织中 occludin、ZO-1 的蛋白水平表达量的变化。结果：与假手术组相比，模型组的神经功能严重受损（$P<0.01$），脑梗塞面积显著增加（$P<0.01$），伊文思蓝的渗漏情况显著增加（$P<0.01$），脑组织中 occludin、ZO-1 的蛋

白表达量明显减少（*P<0.01*）。而与模型组相比，高剂量珍宝丸治疗 7 天后，神经功能得到明显改善（*P<0.01*），脑梗死体积显著减小（*P<0.05*），EB 渗漏明显减少（*P<0.05*），脑组织中 occludin、ZO-1 的蛋白表达量明显升高（*P<0.01*）。结论：珍宝丸通过上调脑缺血再灌注损伤后脑组织中紧密连接蛋白 occludin、ZO-1 的表达来降低 BBB 通透性，减小脑梗死体积，发挥神经保护作用。

关键词：珍宝丸；脑缺血再灌注损伤；血脑屏障；紧密连接蛋白

P18-5 青蒿琥酯通过抑制 cGAS-STING 通路改善缺血性脑损伤的机理研究

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缺血性脑卒中，即缺血性脑损伤，是全球最主要的致残致死性疾病之一。前期研究发现青蒿琥酯（Artesunate）可通过血脑屏障，并具有改善炎症的效应。但此单体对脑缺血导致的神经损伤是否可发挥治疗作用尚不清楚。本研究利用双侧颈总动脉闭塞法（Bilateral common carotid artery occlusion，BCCAO）建立大鼠慢性脑缺血模型和原代神经细胞的氧糖剥夺（Oxygen and glucose deprivation,OGD）模型，探索青蒿琥酯对缺血性脑损伤大鼠认知功能与炎症反应的治疗效果和作用机制。研究发现 BCCAO 模型组大鼠学习和记忆能力下降，脑皮质区和海马区可见神经元细胞排列松散，凋亡细胞增多。而给予青蒿琥酯可以改善 BCCAO 模型大鼠的学习和记忆能力，并缓解神经细胞的损伤；通过细胞活性检测，可见青蒿琥酯可以保护原代神经元细胞免受 OGD 导致的死亡。通过机理研究可知，青蒿琥酯在动物体内和细胞体外模型中均可抑制 cGAS-STING 通路，同时降低神经元细胞促炎因子如 IL-6、TNF-α 的水平，提示青蒿琥酯可以通过抑制 cGAS-STING 改善 CCH 导致的炎症反应；与此同时，青蒿琥酯对神经细胞内溶酶体具有显著激活效果，并可通过激活溶酶体，进而抑制 cGAS-STING 通路，从而保护神经细胞避免脑缺血导致的病理神经损伤。综上所述，青蒿琥酯通过激活溶酶体功能，抑制 cGAS-STING 通路，调节慢性缺血性脑损伤的炎症反应，发挥神经保护作用。本研究为探索开发改善血管性认知功能障碍药物提供了实验室依据。

关键词：缺血性脑损伤；青蒿琥酯；溶酶体；cGAS-STING；炎症反应

P18-6 Microglial sphingolipid metabolism regulate inflammatory response to alleviate ischemia reperfusion-induced cerebral injury

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Microglia are resident innate immune cells in the central nervous system and play an important role in regulating the fate of neurons after cerebral ischemia. Sphingolipid is very abundant in the brain, and the abnormal sphingolipid metabolism is closely related to the occurrence of neuroinflammation and neurodegenerative diseases, but how it affects microglia and the mechanisms of microglial sphingolipid metabolism mediating ischemic reperfusion-induced cerebral injury is not clear. Here, we found that the brain injury of young mice (post-natal day 14) was lower than that of adult mice (post-natal day 56) in the ischemia reperfusion model. Single-nucleus transcriptome profile in P14 and P56 revealed that the microglia of P14 mice were enriched with genes and pathways related to sphingolipid metabolism, suggesting that microglial sphingolipid metabolism mediated ischemia reperfusion-induced brain injury. Especially, we identified the five key genes Cers5, Cers6, Sgpl1, Sptlc2 and Ugcg in sphingolipid metabolism involved in cerebral ischemia injury. However, the specific mechanisms of microglial sphingolipid metabolism-related genes regulating ischemia injury remains to be further explored. Our findings revealed that microglial sphingolipid metabolism plays a critical role in ischemia cerebral injury, which might be a potential target for the neuroprotection against ischemia reperfusion cerebral injury.

Keywords: Cerebral ischemia-reperfusion, microglia, sphingolipid metabolism, inflammation

P18-7 Annexin A2 deficiency alleviates neuronal damage by suppressing microglia-mediated inflammation upon cerebral ischemic reperfusion injury

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Cerebral stroke is one of the leading causes of mortality and disability worldwide. Restoring the cerebral circulation following a period of occlusion recovery tissue oxygenation, which leads to reperfusion injury. Cerebral ischemic reperfusion (I/R) injury triggers immune and inflammatory responses, apoptosis, neuronal damage, and even death, while the molecular and

cellular function and mechanisms of neuronal injury caused by cerebral I/R are incompletely understood. We integrated proteome, phosphoproteome, and transcriptome profile analyses in mouse hippocampi after cerebral I/R. We revealed that the differentially expressed genes (DEGs) and proteins (DEPs) mainly fall into several immune inflammatory response-related events. We identified that Anxa2 was exclusively up regulated in microglial cells in response to OGD/R in vitro and in vivo. Our results showed that Microglial Anxa2 knockdown reduced microglial activation, microglial Anxa2 knockdown markedly decreased the expression of OGD/R-induced pro-inflammatory factors including TNF-α, IL-1β, and IL-6, and reduced cell apoptosis in BV2 microglial cells induced by OGD/R, reduced nuclear translocation of NF-κB p65 subunit, and NF-κB transcriptional activity in response to OGD/R. The conditional medium derived from Anxa2 knockdown-BV2 cell cultures with OGD/R treatment alleviated OGD/R induced-neuronal death. Our findings uncovered an essential role for Anxa2 in microglial function and Anxa2 inhibition exerts neuroprotective effects in cerebral ischemia.

Keywords: Cerebral ischemia-reperfusion, Proteome, Transcriptome, Inflammation, Microglia, Neuronal injury

P18-8 Curcumin targets identify in epileptic mice brain

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Aims： Curcumin has been reported to have multi-targets and multi-cellular signal transduction pathways, but the targets where it plays an important role in the pathogenesis of epilepsy are still inconclusive. The aim of the article is to identify the key pathways and targets of

curcumin in the brain tissue of epileptic mice.

Main methods: Adult male ICR mice 6-8W intraperitoneal inject pilocarpine keep status epilepticus (SE) lasted up to 120 min, sacrificed mice on day 4 after SE to research. We take two approaches, affinity chromatography and drug affinity responsive target stability (DARTS), to identify the key pathways and targets in the mice brain. The results were obtained for biological information and biochemical assessments and analyses.

Key findings: The study screened 70 different targets through affinity chromatography and 232 different targets by DARTS, bioinformatics results showed that leading regulates focal adhesion pathway related to the structural constituent of the cytoskeleton in epileptogenesis. The cell coat experiments verified that curcumin can affect cell migration through focal adhesion. Finally, there are only 5 targets including CADPS, CHM, TNR, TUBB4A, and USP5 in both groups, which may be the significant targets of curcumin in the regulation and effect of the progression of epilepsy.

Significance: Our findings suggest that focal adhesion was a key pathway of curcumin. CADPS, CHM, TNR, TUBB4A, and USP5 are may the significant targets of curcumin in the regulation and affects the progression of epilepsy, and our study provides an example of identifying the targets.

Keywords: DARTS; Affinity chromatography; Curcumin; Epilepsy; targets identification

P18-9 Neural vesicle GABA suppresses lysosomal lipase LIPL-1 to promote anoxia tolerance via PMK-1/p38 pathways

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Oxygen is essential chemical molecule to maintain normal physiological function of most animals. Severe oxygen deprivation result in tissue damage effects and even death. Human brain cells and cardiomyocytes can only survive few minutes upon oxygen deprivation while some animals such as turtle and the nematode *C. elegans* are adapted to live longer in low oxygen or anoxia environment. *C. elegans* is a powerful genetic trackable model to reveal the cellular and

molecular mechanisms underlying anoxia tolerance. To explore the role of neurotransmitters in anoxia susceptibility, we screened all different mutants that lack corresponding neurotransmission in *C. elegans*. We found that γ-aminobutyric acid (GABA) deficiency accelerated animal death upon anoxia treatment. We also demonstrated that intestinal PMK-1/p38 is required for GABA-mediated anoxia tolerance and acts the downstream of GABA signaling. Transcriptomic profiling revealed that the lysosome pathway acted downstream of GABAergic signaling. Further data determined that lysosome pathway was suppressed by GABA-PMK-1/p38 signaling and enhanced the resistance of *C. elegans* to anoxia. Our findings indicate that the GABA signaling promotes anoxia-induced injury through evolutionally conserved p38 MAPK pathway and lysosome pathway in *C. elegans*, which expands our understanding of the nervous system mediated protection to defense against anoxia-related injury, raising the possibility that a similar process may occur in higher organisms.

Keywords: Anoxia; γ-aminobutyric acid (GABA); p38 MAPK pathway; lysosome pathway

P19 人体微生态

P19-1 在菌种水平探究肠道菌群在阿尔茨海默症发生发展中的作用

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阿尔茨海默病（Alzheimer's disease, AD）是一种起病隐匿，进行性发展的中枢神经系统退行性疾病，在中老年人群中发病率高，造成的社会及医疗负担沉重，但目前尚无有效的治愈方法。AD 的典型病理特征是细胞外淀粉样蛋白 Aβ 沉积和细胞内神经纤维缠结。随着肠道菌群-肠-脑轴概念的提出，肠道菌群在 AD 中的作用得到广泛关注，以往的研究发现无菌小鼠或抗生素处理之后的 AD 模型小鼠相比于对照小鼠脑内 Aβ 沉积减少，认为不存在肠道菌群时对 AD 有保护作用，但这种理想状态无法在临床实施。在随后的研究报道中，越来越多的研究采用以 16S 为代表的二代测序方法对 AD 模型小鼠或 AD 患者的肠道菌群进行测序分析，但对细菌的鉴定大多只能精确到菌属水平。因此提高对于肠道菌群研究的精准度，发现有益或有害细菌，对肠道菌群在疾病中的研究具有重要意义。

我们的研究采用基于 Nanopore 三代测序技术和宏基因组学分析方法，利用 AD 模型小鼠-5xFAD 小鼠，尝试在菌种水平找到差异表达的细菌。首先从门水平寻找差异细菌，发现相比于野生型小鼠，转基因小鼠肠道中拟杆菌门丰度降低，而厚壁菌门丰度升高，这与前期的研究报道结果一致。进一步在属水平寻找差异菌属，发现转基因小鼠肠道中拟杆菌属丰度

降低，而梭菌属和蓝绿藻菌丰度增高。进而从这些菌属深入探究，寻找差异改变的菌种，发现拟杆菌属的溶木聚糖拟杆菌，卵形拟杆菌，多形拟杆菌，粪拟杆菌，杜氏拟杆菌，普通拟杆菌等多个拟杆菌菌种丰度降低，而拜氏梭菌，鲍氏梭菌，巴氏芽孢梭菌，丙酮丁醇梭菌等丰度升高。为了验证细菌功能，通过灌胃给转基因型小鼠补充多种拟杆菌和梭菌活性菌液，发现补充卵形拟杆菌可以有效减少小鼠脑内 Aβ 沉积，改善行为学症状。相反，补充拜氏梭菌会加重 Aβ 沉积，提示肠道菌群对 AD 的影响具有双向性，并且可以通过调节肠道菌群发挥治疗 AD 的作用。

关键词：阿尔茨海默症；肠道菌群；拟杆菌；梭菌

P19-2 肠道微生物及其代谢途径对心血管疾病的潜在影响

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背景：人类肠道微生物（GM）在人体健康调控方面发挥着重要作用。虽然 GM 可通过调控宿主炎症和代谢反应来参与心血管代谢，但 GM 对心血管疾病（CVD）的影响程度和机制尚不可知。

方法：本研究利用 16S rRNA 测序技术对 157 名参与者的粪便样本进行了检测，并使用 DADA2 和 Phyloseq R 包对测序数据进行了处理、分析。另外，分别通过调查问卷及尿液生化检测的方式对人群饮食、生活习惯、健康状况和疾病情况等进行了调研、检测。

结果：研究显示高血脂（HL）与高尿酸（HU）人群的总体微生物多样性呈降低趋势，且饮食、生活习惯相关表型变量对微生物多样性有潜在影响。关联性分析结果揭示了 GM 与高血脂、高尿酸症，以及尿液检测指标、健康、保健品相关表型的诸多关联。值得注意的是，我们发现了高血脂与一些微生物的微弱关联，以及高尿酸与菌群代谢途径的显著关联。另外，我们还发现了便秘、易怒、蛋白粉等健康、保健品相关变量与肠道微生物的显著关联。

结论：高血脂和高尿酸与 GM 的关联性，进一步表明了 GM 可能参与 CVD 的发生发展。另外，本研究支持了 GM 介导的代谢途径对高血脂及高尿酸的影响。在下一步研究中，可定向针对 CVD 人群进行多重表型组学（肠道微生物、体液生化检测、用药、饮食情况）分析，以进一步揭示 GM 参与 CVD 发生的潜在机制及靶向干预措施，为 CVD 的临床治疗诊断和治疗提供参考。

关键词：肠道微生物，心血管疾病，高血脂，高尿酸，代谢通路

P20 自主神经

P20-1 Sex-dimorphic kidney-brain connectivity map of mice

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The kidneys are essential organs for maintaining the body's homeostasis and the neural system controls kidney function, extending into the vasculature and tubules of the renal cortex and medulla. Although central autonomic nuclei anatomically multi-synaptically connect with the kidneys, it remains unclear whether there are any differences in neural connections between the nervous systems and those of the renal cortex and medulla in male and female mice. Here, we used the pseudorabies virus to map the central innervation network of the renal cortex and medulla in both sexes. The data revealed that the primary motor and somatosensory cortices and the red nucleus exhibited a contralateral-bias pattern, the paraventricular nucleus of the hypothalamus and parasubthalamic hypothalamus exhibited an ipsilateral-bias pattern, while kidney innervating neurons distributed symmetrically in the midbrain and hindbrain. Sex differences were found in the distribution of left kidney-connected neurons in the lateral hypothalamus and the distribution of renal cortex and medulla-connected neurons in the central amygdala, lateral hypothalamus, and parasubthalamic hypothalamus. The percentage of neurons that simultaneously connected to both the left and right kidneys was higher in the hindbrain, but there were no sex differences. Our findings provide a comprehensive understanding of the brain-kidney network in males and females and can benefit researchers in developing effective treatments for kidney-related brain disorders.

Keywords: kidney innervation, sexual dimorphism, pseudorabies virus, central neural system

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P20-2 Elaborate spontaneous activity atlas-driven behavior patterns in both sexes

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Animal spontaneous behavior is influenced by a combination of genetics, environmental cues, and internal states, resulting in specific behavior patterns. For decades, researchers have traditionally used an open-field test to evaluate animal spontaneous behavior and position preference to determine their level of locomotor activity and anxiety-like behavior. However, the postural changes, the dynamic parameters of movements, and the spatiotemporal variation rules of spontaneous behavior in animals in an open field remain incompletely elucidated. Additionally, there is a lack of data-driven methods for studying spatial preferences in the open field and comprehensive data on spontaneous behavior in male and female mice under different experimental conditions. It is well known that the behavior can be highly variable, with responses differing widely between repeated presentations of identical paradigms. Here, we utilized a posture-based machine learning-driven behavior analysis system to generate a highly reproducible

and reliable atlas of spontaneous behaviors. This atlas includes high-dimensional patterns of spontaneous behavior, transition relationships between different movements, and sex-specific characteristics in spontaneous behavior patterns under different experimental conditions. We also presented a new method for studying spatial preferences in a square open field. Our findings reveal the characteristics of spontaneous behavior and provide empirical support for including both sexes in spontaneous behavior experiments. This is essential for furthering our knowledge of the neural mechanisms of cognition and behavior.

Keywords: behavior pattern, machine learning, sex differences, computational ethology

P20-3 电刺激迷走神经诱导的 SDF-1α 参与梗死心脏的血管生成及修复

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研究目的：探索电刺激迷走神经在梗死心脏的冠状动脉内皮细胞和血管生成中的作用及机制。

材料与方法：结扎左冠状动脉前降支（LAD）制备大鼠心肌梗死（MI）后 7 天，在腹膜内给予 α7-nAChR 抑制剂美加明或 mAChR 抑制剂阿托品后 1 小时或在梗死心脏局部注射 Ad-shSDF-1α 后 3 天，用电刺激处理左颈迷走神经。用 ELISA 法检测心脏组织乙酰胆碱（ACh）和血清 ACh、TNFα、IL-1β 和 IL-6 水平，以确定 VNS 是否成功。利用脂多糖（LPS）建立 HCAECs 炎症损伤模型，通过评估 TNFα、IL-1β 和 IL-6 水平和内皮细胞小管形成进行鉴定。免疫组织化学染色评估梗死心脏中 CD31 阳性血管密度和 SDF-1α 的表达。免疫荧光染色分析 SDF-1α、CXCR4 和 CXCR7 在 HCAECs 中的表达和分布。

研究结果：电刺激迷走神经降低了血清 TNF-α、IL-1β 和 IL-6 水平，增加了心脏组织和血清 ACh 水平，增加了冠状动脉内皮细胞 SDF-1α 表达和 CD31 阳性血管密度，这些都被美卡明或阿托品所取消。此外，Ad-shSDF-1α 可取消电刺激迷走神经在血管新生中的作用。LPS 增加了冠状动脉内皮细胞 TNFα、IL-1β 和 IL-6 水平，降低了小管形成。ACh 逆转了 LPS 对 SDF-1α 表达的抑制作用及其在冠状动脉内皮细胞沿小管分支的分布，美加明或阿托品可显著取消 ACh 的作用。ACh 诱导冠状动脉内皮细胞 SDF-1α 的表达，同时增加 pAKT 和 pSp1 的水平，PI3K/Akt 阻断剂渥曼青霉素或 Sp1 阻断剂光辉霉素可取消 ACh 作用。功能上，电刺激迷走神经改善了左心室功能，而 Ad-shSDF-1α 可取消此效应。

研究结论：电刺激迷走神经通过诱导 SDF-1α 的表达及其沿小管新分支的重新分布促进血管新生以修复梗死心脏，此作用与 m/nAChR-AKT-SP1 信号通路有关。

关键词：心肌梗死，迷走神经刺激，血管生成，SDF-1α，SP1。

P20-4 RGC32 在心肌梗死后心脏重构与血管新生匹配中的作用及机制

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研究目的：探讨 RGC32 对心肌梗死后小鼠心脏重构及缺血心肌血管新生的影响。

材料与方法：选用 8-12 周龄 C57BL/6 雄鼠和 RGC32 全敲雄鼠，将 C57BL/6 雄鼠和 RGC32 全敲雄鼠随机分为假手术组、术后 1d、3d、7d、14d、28d 组，每组 10 只，通过永久性结扎冠状动脉左前降支前 1/3 处建立心肌梗死模型。对其小动物超声进行心功能评价、体内注射伊文思蓝（EBD）检测心肌坏死、TUNEL 染色来检测心肌细胞凋亡、MASSON 染色观察心肌损伤程度、麦胚凝集素（WGA）荧光染色观察心肌肥大，免疫组织化学检测各组 VEGF-A、CD31、α-SMA 阳性密度。

研究结果：小动物超声结果显示，RGC32 全敲小鼠比 WT 小鼠心功能显著改善;MASSON 染色显示，RGC32 全敲小鼠比 WT 小鼠心脏梗死面积显著减少; WGA 荧光染色显示，RGC32 全敲小鼠比 WT 小鼠心肌细胞横截面积显著减小；伊文思蓝和 TUNEL 染色结果显示，RGC32 全敲小鼠比 WT 小鼠心肌细胞坏死和凋亡数目均显著减少；免疫组织化学染色结果显示，RGC32 全敲小鼠比 WT 小鼠 CD31、α-SMA 阳性密度均显著增加。

研究结论：在本研究中我们发现，心肌梗死时，RGC32 的表达水平随着心肌梗死时间延长逐渐升高。在心肌梗死后，与 WT 组小鼠相比，RGC32 全敲组小鼠梗死面积减少，心脏功能改善，大量的血管新生以及少量的心肌细胞凋亡、坏死，降低了心脏破裂的死亡率，改善心肌梗死后不良重塑如心肌肥厚和左室增大。在这里，我们的研究证明 RGC32 缺失通过抑制梗死区域心肌细胞的凋亡、坏死和促进梗死区有效的血管新生，在缺血性心脏损伤时发挥保护作用。

关键词：RGC32;心肌梗死;缺血心肌;血管新生;心脏重构

P20-5 NE 介导 Noggin 调节间充质干细胞成骨分化的作用机制

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研究目的：探索交感神经兴奋过度释放去甲肾上腺素在BM-MSCs成骨分化中的作用及机制。

研究方法：首先，皮下植入 NE 缓释泵建立模拟交感神经长期过度兴奋的动物模型，取股骨行 microCT；免疫组织化学染色检测 OSX、OCN 和 CTSK 表达；组织免疫荧光双染检测 TH 和 MSC 标志物（CD90、Nestin 和 NG2）是否同时存在于骨髓微环境。其次，建立成熟稳定 BM-MSCs 体外培养体系，使用 NE 缓释泵建立模拟交感神经长期过度兴奋的 BM-MSCs 细胞模型，观察 NE 缓释泵对钙结节影响；用 Q-PCR 检测 OSX、Runx2、ALP、OCN 的 mRNA 表达水平变化。最后，收集不同时间段 NE 缓释泵处理的 BM-MSCs，通过 RNA-Array 技术筛选出有显著差异 Noggin 基因，并用 WB 检测 Noggin、AKT 不同亚型的蛋白水平变化；利用 AKT 激动剂 SC79 和 NE 缓释泵共同处理 BM-MSCs，明确钙结节变化情况；免疫组织化学染色检测 Noggin、AKT、p-AKT 等指标变化。

研究结果：在体实验中持续释放NE，小鼠的骨质下降，OSX、OCN表达显著下降，CTSK表达无显著差异。小鼠骨髓微环境中TH分别和（CD90、Nestin、NG2）相互接触。离体实验中持续释放NE，钙结节含量明显减少且具有剂量依赖性的特征，OSX、Runx2、ALP、OCN的mRNA水平均显著下降。Noggin是缓释泵释放NE，BM-MSCs成骨分化不同时间点均发生显著变化的差异基因，并且Noggin蛋白表达亦明显上升。持续释放NE，p-AKT1/AKT1升高、p-AKT2/AKT2、p-AKT/AKT下降，使用SC79会部分逆转缓释泵释放NE降低的钙结节含量。缓释泵释放NE，小鼠胫骨骨组织中P-AKT/AKT比值下降，而Noggin蛋白表达水平明显升高。

研究结论：交感神经纤维与BM-MSCs在空间上存在物理接触，模拟交感神经长期过度兴奋的微渗透压缓释泵持续释放NE呈剂量依赖性的抑制BM-MSCs成骨分化，该作用与PI3K-AKT信号通路介导Noggin上调有关。

关键词：去甲肾上腺素；骨髓间充质干细胞；成骨分化；Noggin

P21 干细胞生理

P21-1 LncRNA-CIR6 诱导间充质干细胞转化为心肌细胞并抵制心肌梗死的作用

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转染 LncRNA-CIR6 至骨髓间充质干细胞（MSCs）和人脐带间充质干细胞（hUCMSCs），第 10 天时观察 cTnT 表达并分析心肌样细胞转化率。C57BL/6 小鼠分为假手术组、心梗组、LncRNA-CIR6 组、LncRNA-CIR6+hUCMSCs 组。LncRNA-CIR6 组和 LncRNA-CIR6+hUCMSCs 组尾静脉注射 100μL 的 AAV9-cTnT-LncRNA-CIR6-ZsGreen，假手术组和心梗组注射等量 AAV9-cTnT-ZsGreen。待 3 周后制备 AMI 模型。术后 1 周，LncRNA-CIR6+hUCMSCs 组小鼠尾静脉注射 hUCMSCs（5×10^5/100μL）。再经 10 天时，测定心功能和心梗面积。转染 LncRNA-CIR6 的 BMSCs 和 hUCMSCs 转化为表达 cTnT 的心肌样细胞，且平均转化率分别为 86.73%±0.3756%和 95.43±2.130%。未转染细胞未能表达 cTnT。与心梗组相比，LncRNA-CIR6 组和 LncRNA-CIR6+hUCMSCs 组小鼠心功能增加，心梗面积减小。而 LncRNA-CIR6+hUCMSCs 组心功能与心梗面积更优于 LncRNA-CIR6 组。LncRNA-CIR6 在体内可能通过诱导 hUCMSCs 转化为心肌细胞从而抵制心肌梗死，改善心功能。LncRNA-CIR6 转录表达区域在人类基因组第 17 号染色体的反向链，功能区域位于序列中的 0-50/190-255 号核苷酸。在 LncRNA-CIR6 相互作用的蛋白中，与功能区域结合位点大于 10 个，同时与心肌细胞增殖和分化相关的蛋白只有 CDK1。LncRNA-CIR6 的作用机制可能与 CDK1 有关。

关键词：LncRNA；间充质干细胞；心肌梗死

P21-2 KPC1 基因敲除小鼠体重、肌纤维类型及其糖代谢变化特征

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研究目的：观察 KPC1 基因对出生后体重、肌纤维类型及其糖代谢变化的影响。

材料与方法：利用已构建的 KPC1 基因敲除小鼠，采用杂合子与杂合子交配繁殖。分别于出生后第 1、3、5、14、28、40、60、90、100 天，测量 KPC1 小鼠体重的变化；随后行糖耐量试验、胰岛素耐受试验；最后取材比鱼目肌、胫前肌，利用肌球蛋白重链 I 抗体（NOQ7.5.4D）染色，计数高倍视野下肌球蛋白重链 I 肌纤维数目。

研究结果：KPC1 基因敲除的纯合子小鼠（KPC1-/-）、杂合型小鼠（KPC1+/-）比野生型小鼠（WT）出生时体重低，但在喂养 90 天左右时纯合子小鼠体重逐渐超过野生型小鼠。KPC1-/-型小鼠糖耐量稍高于 WT 型小鼠；胰岛素耐受实验中，KPC1-/-型小鼠明显高于 KPC1+/-型小鼠。与野生型鼠相比，KPC1-/-鼠肌球蛋白重链 I 抗体阳性慢肌数目减少。

研究结论：KPC1 基因敲除可能通过影响出生体重、骨骼肌纤维类型而影响出生后骨骼

肌糖代谢功能。

关键词：KPC1 基因；体重；肌纤维类型；血糖

P21-3 A novel function of p21 in maintaining the self-renew of normal hematopoietic stem cell through c-Kit

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Hematopoietic stem cells (HSCs) are bone marrow (BM) resident stem cells responsible for maintaining the hematopoietic system throughout life. Mounting studies show that it is an exquisitely regulated complicated process for the maintenance of HSCs involving numerous molecules. P21, encoded by the gene CDKN1A, is a polypeptide containing 164 amino acids, with a molecular weight of about 21 kDa. It associates with various targets including transcription factors and kinases to perform a wide range of critical biological functions. To date, the role of p21 in HSCs has not been thoroughly investigated considering the previous paradoxical results.

In this study, we employed p21-tdTomato mice, a model that can distinguish the p21+ and p21- LT-HSCs based on the fluorescence intensity of tdTomato. Importantly, this approach circumvents the necessity for p21 knockout. Our results suggested that p21+ LT-HSCs possessed increased self-renewal capacity. Therefore, we performed the integrative analysis of RNA-seq, ATAC-seq and CUT&Tag-seq data of H3K4me1, H3K4me2, H3K4me3, H3K27Ac to ascertain the target genes in p21+ LT-HSCs. We found that the expressions of zbtb18 are upregulated in p21+ LT-HSCs compared with p21- LT-HSCs. The knockdown of zbtb18 in c-Kit+ cells severely impaired their reconstitution capability and survival, highlighting the critical role of zbtb18 in maintaining HSC function and homeostasis. Moreover, the results showed that p21 can interact with Zbtb18, a transcriptional repressor to down-regulate the expression of c-Kit which underline the increased repopulating ability of p21+ LT-HSCs. These findings provide novel insights into the physiological function of p21 in LT-HSCs different from the conventional role of CKI during normal nonperturbed homeostasis.

Keywords: p21, hematopoietic stem cell, self-renew, c-Kit

P21-4 Tibetan umbilical cord mesenchymal stem cell exosomes improve hypoxic pulmonary hypertension by inhibiting pulmonary vascular remodeling

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Aims: Pulmonary hypertension (PH) is a progressive disease that involves pulmonary vasoconstriction, pulmonary vascular remodeling, and right ventricular hypertrophy, ultimately leading to right heart failure. However, current treatments for pulmonary hypertension have several limitations. This study aims to explore the therapeutic potential of Tibetan umbilical cord mesenchymal stem cell (MSC) exosomes (exos) in treating PH, and to compare their treatment efficacy with Han Chinese umbilical cord MSC exosomes.

Methods and results: A rat model of hypoxic pulmonary hypertension (HPH) was established in vivo to study the effects of exosomes derived from human umbilical cord mesenchymal stem cell (hUCMSC) supernatant. Additionally, an in vitro model of hypoxia-induced pulmonary artery smooth muscle cell (PASMC) injury was established. The therapeutic effects of Tibetan-MSC-exo and Han-MSC-exo on HPH were investigated using various techniques such as immunohistochemistry, Western blotting, an EdU cell proliferation kit, and Transwell assay. The results demonstrated that Tibetan-MSC-exo had a more significant impact in attenuating pulmonary vascular remodeling and right ventricular hypertrophy (RVH) in HPH rats compared to Han-MSC-exo. In cell culture experiments, Tibetan-MSC-exo showed a stronger inhibition of hypoxia-induced PASMC proliferation and migration. Furthermore, this study revealed that Tibetan-MSC-exo downregulated TGFβ1 expression in HPH rats and hypoxia-induced PASMCs to a greater extent than Han-MSC-exo. It was also observed that overexpression of the TGFβ1 gene diminished the therapeutic effects of both Tibetan-MSC-exo and Han-MSC-exo on hypoxic injury.

Conclusion: In this study, we demonstrated that Tibetan-MSC-exo exhibited a superior effect compared to Han-MSC-exo in treating HPH. Furthermore, we confirmed that this mechanism was associated with the down-regulation of the TGFβ1/p-Smad2/3 pathway.

Keywords: hypoxic pulmonary hypertension, Tibetan-MSC-exo, Han-MSC-exo, TGFβ1

P21-5 Wnt2/β-catenin 通路在 C57BL/6 小鼠肝再生修复中的变化研究

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研究目的：探讨 Wnt2/β-catenin 通路在 C57BL/6 小鼠肝再生修复中的变化特征。

材料与方法：将 C57BL/6 雄鼠随机分为假手术组（Sham 组）、术后 1 d 组、术后 2 d 组、术后 4 d 组、术后 6 d 组、术后 8 d 组，手术组小鼠行部分肝切除术（PHx），分别切除肝左叶和中叶。于术后第 1、2、4、6、8 天收集血浆和肝脏组织，丙氨酸氨基转移酶(ALT)和天门冬氨酸氨基转移酶(AST)生化分析试剂盒检测血浆 ALT 和 AST 活力；免疫组化检测各组 Ki67 阳性细胞数目；免疫荧光检测 HNF4-α 和 Ki67 双阳性细胞数、LYVE1 和 Ki67 双阳性细胞数及 β-catenin 入核细胞数；Western blot 检测各组 Wnt2 蛋白的表达，分析其在肝再生过程中表达的时间特征。

研究结果：PHx 后第 6 天肝质量、肝质量/体质量达到高峰，接近 Sham 组水平。PHx 后第 1 天肝损伤严重，第 4 天即可恢复正常。PHx 后第 2 天主要是肝细胞增殖，第 4、6 天主要是肝窦内皮细胞增殖，同时 Wnt2/β-catenin 通路被激活。

研究结论：肝脏有强大的再生修复功能，与肝实质细胞和肝窦内皮细胞的快速增殖密切相关，Wnt2/β-catenin 通路在小鼠肝脏再生修复中被激活。

关键词：肝部分切除术；肝再生修复；Wnt2；β-catenin

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P21-6 单细胞水平揭示淋系偏向 HSC 亚群的分子及功能特征

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目的：造血干细胞（HSC）利用其自我更新和多向分化能力维持造血系统的动态平衡。Yamamoto 等根据 CD150 和 CD41 的表达将 Lin-Sca1+c-Kit+(LSK)CD34-细胞划分为三个亚群。其中 Fraction III（CD150-CD41-）表现为一过性髓系重建和持续性淋系重建，但其主要维持淋系重建的机制并未被阐明。我们在 Yamamoto 定义的基础上增添 CD201 以得到更加

纯化的表型 HSC，并将 CD150+CD48-CD201+LSK 和 CD150-CD48-CD201+LSK 细胞分别定义为 HSC1 和 HSC2，进一步探索 HSC 向不同谱系分化的潜在机制和可用于进一步分离纯化淋系偏向 HSC 的分子标记。

方法和结果：体外集落形成实验结果显示，HSC2 相较于 HSC1 克隆形成能力显著降低(HSC1 74.6% vs.HSC2 37.1%, P = 0.0002)，但仍可形成 nmEMk 集落，提示其同样具有多向分化潜能。通过非竞争性移植实验我们发现，HSC1 与 HSC2 均具有放射保护作用，且相较于以髓系重建为主的 HSC1，HSC2 表现为一过性髓系高重建后转变为以淋系低水平重建为主，提示 HSC2 可能主要富集淋系偏向的 HSC。竞争性移植和单细胞移植实验结果提示相较于 HSC1，HSC2 的重建比例和重建水平较低，但其中存在可长期（16 周）维持造血重建且以淋系重建为主的 HSC。最后我们将利用单细胞转录组测序深入探索 HSC1 和 HSC2 可能的分子差异和分子机制。

结论：表型 HSC2 生物学功能表现为以淋系偏向为主，其中存在可长期维持造血重建的 HSC。但 HSC2 较低的克隆形成效率和重建比例提示其内部仍存在较大异质性。本研究在单细胞水平揭示了具有长期维持造血能力的、淋系偏向的 HSC 的存在，将为 HSC 向不同谱系分化的潜在分子机制以及淋系偏向 HSC 的分离纯化提供有价值的线索。

关键词：造血干细胞，谱系分化，淋系重建，单细胞移植

P21-7 干细胞在神经肌肉疾病修复中的作用与机制

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高血压、糖尿病、心衰是常见慢病，严重威胁健康，确立肌细胞类型及其代谢模式转变的分子机制和寻找有效防治手段一直是研究的热点和难点。研究建立单次、间断单次、连续单次及微渗透泵持续释放给药模式给予 NE、肾上腺素、异丙肾上腺素模拟交感神经不同模式的过度兴奋，发现其抑制成肌细胞分化融合及其改变肌纤维类型；揭示 Ezrin/Periaxin 在成肌细胞分化融合中时空匹配模式，建立新型 Ezrin/Periaxin 协同基因治疗神经损伤相关肌萎缩方案；建立电刺激迷走神经促进血管新生、动脉生成与心肌细胞肌节组装及其代谢模式的匹配的治疗方法；确认交感神经长期过度兴奋激活补体应答基因 32(RGC32) 在高血压、肌细胞命运与类型及其代谢模式关联机制；建立心脏与神经肌肉类器官新模型，为操纵干细胞活性改变其分化、肌细胞类型及其能量代谢的提供新的可能临床策略。

关键词：干细胞；交感神经过度兴奋；成肌分化；肌节组装；能量代谢

P21-8 Exosomes derived from hypoxia-pretreated human umbilical cord mesenchymal stem cells inhibit endothelial-to-mesenchymal transition of human pulmonary arteriole endothelial cells

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Objective To investigate the effects of exosomes (Exo) derived from hypoxic-pretreated human umbilical cord mesenchymal stem cells (hUCMSCs) on endothelial-to-mesenchymal transition of human pulmonary arteriolar endothelial cells (HPAECs). **Methods** Primary hUCMSCs were isolated by tissue adhesion method, cultured and identified. HUCMSCs-Exo was extracted by ultrafiltration and identified. HPAECs were cultured and identified by CD31 and α-SMA immunofluorescence. HPAECs were divided into normoxia control group (N-Con), hypoxia control group (H-Con), hypoxia+normoxia exosome group and hypoxia+hypoxia exosome group. The migration ability was detected by Transwell experiment. Tube formation ability was detected by tube formation experiment. The expression levels of endothelial cell markers and mesenchymal markers were detected by immunofluorescence and Western blot. **Results** Compared with the N-Con group, cell migration and tube formation were increased in the H-Con group (P<0.01), the expression levels of endothelial markers CD31 and VE-Cadherin were decreased, and the expression levels of mesenchymal markers α-SMA and vimentin were enhanced(P<0.01). Compared with the H-Con group, cell migration and tube formation were decreased in the H-NExo group (P<0.01), and expression levels of endothelial marker CD31 was increased (P<0.01), but VE-Cadherin, α-SMA and vimentin were not different. Compared with H-NExo group, cell migration and tube formation were less in H-HExo group (P<0.05), and the expressions levels of endothelial markers CD31 and VE-Cadherin were increased (P<0.05), the expressions levels of mesenchymal markers α-SMA (P<0.05) and vimentin were increased (P<0.01). **Conclusion** Exosomes derived from hypoxia-pretreated human umbilical cord mesenchymal stem cells inhibit endothelial-to-mesenchymal transition of human pulmonary artery endothelial cells.

Keywords: hypoxia; human umbilical cord mesenchymal stem cells; exosomes; human pulmonary arteriole endothelial cells； endothelial-to-mesenchymal transition

P22 血栓与止血

P22-1 Potential mechanism of platelet-derived miR-126-3p/PI3K/Akt axis in modulating the platelet responsiveness

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Background: Platelets contain a broad repertoire of microRNAs (miRNAs) that with the expression of miR-126-3p ranked the second in the platelet. This study aimed to explore the mechanism of platelet-derived miR-126-3p in regulating platelet responsiveness.

Methods: Ticagrelor treated patients with acute coronary syndrome (ACS) were recruited and divided into the HTPR (high on-treatment platelet reactivity) group and the LTPR (low on-treatment platelet reactivity) group according to PI_{ADP} > 98 % designated as the extremely low-responder and PI_{ADP} < 52% as the extremely high-responder. The expression of miR-126-3p derived from the platelets of the patients was detected by qPCR. The interaction between miR-126-3p and PIK3R2 was screened by bioinformatic softwares of miRDB and Starbase, and verified by dual-luciferase reporter assay in 293T cell line. The regulation of miR-126-3p on PIK3R2 (the protein coded by the gene of PI3K) expression was detected by qPCR and western blot in MEG01 cell lines, which could be regularly applied for the in vitro molecular signal analysis of platelet. The mechanism of platelet-derived miR-126-3p via PIK3R2 signal in modulating the platelet responsiveness was investigated by collagen-induced fibrinogen binding inhibition levels in flow cytometry.

Results: Compared to the patients with HTPR (n=49), significantly higher expression of miR-126-3p could be observed in the patients with LTPR (n=49) (p=0.002). Bioinformatic analysis and dual-luciferase reporter assay showed that miR-126-3p could directly bound to PIK3R2. While PIK3R2 protein levels were significantly decreased when miR-126-3p was over expressed, and significantly increased when miR-126-3p was knockdown in MEG01 cells lines. The expression of PIK3R2 mRNA was unchanged when miR-126-3p was over expressed or knockdown. Flow cytometry showed that platelet responsiveness was significantly increased when miR-126-3p was knockdown. LY294002, as a specific inhibitor of PIK3R2 could rescue the inhibitory effect of platelet responsiveness in miR-126-3p knockdown MEG-01 cells.

Conclusion: Platelet derived miR-126-3p could regulate platelet responsiveness via the

PI3K/Akt signal axis. It could be further investigated as a potential microRNA derived drug for antiplatelet treatment in patients with ACS.

Key words: miR-126-3p; platelet responsiveness; PI3K/AKT signaling; platelets

P22-2 单血小板力学图谱的观测

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在止血和血栓形成过程中，整合素传递的细胞力对于血小板粘附、激活、聚集和收缩至关重要。 研究者期待测量和绘制单个血小板力，这也有助于临床应用。 传统的基于力应变的细胞牵引力显微镜分辨率较低，这对于血小板的细胞力图绘制来说并不理想。为了解决这个问题，实现亚微米血小板力图的描绘，我们开发了一种可被力激活的生物传感器，命名为集成张力传感器（ITS），它可以直接将分子张力转换为荧光信号，因此可以直接通过荧光成像。 利用 ITS，我们以 0.4 μm 的分辨率绘制了单个血小板中的细胞力图。 我们发现血小板力分布具有强极化，对抗血小板药物治疗敏感替罗非班，表明 ITS 力图可以报告抗血小板药物效果。ITS 还进行了校准血小板中的整合素分子张力，并揭示了血小板粘附过程中产生的张力存在两种不同的水平：12-54 皮牛顿（标称值）。血小板收缩过程中产生的高于 54 皮牛的张力。总体而言，ITS 是用于血小板力学生物学研究的强大生物传感器，并且具有很大的潜力用于抗血栓药物开发和评估健康和疾病中血小板活性。

关键词：血小板 整合素 传感器

P22-3 Repurposing of Rilpivirine for preventing platelet β3 integrin-dependent thrombosis by targeting c-Src active autophosphorylation

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Background: HIV-infected individuals are known to be at higher risk for thrombotic cardiovascular disease (CVD), which may also be differentially affected by components of anti-HIV drugs. To identify the effects of a series of FDA-approved anti-HIV drugs on platelet aggregation in humans, focusing on the novel pharmacological effects of rilpivirine (RPV), a reverse transcriptase inhibitor, on platelet function both in vitro and in vivo and the mechanisms involved.

Methods and Results: *In vitro* studies showed that RPV was the only anti-HIV reagent that consistently and efficiently inhibited aggregation elicited by different agonists, exocytosis, morphological extension on fibrinogen, and clot retraction. Treatment of mice with RPV significantly prevented thrombus formation in $FeCl_3$-injured mesenteric vessels, postcava with stenosis surgery, and ADP -induced pulmonary embolism models without defects in platelet viability, tail bleeding, and coagulation activities. RPV also improved cardiac performance in mice with post-ischemic reperfusion. A mechanistic study revealed that RPV preferentially attenuated fibrinogen-stimulated Tyr773 phosphorylation of β3-integrin by inhibiting Tyr419 autophosphorylation of c-Src. Molecular docking and surface plasmon resonance analyses showed that RPV can bind directly to c-Src. Further mutational analysis showed that the Phe427 residue of c-Src is critical for RPV interaction, suggesting a novel interaction site for targeting c-Src to block β3-integrin outside-in signaling.

Conclusion: These results demonstrated that RPV was able to prevent the progression of thrombotic CVDs by interrupting β3-integrin-mediated outside-in signaling via inhibiting c-Src activation without hemorrhagic side effects, highlighting RPV as a promising reagent for the prevention and therapy of thrombotic CVDs.

Key Words: rilpivirine; Platelet; β3 integrin; Src autophosphorylation; Thrombosis; Thrombotic disease.

P22-4 胞外巯基异构酶 ERp72 调控整合素 Mac-1 活性影响中性粒细胞募集

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目的：本研究拟检测巯基异构酶 ERp72 通过调节整合素 Mac-1 活性从而影响中性粒细胞 PMNs 粘附和募集的分子机制。**方法：**CRISPR/Cas9 构建 *Erp72*$^{-/-}$小鼠，骨髓移植构建髓系敲除小鼠。荧光活体成像检测小鼠睾提肌微血管内 PMNs 的滚动和黏附。内毒素 LPS 诱导急性肺损伤 ALI 模型。Calcein-AM 染色检测 PMNs 静态粘附。荧光共聚焦显微镜和脂筏梯度分离法检测 PMNs 表面 Mac-1 与 ERp72 的分布。免疫共沉淀法结合 Maleimide 标记，测定 ERp72 与 Mac-1 的巯基反应。生物膜力学探针 BFP 技术定量检测 Mac-1 与其配体 ICAM-1 的结合力。**结果：**荧光活体成像显示 *Erp72*$^{-/-}$体内 PMNs 在睾提肌微静脉内的粘附减少但滚动增多；在 LPS 诱导的 ALI 模型中，*Erp72*$^{-/-}$小鼠 PMNs 渗出减少；骨髓移植实验证实 PMNs 的迁移缺陷由髓系 ERp72 敲除导致。体外实验显示 *Erp72*$^{-/-}$ PMNs 存在黏附缺陷，且可以被 ERp72-C（野生型）而不是 ERp72-A（无活型）拯救。抑制整合素 LFA-1 能进一步减少 *Erp72*$^{-/-}$ PMNs 的黏附，而阻断 Mac-1 无显著效应，提示 *Erp72* 敲除导致的黏附缺陷是由 Mac-1 介导的。流式细胞术进一步证实 *Erp72*$^{-/-}$ PMNs 上 Mac-1 特异性的 Fibrinogen 结合显著减少,证实 Mac-1 活化受阻。BFP 实验证实 ERp72 通过其 CGHC 催化基序能增强 Mac-1 与 ICAM-1 的结合力。荧光共聚焦与梯度离心显示 Mac-1 与 ERp72 在 PMNs 表面脂筏中富集。免疫共沉淀结合活性巯基标记证实 ERp72 能结合 Mac-1 并参与 CD11b 亚基的二硫键重排。**结论：**ERp72 通过催化 CD11b 亚基的二硫键重排调控 Mac-1 活性从而影响 PMNs 的募集。

关键词：ERp72；整合素 Mac-1；中性粒细胞

P23 衰老与健康

P23-1 巨噬细胞胰岛素敏感性下降促进内皮细胞衰老及其机制

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背景 以胰岛素抵抗为特征的疾病显著加速机体衰老，但机制不明，巨噬细胞在胰岛素抵抗的相关疾病中发挥作用，但是巨噬细胞的胰岛素信号对内皮细胞衰老的影响尚不清楚。**目的** 明确巨噬细胞的胰岛素信号对内皮细胞衰老的影响并探讨其机制。**方法** 分离培养巨噬细胞特异性胰岛素受体敲除小鼠（MΦ-InsR KO 小鼠）及野生对照小鼠（WT 小鼠）骨髓来源的巨噬细胞（BMDMs），利用 BMDMs 条件培养基（CM）处理人脐静脉内皮细胞（HUVECs），检测内皮细胞增殖、迁移和成管功能及衰老水平变化，提取 BMDMs 外泌体进行 miRNA 测序，选择差异表达较为显著的 miR-29b-3p，向内皮细胞转染 miR-29b-3p 过

表达模拟物，测定内皮细胞的增殖、迁移、成管能力和衰老水平。**结果** （1）与 WT 小鼠的 BMDMs 的条件培养基相比，MΦ-InsR KO 小鼠的条件培养基可导致:内皮细胞增殖、迁移和成管能力显著降低（P<0.01)；SA β-半乳糖苷酶染色阳性率显著升高（P<0.01）；内皮细胞衰老相关通路蛋白 p53、p21、γH2AX 表达显著增加（P<0.05）；(2）miRNA 测序结果显示，与 WT-CM 相比，miR-29b-3p 在 MΦ-InsR-KO-CM 中表达量显著升高（P<0.05）;（3）与对照组相比，过表达 miR-29b-3p 后，内皮细胞增殖、迁移和成管能力显著降低 (P<0.05)；SA β-半乳糖苷酶染色阳性率显著升高（P<0.05）；内皮细胞衰老相关通路蛋白 p53、p21 表达显著增加（P<0.05）。**结论** 巨噬细胞胰岛素敏感性下降可抑制内皮细胞的增殖、迁移和成管能力，诱导内皮细胞衰老，其机制可能与巨噬细胞分泌的外泌体 miR-29b-3p 升高有关。

关键词：巨噬细胞胰岛素敏感性；人脐静脉内皮细胞；衰老；外泌体

P23-2 6PPD-quinone induced cellular senescence in differentiated H9c2 cardiomyocytes via blockage of autophagic flux

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Growing evidence demonstrated the link between the atmospheric pollutants and cardiovascular disease, which has been becoming main cause of human mortality. Recently, N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine (6PPD) as an additive in tires, and its oxidation product, 6PPD-quinone have gained widespread attention due to their toxic effects on human health. Apart from the reproductive toxicity, 6PPD-quinone has been observed to damage the intestinal permeability, liver and lung however, the effects of 6PPD-quinone on the heart remain largely unknown. In the current study, H9c2 myoblast were induced toward cardiac specific differentiation and subjected to 6PPD-quinone exposure continuously for 72h. Our results showed that 6PPD-quinone at a concentration of 500 μg/L changed the cell morphology, mainly manifested in becoming flattened and fibrous. Meanwhile, 6PPD-quinone downregulated the expression of MyoG (2-fold change), indicating the cardiac differentiation were partilly inhibited.

Notably, 6PPD-quinone exposure induced senescence in rat cardiomyocytes, the proportion of β-galactosidase positive cells was significantly higher in the 6PPD-quinone treated group (3.7% vs 13%, p<0.01). Immunofluorescence staining and western blot analysis revealed that 6PPD-quinone significantly upregulated the expression of p21, which mediates cellular

senescence via inhibiting cell cycle. To further evaluate the nucleus status, Laminin B and DNA double strand breaks which are associated with cellular senescence were also examined by immunofluorescence. Most importantly, our results revealed that 6PPD-quinone exposure upregulated the expression of protein which responsible for autophagy initiation and autophagosomes formation, respectively, Beclin1 (2.38-fold change, $P < 0.05$) and LC3-II/LC3-I (2.45-fold change, $P < 0.05$). However, p62, as a substrate for autophagy, was not degraded, but was upregulated (1.4-fold change, $P < 0.05$). By using Ad-mCherry-GFP-LC3B transfection experiment, the autophagic flux were emamined. It clearly revealed that the number of autophagosomes（69%）increased but the autophagolysosomes（29%）decreased in 6PPD-quinone group. Meanwhile, the addition of RAPA, autophagy activator, significantly restored the autophagolysosomes formation compared with the 6PPD-quinone treatment group. Interestingly, rapamycin significantly antagonizing increased proportion of β-galactosidase-positive cells, DNA double-strand damage, upregulation of p21 and remodeling of nuclear fibrillar layer proteins induced by 6PPD-quinone.

In conclusion, our experiments revealed that 6PPD-quinone exposure induced cardiac senescence via blockage of autophagic flux , thus deepening our understanding will help to reveal the mechanism of myocardial aging caused by environmental pollution.

Keywords: 6PPD-quinone, cardiac differentiation, autophagy, senescence

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P23-3 推拿促进肌肉干细胞自我更新改善肌少症的作用研究

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研究目的：肌少症是一种与增龄相关的进行性、全身肌肉量丢失，伴力量下降，乃至身体功能减退的综合征。其表现类似中医痿证，病机为脾胃脏腑虚弱，气血津液耗损。推拿从“治痿独取阳明”着手，辅以机械力效应，调和卫气营血，运化水谷精微，使脾气健运，濡养骨骼肌，以达改善机体功能之效。肌肉干细胞是骨骼肌重塑的关键靶细胞，其增殖分化是萎缩肌肉再生的基石。本研究旨在观察推拿能否通过促进肌肉干细胞自我更新，延缓骨骼肌萎缩，增强肌肉力量，从而改善机体功能。

研究方法：8 只 32 周龄健康雄性 SAMR1 小鼠设为对照组（C 组），16 只同龄 SAMP8 小鼠，随机分为模型组（M 组）和推拿组（T 组），每组 8 只。C 和 M 组正常喂养。T 组采用点按手法干预，借助压力传感器量化和监测推拿参数，术者拇指以金属球为媒介，节律

性点按小鼠后三里，力度约 4N，10 次/min，每侧 5min，每天 1 次，每周 5 天。每日观察各组小鼠的一般生活状态，每周测量并记录抓力和体重。末次推拿后 24h 取两侧小腿三头肌并记录肌质量，采用 HE 染色观察骨骼肌萎缩情况；RT-qPCR 和 Western Blot 技术分别检测骨骼肌增殖分化相关标志物 Pax7 与 MyoD 的基因和蛋白表达水平；双重免疫荧光染色检测 Pax7 与 MyoD 共定位情况；单因素方差分析统计分析实验数据。

研究结果：实验过程中，M 组小鼠进食及自主活动较 C 组减少，毛发干枯无光泽，脱毛严重；骨骼肌肌纤维排列松散；四肢相对抓力、肌肉质量/体重比值、肌纤维横截面积、Pax7 和 MyoD 的基因和蛋白表达显著下降（$P<0.05$），共定位趋势与 PCR、WB 一致。T 组较 M 组有明显改善，进食及自主活动增加，脱毛相对较少；肌纤维排列紧密，类似 C 组；干预前期抓力出现下降，而后增长（$P<0.05$）再趋于平稳，肌肉质量/体重比值、肌纤维横截面积、Pax7 和 MyoD 基因和蛋白表达显著提升（$P<0.05$），共定位趋势与 PCR、WB 一致。

研究结论：推拿可能通过促进肌肉干细胞自我更新延缓 SAMP8 小鼠骨骼肌萎缩，改善肌少症。

关键词：推拿；肌少症；肌肉干细胞；自我更新

P23-4 推拿改善 SAMP8 小鼠骨骼肌衰老的炎性机制研究

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目的：随着社会老龄化加剧，肌少症已成为重要的公共健康问题。新近研究不断强调炎症反应或是其发生发展的重要诱因之一，其中 NAMPT/NAD^+是调节骨骼肌代谢的重要物质，受炎性因子抑制。本实验从行为学、炎性因子以及 NAMPT/NAD^+等方面观察推拿对骨骼肌衰老的干预效果，为推拿改善骨骼肌衰老的炎性机制提供实验依据。 **方法：**健康雄性 28 周快速老化 SAMP8 小鼠 16 只，随机分为模型组(M 组)和推拿组(T 组)，每组 8 只，另设 8 只同龄抗老化 SAMR1 小鼠作年轻对照组 (C 组)。对 T 组小鼠进行为期 8 周的推拿干预，期间每周进行一次行为学测试，M 组不进行干预。最后，处死所有组的小鼠，收集并称重其股四头肌，本研究采用单因素方差分析。 **结果：**（一）40 周肌力测试：与 C 组相比，M 组的抓力数据有显著下降，（$p<0.01$）T 组与 C 组相比，有明显差异（$p<0.05$）。T 组与 M 组相比，有显著差异（$p<0.01$）（二）炎性因子：采用 elisa 技术测得相关数据：与 C 组相比，M 组的 IL-1β、TNF-α 水平有明显上升（$p<0.01$），T 组无明显差异（$p>0.05$）。T 组与 M 组相比，有明显下降趋势（$p<0.01$）。采用 PCR 技术，与 C 组相比，M 组 NF-kβ-P65 的水平有明显上升（$p<0.01$），而 T 组无明显差异（$p>0.05$）。T 组与 M 组相比，有显著下降趋势（$p<0.01$）。（三）蛋白表达：采用 PCR 技术，M 组 NAMPT 含量较 C 组和 T

组有显著下降（p＜0.05），C 组与 T 组无明显差异（p＞0.05）。采用 elisa 测得 NAD^+结果，与 C 组相比，M 组、T 组均有明显下降趋势（p＜0.01），M 组与 T 组相比，有明显下降趋势（p＜0.05）。NAMPT 的结果显示，M 组与 T 组相比无显著性差异（p＞0.05），但 C 组与 M 组、T 组相比有显著性差异（p＜0.01）。**结论：**经过 8 周的推拿干预，SAMP8 骨骼肌的炎症反应有明显改善，说明推拿相关穴位对延缓 SAMP8 小鼠骨骼肌衰老有积极作用。

关键词：肌少症；推拿；衰老；炎症

P23-5 The neuroinflammation mediates extracellular matrix remodeling to regulate the pathogenesis of Alzheimer's disease

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Alzheimer's disease (AD), the most prevalent form of dementia, poses a significant and escalating global health concern. Neuroinflammation and extracellular matrix (ECM) play crucial roles in the preservation of homeostasis and serve as pathological manifestations of AD. However, the precise mechanisms by which neuroinflammation influences ECM remodeling and subsequently modulates the pathogenesis of AD have yet to be fully elucidated. Here, we find neuroinflammatory stimulation can enhance the expression of ECM components aggrecan and versican, while influence the expression of ECM remodeling enzymes (such as MMP9, ADAMTS-1). Furthermore, the co-localization of aggrecan and astrocytes and microglial significantly increased under neuroinflammatory stimulation. In addition, the expression of neuroinflammation, ECM components and remodeling enzymes markedly increase in the brain of AD mouse model. Inhibition of ECM remodeling in the brain significantly alleviates AD neuroinflammation and cognitive behaviors. Our data revealed that neuroinflammation maybe regulate ECM remodeling to protect the pathology of AD. Consequently, this study establishes a robust theoretical and empirical foundation for comprehending the pathogenesis of AD, as well as devising diagnostic and therapeutic approaches.

Keywords: Alzheimer's disease; Neuroinflammation; Extracellular matrix remodeling.

P24 细胞和分子生理

P24-1 The ATF4-RPS19BP1 axis modulates ribosome biogenesis to promote erythropoiesis

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Erythroid cell production is driven by numerous transcription factors. Investigations into the signals and regulatory networks involved in erythropoiesis have provided significant insights into the biology of erythroid cells and clinical therapy. Previous work reported by our group and others have demonstrated that Atf4, a basic region-leucine zipper transcription factor, plays pivotal roles in fetal liver hematopoiesis, hematopoietic stem cell (HSC) maintenance, bone formation and tumorigenesis. Here, we demonstrated that loss of Atf4 in the hematopoietic system resulted in severe anemia. Atf4 deficiency led to cell cycle arrest in erythroid progenitor cells (EPCs) and impaired their CFU-E and BFU-E colony-forming ability. Single cell RNA-seq (scRNA-seq) analysis of bone marrow (BM) $Lin^{-}cKit^{+}$ cells confirmed the defects of erythropoiesis after Atf4 depletion. GO analysis of the downregulated genes from RNA-seq, ATAC-seq and H3K4me3 Cut&Tag data of Atf4-deleted MEP cells revealed that several terms related to erythrocyte differentiation and translation process were diminished. Combined multiple omics analysis and molecular assays indicate that Atf4 functions as a transcriptional activator of Rps19bp1. Downregulation of Rps19bp1 caused by Atf4 deletion led to decreased assembles of 40S proteins, such as RPS3, RPS6 and RPS19. The protein synthesis defect and impaired erythropoiesis were rescued upon Rps19bp1 overexpression in Atf4 knockdown MEL cell line or BM $cKit^{+}$ cells from Atf4-deficient mice. O-propargyl-puromycin (OP-Puro) incorporation and SUnSET assays further confirmed the global protein synthesis defect in Atf4-deficient MEP cells. Taken together, Atf4 promotes erythroid differentiation by regulating ribosome assembly via facilitating the transcription of Rps19bp1. Our current study uncovers an essential role of Atf4/Rps19bp1 in erythropoiesis.

Keywords: Hematopoiesis, Erythropoiesis, Atf4, Rps19bp1

P24-2 7,8-二羟基黄酮对 H_2O_2 诱导的 H9c2 心肌细胞损伤的保护机制

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目的：探讨 7, 8-二羟基黄酮（7, 8-Dihydroxyflavone，DHF）对 H_2O_2 诱导的 H9c2 心肌细胞损伤的保护作用及机制。**方法**：DHF 预处理 1 h 后，加入 700 μmol/L H_2O_2 共培养 24 h，通过 MTT 法和 TUNEL 法观察 DHF 的保护作用，通过 Western blot 法检测各种蛋白表达。**结果**：MTT 结果显示：DHF 对 H_2O_2 诱导的 H9c2 心肌细胞损伤具有明显的保护作用，以 10 μM 效果最显著。TUNEL 染色结果发现：H_2O_2 组 TUNEL 阳性细胞数明显增加，而 DHF 预处理可抑制上述变化。Western blot 结果显示：H_2O_2 损伤可导致两种炎症相关蛋白 iNOS 和 COX-2 表达量增加，而 DHF 有效抑制二者的上调。DHF 还抑制了 H_2O_2 诱导的 MAPK 信号通路（包括 p38MAPK 和 JNK）和核因子-κB (NF-κB)信号通路的激活。**结论**：DHF 对 H_2O_2 诱导的 H9c2 心肌细胞损伤具有明显的保护作用，该作用可能和抑制 MAPK 和 NF-κB 信号通路从而抑制炎症反应有关。

关键词：H9c2; 7,8-二羟基黄酮; 炎症; MAPK; NF-κB。

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P24-3 Inhaled nanotherapeutic agent for ischemic cerebrovascular disease by inducing ROS and abnormal mitochondrial autophagy

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Currently, human *health* is under seriously threat because of ischemic cerebrovascular disease (ICVD). Some studies show that high levels of reactive oxygen species (ROS) and mitochondrial dysfunction are key factors causing ischemic cerebrovascular disease. Therefore, the disease can be effectively treated by removing ROS and damaged mitochondria. Based on this principle, an Inhaled nanotherapeutic agent, P/D@Mn/Co_3O_4, was designed to achieve the treatment of ischemic cerebrovascular disease. It is a nanoparticle composed of platelet membrane and cationic liposome (2,3- (dioxy propyl)-trimethylammonium chloride, DOTAP) encapsulated with Mn/Co_3O_4. The platelet membrane endows the nanotherapeutic agent with the ability to target brain inflammatory regions; cationic liposome carries a strong positive charge on the surface of the nanotherapeutic agent, which can promote its strong electrostatic adsorption on the

mitochondria of inflammatory cells; Mn/Co_3O_4 can not only effectively removed excess ROS in cells, reduced oxidative stress of cells, protected nerve cells from apoptosis, but also depleted the H^+ around mitochondria, depolarized the mitochondrial membrane potential, induced mitochondrial autophagy, and removed abnormal mitochondria, thus eliminating excessive ROS from the source. When administered intranasally, Mn/Co_3O_4 encapsulated by platelet membrane and cationic liposome can bypass the blood–brain barrier, enter the brain through the trigeminal nerve and olfactory pathway, target the inflammatory region, and clear the ROS and damaged mitochondria in the affected area. In rat models of stroke and vascular dementia, P/D @ Mn/Co_3O_4 achieved effective inhibition of acute and chronic cerebral ischemia by removing ROS and damaged mitochondria from the affected area. These research results indicate that the nanotherapeutic agent $P/D@Mn/Co_3O_4$ developed in this study can achieve effective treatment of ischemic cerebrovascular disease.

Keywords: Mn/Co_3O_4; reactive oxygen species; mitochondrial dysfunction; nanotherapeutic agent; ischemic cerebrovascular disease; inhalation therapy

P24-4 GJB2/HNRNPA2B1 axis promoted the metastasis of pancreatic cancer under hypoxia via suppressing the exitrons-splicing of CTNNB1

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Background: Hypoxia constitutes a significant characteristic of pancreatic cancer (PC), which can propel the metastasis of PC cells. Nonetheless, the precise regulators implicated in the metastasis of PC cells under hypoxic condition remained largely obscure. The objective of the present investigation was to ascertain the function and underlying molecular mechanisms of gap junction protein beta 2 (GJB2) in the metastasis of PC cells under hypoxic environment.

Methods: CRISP-CAS9 library screen in conjunction with bioinformatics analysis were combinedly used to identify the pivotal role of GJB2 in both hypoxia and PC cell mobility. The expression and clinical significance of GJB2 in PC tissues and patients were assessed through the application of qRT-PCR, immunohistochemical staining, and Cox regression analysis. The impacts

of GJB2 on the metastasis of PC cells were accessed through the utilization of wound healing assays, transwell assays, immunofluorescence, and an *in vivo* lung metastasis model. Mechanically, the regulatory association between GJB2, heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1) and catenin beta 1 (CTNNB1) was determined through a combination of mass spectrometry analysis, mutant protein binding analysis, RNA-sequencing, and alternative-splicing related analysis. Moreover, the regulatory correlation between hypoxia-induced 1a (HIF1A) and GJB2 during hypoxic environment was examined through chromatin immunoprecipitation-PCR and luciferase reporter assays. Finally, computer molecular docking and biofilm interference technique were combinedly used to select appropriate pharmaceutical agents for targeting GJB2.

Results: The CRISPR-Cas9 library screen identified GJB2 as one of top factors influencing the migration of PANC-1 cells under both normoxic and hypoxic conditions; elevated mRNA and protein levels of GJB2 were observed in PC tissues in comparison to the non-tumor adjacent tissues, as well as in PC cells that were cultured under hypoxic conditions (1% O2) in comparison to those cultured under normoxic conditions (21% O2); increased GJB2 was most located in cytoplasm and nucleus of PC cell; expression of GJB2 was associated with the lymph node invasion, distant metastasis and TNM stage; elevated levels of GJB2 have been found to be correlated with unfavorable prognosis and may serve as a standalone prognostic indicator for patients with PC; in comparison to PC tissues characterized by low hypoxia, those displaying high hypoxia demonstrate heightened levels of GJB2; the downregulation of GJB2 resulted in a reduction of migration, invasion, EMT phenotype, and distant metastasis ability of PC cells both in vitro and in vivo, as well as mitigating the hypoxia-induced promotion of PC cell mobility; through the utilization of mass spectrometry analysis, GJB2 can bind with various proteins involved in alternative splicing process; among these proteins, HNRNPA2B1 was identified as a principal binding partner of GJB2, exhibiting the most substantial binding abundance; the strong hydrogen bond formed between the PHE-142 and SER-162 sites of GJB2 and the LYS-112 and ARG-60 sites of HNRNPA2B1 constituted the primary mechanism underlying their binding, while the absence of any of these sites resulted in a decrease in binding; the destabilization and protein levels of HNRNPA2B1 protein under hypoxic conditions was observed upon knockdown of GJB2, which was attributed to the upregulation of its ubiquitination and can be rescued by MG132 (26S inhibitor); under hypoxic conditions, GJB2 regulated the metastasis of PC cells in a manner dependent on wildtype HNRNPA2B1, but not mutational HNRNPA2B1 without binding sites with GJB2; the suppression of GJB2 resulted in a notable decrease in the activation of the WNT/β-catenin signaling pathway during hypoxic conditions, concomitant with an elevation in the degradation of CTNNB1 mRNA expression levels; under hypoxic conditions, GJB2 binds to exon 18.2-18.3 of CTNNB1 in a HNRNPA2B1-dependent manner, thereby inhibiting the splicing

of exitrons from exon 18.2-18.3 of CTNNB1 and suppressing the formation of CTNNB1 transcript with short 3'-UTR; when comparing the CTNNB1 transcript containing a long 3'-UTR to that containing a short 3'-UTR, it was observed that the latter exhibited a higher rate of degradation; HIF1A was found to bind with the promoter of GJB2, and increased its transcription under hypoxia; furthermore, we found that conivaptan, an FDA-approved diuretic, had potential activity to GJB2 protein and exhibited distinguish anti-metastasis effects of PC cells.

Conclusion: GJB2 has been identified as a target associated with hypoxia and the metastasis of PC. This target has been found to enhance the protein stability of HNRNPA2B1, leading to a decrease in the exitrons-splicing of CTNNB1 and ultimately promoting the metastasis of PC cells. The GJB2 protein presents a noteworthy target for pharmacological intervention.

Keywords: Pancreatic cancer; hypoxia; GJB2; HNRNPA2B1; alternative-splicing

P24-5 A novel cuproptosis-related LncRNA signature predicts prognosis in patients with esophageal carcinoma

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Background: Esophageal cancer (ESCA) is a significant cause of tumor-related mortality worldwide. Cuproptosis is a novel cell death which is different from other regulate cell death, including ferroptosis, pyroptosis and apoptosis. However, the role of cuproptosis in the initiation and progression of ESCA remains unknown.

Methods: The transcriptome data and clinical data of 173 patients with esophageal cancer in TCGA database were sorted and extracted with Perl software. Pearson correlation analysis was performed on cuproptosis related genes and all lncRNAs. The prognostic related lncRNAs were determined by univariate and multivariate Cox regression analysis, and a new prognostic model was constructed to calculate the risk score of each patient. C-Index curve, PCA analysis and ROC curve analysis were used to evaluate the prognosis prediction performance of 3- cuproptosis related lncRNAs (CRLs) model. In addition, multivariate Cox analysis was used to assess the prognostic value of the model in the entire cohort and in different subgroups.

Results: The 3-CRLs risk scoring criteria including EWSAT1, AC125437.1 and GK-IT1 was

established to evaluate the overall survival (OS) of ESCA. Survival analysis and ROC curve showed that the score had good prediction performance in TCGA train group and test group. The coefficients of each lncRNAs were analyzed using Lasso regression and lambda values were determined. principal component analysis was used to determine whether 3-CRLs can clearly distinguish the gap between high and low risk samples. Multivariate Cox regression showed that 3-CRLs characteristics were independent prognostic factors of OS. Norman map showed robust effectiveness in prognosis prediction.

Conclusion: The risk characteristics based on 3-CRLs may be used to predict the prognosis of esophageal carcinoma patients.

Key words Esophageal cancer; Cuproptosis; LncRNA; Survival analysis; Cox proportional hazards model

P24-6 血管平滑肌细胞外泌体对模拟失重所致心肌重塑的生物学作用及机制研究

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目的 探究血管平滑肌细胞及其外泌体对模拟失重所致心肌重塑的生物学作用及机制。**方法** 构建苯肾上腺素诱导心肌细胞肥大模型，建立血管平滑肌细胞与心肌细胞共培养体系，使用 GW4869 及 siRNA 技术抑制血管平滑肌细胞外泌体，通过细胞染色、qRT-PCR 检测心肌细胞面积及重塑基因表达。构建小鼠尾部悬吊模拟失重模型，经尾静脉注射外泌体，通过超声评价小鼠心脏功能，通过心脏组织切片分析心肌纤维化水平及心肌细胞面积，qRT-PCR 分析心肌重塑基因表达。分别对小/大鼠血管平滑肌细胞外泌体及高血压合并左心室肥厚患者的血浆样本进行 miRNA 测序分析，通过 qRT-PCR 及 Pearson 相关性分析进行筛选验证，并在模拟失重小鼠心肌组织中检测其水平。**结果** 在苯肾上腺素诱导下，与对照组相比，共培养组心肌细胞面积和 ANP（P<0.001）、BNP（P<0.001）表达水平显著减低。抑制血管平滑肌细胞外泌体后，共培养组心肌细胞面积及 ANP、BNP 表达水平显著增高。模拟失重小鼠中，与 PBS 组相比，外泌体组小鼠左心室收缩功能、纤维着色面积与心肌细胞面积均得到改善。miR-155-5p、miR-532-5p 以及 miR-939-5p 或与压力负荷相关心肌重塑有关，其中 miR-155-5p 和 miR-532-5p 包含在外泌体 miRNA 测序结果中。模拟失重小鼠心肌组织中 miR-155-5p 水平显著下降（P<0.001），miR-532-5p 水平显著升高（P<0.001），外泌体组

小鼠心肌组织中 miR-155-5p 水平显著升高（$P<0.01$），miR-532-5p 水平无明显变化（$P>0.05$）。**结论** 血管平滑肌细胞外泌体介导血管平滑肌细胞与心肌细胞之间的通讯互作，对心肌细胞病理性肥大具有抑制作用，并且能够改善模拟失重所致左心室重塑。miR-155-5p 可能是介导血管平滑肌细胞外泌体调控模拟失重所致心肌重塑的关键 miRNA 分子。

关键词：模拟失重；心肌重塑；血管平滑肌细胞；外泌体；miRNA

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P24-7 内质网应激促进模拟失重相关的内皮细胞炎症和凋亡

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目的 血管内皮细胞(endothelial cells, ECs)可以维持血管稳态、调节血流量并分泌血管活性和免疫因子。失重导致内皮功能障碍和 ECs 促炎状态，但其分子机制尚不明确，本研究旨在探讨内质网应激是否会诱导血管内皮细胞炎症和凋亡。**方法** 将人脐静脉内皮细胞（HUVEC）进行二维回转模拟微重力，并检测内质网应激标志物、诱导型一氧化氮合酶 iNOS/NO 含量、促炎细胞因子的产生、核因子 kappa B (NF-κB)/IκB 信号、NLRP3 炎症小体，并检测 HUVEC 细胞凋亡。**结果** 我们发现二维回转后 HUVEC 中的 CHOP 和 GRP78、促炎细胞因子（IL-6、TNF-α、IL-8 和 IL-1β）和 iNOS/NO 含量的水平显著上调。内质网应激抑制剂 TUDCA 和 4-PBA 和 iNOS 抑制剂 1400W 显著抑制了 NF-κB/IκB 通路和 NLRP3 炎性小体的激活，并减少了促炎细胞因子的产生。通过抑制内质网应激、iNOS 活性、NF-κB/IκB 和 NLRP3 炎症小体信号通路，显著抑制了 HUVECs 在二维回转过程中凋亡的增加。**结论** 模拟失重导致 HUVEC 内质网应激，随后激活 iNOS/NO-NF-κB/IκB 和 NLRP3 炎症小体信号通路，在诱导内皮炎症和细胞凋亡中发挥关键作用。该研究为失重状态下心血管功能障碍的机制提供了理论基础。

关键词：失重, 内质网应激, 内皮细胞, 炎症反应, 细胞凋亡

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P24-8 The unfolded protein response (UPR) regulates phenotype switching and proliferation of vascular smooth muscle cells of cerebral artery under simulated microgravity

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Abstract: Exposure to microgravity results in vascular remodeling and cardiovascular deconditioning in astronauts, which poses a threat to spaceflight safety and the health in astronauts. To elucidate the mechanism for this condition, we investigated whether unfolded protein response (UPR) during simulated microgravity regulates phenotype switching and proliferation in. Hindlimb unweighting rats was used to simulate the pathophysiological effects of cardiovascular system in present study. We examined the biomarkers of endoplasmic reticulum and mitochondrial (UPR^{ER} and UPR^{mt}), the mitochondrial oxidative stress, protein abundance of contractile and synthetic makers and structure of cerebral arteries. We found that the levels of CHOP, GRP78, PERK, eIF2α and ATF4, which are makers of UPR^{ER} are increased, while ERα, SIRT3, FOXO3a, SOD2 and Catalase, which are makers of UPR^{mt}, were decreased in cerebral arteries. Besides, the contractile markers α-SMA, calponin, SM-MHC and caldesmon were decreased, while the synthetic makers OPN and elastin as well as PCNA were increased in cerebral VSMCs. These alterations were partially restored by mitochondria-targeted antioxidant MitoTempo. Therefore, simulated microgravity upregulates UPR^{ER} while inhibits UPR^{mt} in cerebral VSMCs of simulated microgravity rats, and mitochondrial oxidative stress regulate switching and proliferation of cerebral VSMCs through modulating UPR^{ER} and UPR^{mt} differently.

Keywords: microgravity, unfolded protein response, mitochondrial oxidative stress, vascular smooth muscle cells, cellular phenotype

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P24-9 Propionic acid maintains neuronal mitochondrial division and autophagy homeostasis during Alzheimer's Disease pathologic process via GPR41 and GPR43

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Alzheimer's disease (AD) is a prevalent neurodegenerative disease (ND). In recent years, multiple clinical and animal studies have shown that mitochondrial dysfunction may be involved in the pathogenesis of AD. Moreover, the gut microbiota and its metabolites, short-chain fatty acids (SCFAs), have gained recognition as significant factors affecting central nervous system (CNS) homeostasis. Among the main mediators of host-microbe interactions, volatile fatty acids play a crucial role. Nevertheless, the influence and pathways of microorganisms and their metabolites on Alzheimer's disease (AD) remain uncertain. In this study, we present distinctions in blood and fecal SCFA levels and microbiota composition between healthy individuals and those diagnosed with AD. We systematically explored the effect of SCFAs administration on AD in AD mice and cultured neuronal cells. Results showed that oral propionate supplementation ameliorated cognitive impairment in AD mice and that propionate downregulated mitochondrial fission protein (DRP1) via GPR41 and enhanced PINK1/PARKIN-mediated mitophagy via GPR43 in AD pathophysiology. We also found that the absolute level of Akkermansia muciniphila in the feces of AD patients was significantly lower than that of normal people, and propionic acid is one of the main metabolites of Akkermansia muciniphila. When we administered A. muciniphila to AD mice before disease onset, AD mice also showed improved cognition and mitochondrial division, and mitophagy. Taken together, our results demonstrate that A. muciniphila and its metabolite propionate protect against AD-like pathological events in AD mouse models by targeting mitochondrial homeostasis, making them promising therapeutic candidates for the prevention and treatment of AD.

Keywords: Propionic acid; Alzheimer's disease; *Akkermansia muciniphila*; Mitochondrial division and mitophagy

P24-10 Polystyrene microplastics induced inflammation with activating the TLR2 signal by excessive accumulation of ROS in hepatopancreas of carp (Cyprinus carpio)

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Abstract: Polystyrene microplastics (PS-MPs) affect the immune defense function on carp (Cyprinus carpio). The PS-MPs model of carp was established by feeding with PS-MPs particle size of 8 μm and concentration of 1000 ng/L water. Hepatopancreas function test revealed the activities of AKP, ALT, AST and LDH abnormal increase. PS-MPs induced tissue damage and lead to abnormal hepatopancreas function. The PS-MPs also induced a oxida-tive stress with the antioxidant enzymes SOD, CAT, GSH-PX, and T-AOC activities decreasing and reactive oxygen species (ROS) excessive accumulation. PS-MPs activated the Toll like receptor-2 (TLR2) signaling pathway.The mRNA and protein expressions of TLR2, Myeloid differentiation primary response 88 (MyD88), tumor necrosis factor receptor-associated factor 6 (TRAF6), NF-κB p65, Tumor necrosis factor (TNF-α), Interleukin-1β (IL-1β), Inducible Nitric Oxide Synthase (iNOS), and cycooxygenase 2 (COX2) was revealed increased in both hepatopancreas and hepatocytes with the qPCR and Western blotting analysis mode. ELISA showed the expressions of TNF-α, IL-1β, iNOS, and COX2 inflammatory molecule were increased in both hepatopancreas and hepatocytes. The results showed that PS-MPs caused a serious injure in the hepatopancreas and brought serious effects on the inflammatory response of carp. The present study displayed the harm caused by PS-MPs in freshwater fish, and provided some suggestions and references for toxicological studies of microplastics in freshwater environment.

Keywords: Liver Toxicology Oxidative stress Polystyrene microplastics Cell signaling

P24-11 聚苯乙烯微塑料通过破坏鲤鱼肠道菌群诱导内质网应激、细胞凋亡和炎症

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微塑料（PS-MPs）作为一种广泛存在于自然界的新型污染物，已引起鲤鱼多种疾病的发生。本研究成功地在水环境中建立了微塑料摄食动物模型。使用 16s 方法分析肠道微生物群。结果表明，PS-MPs 处理显著降低了 Lactococcus garvieae、Bacteroides_paurosaccharolyticus 和 Romboutsia_ilealis 的相对丰度。使用 16S Silva 数据库预测和分析已知基因。发现 PS-MPs 摄入引起的肠道菌群紊乱与传染病、癌症、神经退行性疾病、内分泌和代谢疾病、心血管疾病等疾病有关。摄入 PS-MPs 可导致鲤鱼肠组织损伤和肠上皮细胞凋亡。鲤鱼肠组织中炎症因子 IL-1β、IL-6 和 TNF-α 水平因 PS-MPs 的摄入而显著升高。进一步检测微塑料组 GRP78、Caspase-3、Caspase-7、Caspase-9、Caspase-12、PERK、IRE1、ATF6 基因和蛋白水平，其结果证实了鲤鱼肠组织存在 ERS 和细胞凋亡。综上所述，水体环境中 PS-MPs 的积累会扰乱鲤鱼肠道菌群，诱发肠道组织内 ERS、细胞凋亡和炎症。

关键词：聚苯乙烯微塑料，肠道菌群，ERS，炎症，细胞死亡

P24-12 程序性细胞死亡分子 5 在自噬中的作用研究进展

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目的：自噬是真核生物体内降解不必要蛋白质和细胞器的主要方式之一。程序性细胞死亡分子 5（PDCD5）最初被发现为细胞凋亡因子，近年研究表明，PDCD5 同样参与自噬的调控。因此本文综述了 PDCD5 在自噬中的作用机制，以期为今后自噬相关分子机制研究提供理论基础。

方法：以“自噬”、“PDCD5”、“线粒体自噬”等关键词在 CNKI、PubMed 以及谷歌学术上进行文献检索，总结 PDCD5 在自噬中的作用机制。

结果：（1）PDCD5 可与 Beclin-1、NF-κB、Caspase-3、OTUD5、CK2 等因子相互作用，对自噬通路的膜转运等过程发挥直接调控作用。Beclin-1、NF-κB 及 Caspase-3 在自噬发生过程中均扮演重要角色，研究显示，沉默 *PDCD5* 后 Beclin-1 表达、NF-κB 通路以及 Caspase-3 蛋白含量均被显著抑制，自噬水平下调。此外，PDCD5 经与 OTUD5、CK2 等因子互作后，其自身去泛素化及磷酸化增加，从而促使自噬发生。（2）PDCD5 可与 P53、HIF、pVHL、Akt 等蛋白结合，通过影响细胞自噬的中心调控分子哺乳动物雷帕霉素靶蛋白（mTOR）的活性，实现对自噬过程的间接调节。肿瘤蛋白 53（P53）可通过活化 AMPK 以抑制 mTORC1 的活性，进而诱导细胞自噬，作为该通路的重要调节分子，PDCD5 可激活 P53 的多个位点的磷酸化和转录活性，间接促进细胞自噬的发生。此外，动物实验指出，MCAO 后野生型小鼠体内的 pVHL 表达降低可能会导致 HIF-1α 和 BNIP3 的表达增加，然而，在缺乏 PDCD5 的小鼠体内 pVHL 表达却没有明显变化，提示 PDCD5 可通过 pVHL-HIF-1α-BNIP3 途径促进细胞自噬发生。（3）PDCD5 在线粒体自噬中亦发挥重要调节功能。最新研究证实，肌肉特异性 PDCD5 缺乏能够增加老年心脏中 Parkin 介导的线粒体自噬。实验还指出，PDCD5 可与经生理盐水或 DOX 处理的小鼠心脏中的 P53 相互作用，提示 PDCD5 可能通过 P53 调节心肌细胞线粒体自噬发生。

结论：PDCD5 可通过与多种自噬关键分子结合从而正向调控自噬发生，其在线粒体自噬中亦发挥重要调节作用。

关键词：自噬；PDCD5；线粒体自噬

P25 脑节律

P25-1 突触结合蛋白 7 通过弓状核 kiss1 神经元调控小鼠休息-运动节律的机制研究

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目的：机体的睡眠和觉醒受中枢多种核团共同调控完成，其中睡眠-觉醒的昼夜节律主要受下丘脑视交叉上核（Suprachiasmatic nucleus，SCN）调控。SCN 壳区内含有大量的 Vasopressin（AVP）能神经元，AVP 的昼夜节律释放可通过 vSPZ-DMH-LHA 通路调控睡眠-觉醒节律。突触结合蛋白 7（Synaptotagmin 7，SYT7）是一种具有高钙亲和力的慢钙感受器，在调节突触易化和神经递质异步释放中发挥重要作用，但 SYT7 是否参与 SCN 内 AVP 释放的调控还未见报道。本课题组前期研究发现 Syt7 敲除小鼠休息-运动节律发生改变。因此本文旨在探究 SYT7 是否通过调控 AVP 节律释放，从而调控小鼠休息-运动节律及其相关的机制。**方法：**分别通过 RT-PCR、DNA 琼脂糖凝胶电泳和 Wersten Blot 验证 Syt-7 基因敲除小鼠模型构建成功；ActiView 小鼠运动节律检测系统检测 Syt7 敲除小鼠休息-运动节律；免疫荧光和共聚焦显微镜检测 SYT7 在下丘脑的表达及 SYT7 与 kiss1 神经元和 AVP 能神经元的定位关系；小鼠脑内定点微透析和 HPLC 检测 kisspeptin 和 AVP 的分泌节律；脑内 SCN 定点注射检测 Kisspeptin 对 AVP 分泌的影响。 **结果：**Syt7 敲除雌鼠在 DD 环境下的 24 小时运动量下降，运动时程延长，休息时程缩短，规律的 L12: D12 光照环境可部分恢复 Syt-7 敲除雌鼠的异常运动节律；syt-7 在弓状核 kiss1 神经元高表达，而在 SCN 无特异表达；表达 syt-7 的 kiss1 神经元纤维可投射到 SCN 内的 AVP 能神经，调节 AVP 的分泌；且 kiss1 神经元分泌 kisspeptin 存在昼夜节律特征，随着运动时程的延长的分泌量逐渐增多，随着睡眠开始，分泌量逐渐下降；AVP 的分泌量也表现出与 kisspeptin

一致的分泌节律。**结论：**SYT7 通过调节弓状核 kiss1 神经元节律分泌 kisspeptin 来调控 SCN 壳区内 AVP 的分泌节律，从而调控小鼠的睡眠-觉醒节律。

关键词：突触结合蛋白 7，kiss1 神经元，视交叉上核，AVP 神经元，睡眠-觉醒节律

P26 虚拟仿真与人工智能

P26-1 人工智能与虚拟仿真技术在 PBL 教学中的应用探索

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随着互联网、大数据以及人工智能等的发展，党中央、国务院高度重视教育信息化工作，明确指出：“加强网络教学资源体系建设，引进国际优质数字化教学资源，开发网络学习课程，建立数字图书馆和虚拟实验室，建立开放灵活的教育资源公共服务平台，促进优质教育资源普及共享。”虚拟仿真平台也开始在高校教育教学中开始逐渐开展，但有关人工智能和虚拟仿真在 PBL 教学中尚未得到广泛的研究和实践。基于现有 PBL 教学，情景化案例难以实现、参与意愿度不够、自主讨论的深度广度不足、个性化培养难以做到、评价体系不客观等缺点，我们利用人工智能和虚拟仿真技术，构建了以“自主、探究、合作”为特征的，以课程为单元，虚实融合的人工智能 PBL 教学平台和模式。

利用虚拟现实技术，为学生提供生动、逼真的学习环境，实时呈现临床场景和知识链接，增强了学习者的参与性和体验性；基于人工智能技术的虚拟机器人，更好的实现了 PBL 案例的推送和互动；基于人工智能技术的虚拟 PBL 参与者，使教师能更好的的控制 PBL 讨论的进程的节奏，同时人工智能的同伴教育会更好的激发学生的参与度和进取心；通过基于人工智能统计的后台实时记录学生在虚拟 PBL 课程中的表现，并有针对性的设计对学生的指导，实现个性化培养；设置的基于人工智能的自动抢答模式及排行榜极具挑战性和竞技性，可以很好地实现个性化学习；可以将声、光、动作等能够影响学生情感的因素有效地展现出来，使学生具有更高的学习热情和主观能动性。

本研究通过基于人工智能的虚拟仿真技术，全面优化了现有的 PBL 教学模式，建立了集知识性、实践性、互动性、趣味性、智能性“五位一体”的虚拟人工智能 PBL 课程平台，未来将广泛听取学生合理建议、同行评议和教学督导部门反馈意见，对该体系予以动态更新与完善。

关键词：人工智能，虚拟仿真技术，PBL 教学

P26-2 新冠疫情下基于“人工智能和虚拟仿真”的生物安全实验室“PAIOT”监管模式构建及实施

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目前国内外尚无基于物联网、大数据及多级身份认证等针对高等级病原微生物实验室的电子监管体系。

根据国家卫健委颁布的《人间传染的高致病性病原微生物实验室和实验活动生物安全审批管理办法》（卫生部令第 50 号）第十七条“高致病性病原微生物实验活动审批程序”所建设，在此基础上构建了新型高等级病原微生物实验室电子监管体系——基于物联网、人工智

能及大数据等现代信息技术，由多级身份认证、现场专人监督下的准入、实验操作、准出、数据实时上传至第三方监管平台等核心环节构成的新型“全过程、全方位”的实验室生物安全监管体系，①创新性地加入了“多级身份认证”的准入准出体系；；首次实现了关键的“现场监督”；②首次应用“物联网”实时定位技术；③首次将“人工智能”技术加入到“全流程”监管体系；④创新地实现了“以虚强实”。

基于数智时代的人工智能与虚拟仿真等现代信息学手段，将实验室生物安全与监管领域交叉融合，构建基于物联网、多重“身份证”认证的“PAIOT” 生物安全实验室实时电子监管系统，通过横向到边、纵向到底的互联互通实时动态数据库，使实验室的任何行为及要素随时随地上传到本系统，通过多级认证方可进行相关操作，保证生物安全实验室的“事前审批、事中监督和事后追溯”。针对高生物安全防护级别实验室的管控，以物联网为支撑，创新性地构建了全流程“现场监督”和“实时授权”相结合的监管模式，实现线上线下同时监督管理，从源头、过程及追踪等全过程上根本上杜绝其生物安全隐患。

关键词：人工智能；虚拟仿真 ；生物安全；PAIOT

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P26-3 人工智能在教育信息化中的应用与挑战

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随着人工智能技术的不断发展，其在教育信息化中的应用也越来越广泛。本文将重点探讨人工智能在教育信息化中的应用以及所面临的挑战。

首先，人工智能在教育信息化中的应用可以提供个性化的学习体验。通过分析学生的学习数据和行为模式，人工智能可以为每个学生量身定制学习计划，并提供个性化的教学内容和学习资源。这种个性化的学习方式可以更好地满足学生的学习需求，提高学习效果。

其次，人工智能在教育信息化中的应用还可以提供智能化的评估和反馈。传统的教育评估往往只注重学生的成绩，而忽视了学生的学习过程。而人工智能可以通过对学生的学习数

据进行分析，给予学生更加全面和准确的评估和反馈。这种智能化的评估和反馈可以帮助学生更好地了解自己的学习情况，及时调整学习策略。

然而，人工智能在教育信息化中也面临一些挑战。首先，人工智能的应用需要大量的数据支持。要实现个性化的学习和智能化的评估，需要收集和分析学生的大量学习数据。然而，学生的隐私问题成为了一个亟待解决的问题。如何在保护学生隐私的前提下，充分利用学生的学习数据，是一个需要解决的难题。

其次，人工智能的应用还需要解决算法的可解释性问题。人工智能算法往往是黑盒子，难以解释其决策过程。在教育领域，教师和学生需要了解人工智能算法是如何评估和评价学生的，以便更好地与之合作。因此，提高人工智能算法的可解释性，是一个需要重视的问题。

综上所述，人工智能在教育信息化中的应用有着广阔的前景，可以提供个性化的学习体验和智能化的评估和反馈。然而，人工智能在教育信息化中也面临着数据隐私和算法可解释性等挑战，需要我们共同努力解决。只有充分发挥人工智能的优势，解决相应的挑战，才能更好地推动教育信息化的发展。

关键词：人工智能，信息化，应用，挑战

P27 生理学教学专题研讨会

P27-1 Physiology education in China: The current situation and changes over the past 3 decades

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As an experimental biological science, physiology has been taught as an integral component of medical curricula for a long time in China. The teaching effectiveness of physiology courses will directly affect students' learning of other medical disciplines. To understand the current situation and changes in physiology teaching during 30 years in Chinese medical schools, a nationwide survey was conducted. At last, response of 80 leaders of the department of physiology from Chinese mainland medical schools was included in the study. The survey showed that the contact hours for physiology curriculum ranged from 71 to 90 was predominant. 58, 56 and 51 schools had ≤30 students and 19, 21, 26 had ≥121 students, in each practical laboratory in the three period, 1991-2000, 2001-2010, and 2011-2020, respectively. During the past 20 years, both

the total number of physiology teachers, the number of physiology teachers that have been educated in medical schools, and the number of technicians have been reduced, whereas teachers with doctor's degree have been increased. In addition to the traditional didactic teaching, new teaching approaches, including problem based learning/case based learning/team based learning, integrated curriculum and formative evaluation systems, have been employed, mostly for more than 5 years, in some of the medical schools. The present study enables to understand the development of the physiology discipline in medical schools in China.

Keywords: physiology, medical education, problem based learning, case based learning, integrated curriculum

P27-2 课内课外结合，全面开展生理学课程思政

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在生理学教学中，基于课程特点，课内课外结合，引导学生开展有关无偿献血、实验动物日、世界艾滋病日等科普宣传活动，引领学生知行合一，在实践中成长。

1. 无偿献血的科普宣传活动

在学习血液相关知识时，课堂上和同学们一起了解血型的分类、输血的原则、输血对身体的影响等。借此契机，安排课外作业，同学们在课堂上通过 PPT、动画、视频等，交流国内目前血库的状况、献血的意义和注意事项等。

另外同学们还走出课堂，参加河南省红十字会在校园的献血活动，结伴到河南省红十字会献血站进行献血等。通过校园宣传活动，鼓励大家在身体许可的情况下无偿献血，向社会奉献爱心。

2. 实验动物日的科普宣传活动

在“世界实验动物日”来临之际，同学们先是分组设计方案，课堂上交流策划活动内容。然后在校内宣传活动中，同学们设计了有奖知识问答、游戏等多个环节，宣传爱护和尊重实验动物的理念，倡导大家科学、人道的开展动物实验，增强同学们的保护动物意识。

通过此类活动加强师生的生命教育、生态教育和和谐发展教育，引导学生树立敬畏生命、尊重生命、人和动物互惠发展的理念。

3. 世界艾滋病日的科普宣传活动

在“世界艾滋病日”来临之际，结合教育部宣传活动主题，老师和同学们在课堂内外采用多种形式开展相关宣传活动。

首先同学们分组设计活动方案，在课堂上进行交流和完善方案设计。然后同学们在校园

内通过防艾抗艾知识问答、签名、知识讲座等多种形式，向广大青年学子普及有关知识，提升大学生防艾知识知晓率，避免和最大限度减少易感染艾滋病危险行为的发生，不断提高青年学生健康素养。

通过以上课内课外结合，开展课程思政教书育人实践活动，改变传统的以教室为中心、以教师为中心、以教材为中心举措，既提高了学生学习力，又提高了学生的社会公益心。

关键词：生理学；课程思政；课内课外；科普宣传

P27-3 以岗位胜任力为导向的临床专业《生理学》教学模式的构建

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《生理学》是高职临床医学专业重要的专业基础课程，秉承基础课紧密对接、服务专业课的理念，提出了构建以岗位胜任力为导向的“三对接、三融入”教学模式：将课程知识对接正常结构、临床应用、专业拓展，组织递进式教学；在授课中融入健康宣教、课程思政、职考大纲，注重学生对知识的主动探索、主动建构，助力培养高素质临床医学人才。

首先，规划系统性教学内容，提高基础知识的应用能力。以“能学、辅教”为建设思路汇整教学资源。“能学”为学时利用微课巩固基础知识；利用临床案例提升基础知识的转化应用能力。“辅教”为教师针对不同的学习对象灵活组织教学，开展“线上线下、随时随地、个性化学习”的教学活动。

其次，贯彻以学生为主体的教学方法，激发学生的内在能动性。教学设计注重对接职业能力培养，与临床常见病、多发病相结合，引导学生探究式学习。教学实施过程以模块导学为载体，精心设计任务式教学模块，明确重难点。采用以问题为导向的探究式教学，提高学生主动探索能力。

再者，依托学校省级虚拟仿真实训基地和机能学实训室，打造“虚—实结合”的实训课程。通过虚拟仿真实训平台的实验技术演示，让学生提前熟悉实验原理和步骤，提升学生的实验操作技术准确与熟练程度。

最后，思政元素深度融合。结合思政视频或文档等资源，有效弥补课堂学时有限的不足。积极拓展第二课堂，举办多项技能竞赛，夯实学生实践技能。引导学生参与社会实践、健康宣教，提升作为未来医者的责任感，培养“敬佑生命、救死扶伤、甘于奉献、大爱无疆”的职业精神。

以岗位胜任力为导向构建“三递进、三融入”的混合式教学模式，提升学生解决问题和自主学习能力，打造“三有”课堂：让教学内容“有用”、让学习过程“有趣”、让教学结果“有效”，

能有梯度、有实效地完成基础知识、能力、素质三维目标，提升基础知识的临床运用能力、健康宣教的职业能力。

关键词：生理学；临床专业；教学模式；岗位胜任力

P27-4 案例教学改革在体育院校运动人体科学专业课程中的实践

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体医融合背景下，体育院校运动人体科学专业本科生是未来体育与健康事业发展的生力军，培养高质量的专业人才，特别是运动健康管理人才，有助于加快体育强国和健康中国建设。本专业主干课程包括《人体生理学》、《人体解剖学》、《诊断学》、《临床医学概论》、《流行病学》、《运动处方》等，保证这些课程的学习效果对于提高学生培养质量非常重要。

通过教学实践发现，运动人体科学专业学生对部分专业课不感兴趣是影响学生培养质量的一个重要方面，这与专业课教学内容比较枯燥、教学模式比较单一等因素有关，在主干课程中开展案例教学改革是解决教学问题的一个有效方法，也是提升教学质量的良好途径。

以《流行病学》为例，课程具有综合性强、知识结构紧密、实践性强等特点。课程的主要内容大都是典型流行病学研究方法，它来之于实践，用之于实践，这一特点为本课程进行案例教学改革奠定了知识体系基础。案例教学改革的基本思路如下：分析流行病学理论知识→提出需要解决的问题→归纳、提炼、讲解案例→启发学生独立解决问题→掌握案例相关理论知识。实际应用中，把授课内容分解为相对独立的知识点，确定案例涉及的知识内容，每个知识点对应一个案例，确定各案例所涉及的教学内容并规划教学环节，明确教学重点和难点。进行案例设计时，每个案例包括以下内容：针对核心知识的讲授、展示针对核心知识的案例、提出针对本案例核心知识的问题、课堂讨论并解决所提出的问题。案例教学改革中，如何选择案例是教学成功的关键，案例与教学内容的匹配直接关系到案例教学的效果，需要根据核心知识点认真准备，并在实际教学过程中逐渐完善。

通过案例教学，预期激发学生浓厚的学习兴趣，培养学生主动学习、分析问题和解决问题的能力，从而全面提升人才培养质量。

关键词：案例教学，运动人体科学，课程

P27-5 人体生理科学实验教学改革的初步探索

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摘要：由于具有贴近于实际生活、有助于理论向实践的过渡的特点，人体生理科学实验逐渐成为生理科学实验中不可缺少的实验项目，而现有的人体实验普遍存在实验内容简单、数据结果不稳定、学生兴趣度较低等问题。为提高人体实验教学质量，针对人体实验特点，充分发挥人体实验优势，逐步形成了侧重于培养学生科学分析处理问题能力、理论知识综合运动能力和强化人体研究伦理认知的人体生理学实验教学目标，经过三年的不断摸索和改进，教学目标基本实现，教学效果不断提升，学生满意度和支持率也得到不断提高。而本课题组在人体生理科学实验教学目标、教学内容、运行和考评等方面的经验总结具有普适性，值得参考和推广。

关键词：人体生理科学实验，实验教学，教学目标，教学成效

P27-6 Improving undergraduate medical students' science communication: from the perspective of new media

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To understand medical students' intention on the science popularization and evaluate the effects of We-Media on the health science popularization, a health science popularization competition was held among medical undergraduates. Outstanding works were selected for publication in our health science popularization WeChat official account. After the activity, those participants volunteered to participate in the questionnaire survey to help us understand the effects of the activity and the feedback of students. The results showed that students had a strong willingness to serve the society, and they were more willing to participate in science popularization work. Moreover, students generally agreed that science popularization work had a very good promotion effects on professional knowledge and skills related to science popularization.

Keywords: public services; medical education; online health science communication; We-Media

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P27-7 机能学实验报告书写分析及举措

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实验报告是学生需要掌握的重要技能，学生除了需要认真实验，还须具有良好的知识储备、分析思维能力以及较高的人文素质。本文通过对 2016 级机能学实验报告进行分析，总结和归纳了实验报告中常见的错误，并加以分析和提出解决措施。

机能学实验报告是在实验操作的基础上，记录资料整理思考而完成的，它最重要的特点是对实验现象和实验结果表述相对开放；它更加强调学生必须根据实际情况进行描述和分析。

1.实验报告的基本情况

基本情况主要问题有①态度问题、②文化基础问题

2.实验报告书写技术

这部分错误主要集中在对实验操作和实验结果的表述，图片的处理及讨论上。

2.1 实验结果的表述

实验结果是实验报告的核心，对实验结果表述要求：①客观、②细致

2.2 图表应用情况

实验报告中的图表是最直观形象的表达形式。图片能清楚地反映实验结果的客观性和细节。

2.3 讨论的书写技术

讨论是实验报告的灵魂，是培养学生自我创新意识的重要环节。讨论是根据已知的理论知识对结果进行解释和分析。它是报告中对学生锻炼价值最高的部分。

3.逻辑关系

实验报告各个项目中的逻辑关系维系着整个实验报告的结构，它反映出学生对实验报告的整体架构的理解和应用能力，在这方面经常出现的问题主要是：①所列出的实验目标与观察结果之间的匹配度欠缺 ②实验结果－讨论－结论之间失联

4.科学素养

实验报告中所出现的科学素养问题，主要表现在对实验现象和结果描述的客观性上。在对实验结果的表述中常常误将真实性和正确性也当成了客观性。

5.纠正措施

①学生认真书写的实验报告就是他们的成果，教师一定认真批改和点评；②教师对待学生要结合学生个人的特质，做到个体化；③通过实验报告的书写，延伸了课程的时间和空间，这一点才是我们教育的真正目的。

关键词：机能学实验报告，分析

P27-8 The quality of group interactions in medical problem–based learning in China: The roles of intercultural sensitivity and group ethnic composition

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Background: Chinese universities are increasingly recruiting foreign students, and problem-based learning (PBL) is an effective approach to integrating those students. This study focuses on the role of intercultural sensitivity and group ethnic composition on the quality of group interaction in medical problem-based learning in China. **Methods**: This paper reports an investigation of the differences in three types of group interaction (exploratory questions, cumulative reasoning, and handling conflict) among 139 second-year medical undergraduates from two backgrounds (Chinese and foreign) in a PBL setting. The roles of intercultural sensitivity, group ethnic composition, and students' personal characteristics including age, gender and ethnicity on students' perceptions of the three types of interaction were quantitatively analyzed. A 35-item questionnaire and demographic survey were administered to second year medical undergraduates. **Results**: The results indicated that group ethnic composition was a significant negative predictor while intercultural sensitivity was a strong positive predictor of group interactions involving exploratory questions and cumulative reasoning. In addition, group heterogeneity in terms of age and ethnicity were significant predictors of group interaction. **Conclusions**: The findings of this study provide insights for strategically designing effective multiethnic group learning environments that encourage interaction and collaboration.

Keywords: PBL; Interaction; collaborative learning; Intercultural sensitivity; Foreign students; Mixed group

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