



运动促进健康的分子机制： 代谢标志物的多组学解析

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摘要 运动促进健康的分子机制尚未完全阐明, 代谢物作为连接遗传、运动与表型的关键桥梁, 通过多组学技术可高通量检测, 为机制研究和疾病预测提供重要线索。运动可显著改变体内代谢物谱, 如乳酸作为运动强度标志物, 可调控脂肪棕色化、血管生成和线粒体功能, 丙酮酸与其比值异常则提示线粒体功能障碍, 酮体为机体供能且调控脂代谢, 或与中枢疲劳相关, 肉碱是线粒体代谢枢纽且具有改善体成分、提高认知等功能, 丙氨酸通过糖异生和肌肽合成参与能量代谢, 肌酸为短时高强度运动供能并具有增肌等健康效应。代谢物在疾病预测中具有重要价值, 如糖蛋白乙酰基和酰基肉碱可提升心血管疾病和糖尿病的预测效能。基因组学发现了与最大摄氧量相关的卵泡刺激素受体基因, 并由此探索出肌酐等运动代谢标志物; 转录组学揭示了运动通过快速调控果糖、胆碱等基因表达影响代谢通路, 可改善帕金森病、提高肌肉力量、缓解胰岛素抵抗等; 蛋白质组学则发现运动通过特异性调控 SLC25A15 等代谢相关蛋白的表达水平或磷酸化修饰, 影响精氨酸等代谢通路, 进而介导运动适应性反应。多组学联用策略可同步解析代谢标志物及其调控机制, 但仍面临数据整合不足等挑战。未来需结合动态监测、单细胞/空间组学和 AI 算法等, 构建精准运动模型以实现最大化健康收益。

关键词 多组学, 代谢标志物, 运动, 健康

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运动作为调控机体健康的重要手段, 在代谢、免疫和心血管等领域的健康效应已得到广泛证实。规律运动通过提高骨骼肌葡萄糖转运蛋白 4 (glucose transporter 4, GLUT4) 活性增强胰岛素敏感性, 重塑糖脂代谢稳态, 防治 2 型糖尿病 (diabetes mellitus type 2, T2DM) 等代谢性疾病^[1], 通过平衡促炎/抗炎细胞因子网络调节免疫稳态, 降低慢性炎症相关疾病风险^[2], 通过增强心血管保护效应, 降低全因死亡率^[3]。然而, 运动促进健康背后的分子机制尚未完全阐明。近年, 随着高通量检测技术的快速发展, 融合基因组学、转录组学、蛋白质组学和代谢组学的多组学技术可从整体视角深入揭示生物体内分子网络变化图谱^[4]。其中, 代谢组学与表型具有直接关联性, 同时通过高通量检测小分子代谢物可深入解析细胞代谢应答^[5]。在此基础上, 联合其他组学技术可加深对代谢标志物的认识和功能理解^[6]。比如蛋白质组-代谢组联合分析可逆向溯源代谢标志物的上游调控蛋白, 阐明其分子基础^[7], 转录组-蛋白

质组-代谢组整合可构建“基因表达调控-代谢网络重编程-生理表型输出”的级联网络, 系统揭示运动干预的生物学效应^[8]。运动健康领域的多组学协同研究策略一方面可提升生物标志物的筛选效能, 另一方面还可整合其上游通路, 完善运动调控代谢网络的分子图谱, 为精准运动干预奠定科学基础。因此, 本文从多组学视角出发, 阐述运动代谢标志物的发现与应用现状。

1 运动、健康相关代谢标志物的发现与应用

1.1 响应运动的代谢标志物

运动可引起体内代谢物的广泛变化。比如, Contrepois 等^[9]研究发现, 单次急性运动即可导致体内 634 种代谢物的含量发生显著变化。借助代谢组学高通量检测的技术特点, 研究者可广泛识别不

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同运动干预后体内小分子代谢物的变化,这是揭示运动促进健康背后分子机制的有效策略^[10]。运动代谢组学研究是一个新型的领域,自2007年第一篇利用代谢组学开展运动生理研究的文章发表,至今已有数百篇相关研究,并有学者对其先后进行过系统梳理^[11-13]。其中,Khoramipour等^[13]的系统梳理最为全面,最后共纳入了122篇研究,发现不同研究中差异代谢物的数量范围在2~634之间。因此本部分仅聚焦糖、脂、蛋白质代谢,举例简述典型和新型运动代谢标志物的鉴定发现与功能解析。

与糖代谢相关的典型运动代谢标志物有乳酸、丙酮酸等。乳酸作为糖酵解与三羧酸循环的关键代谢中间体,是运动生理学中最早被表征的代谢物之一^[14]。运动诱导体内乳酸产生的水平与运动强度、时长、时间点等密切相关^[15-16]。在运动状态下,骨骼肌收缩增加了对三磷酸腺苷(adenosine triphosphate, ATP)的需求,促使糖酵解速率加快,当丙酮酸生成速率超过线粒体氧化能力时,其在乳酸脱氢酶催化下生成乳酸。即使在充分供氧条件下,糖酵解过程仍持续产生乳酸,说明乳酸生成并非缺氧导致,而是糖酵解必然产物^[17]。乳酸的生成可以进一步通过G蛋白偶联受体81调控环磷酸腺苷信号通路,影响免疫细胞代谢状态与功能分化。在高强度力竭间歇训练中,骨骼肌乳酸浓度可瞬时升高8~12倍^[18]。乳酸还是体内重要生物信号分子,广泛参与机体代谢调控。解偶联蛋白1(uncoupling protein 1, UCP-1)作为白色脂肪棕色化的核心物质,可通过解偶联抑制ATP合成,使游离脂肪酸以热能形式消耗来调节体温^[19]。乳酸可通过诱导UCP-1促使白色脂肪棕色化,进而控制体重^[20],通过上调巨噬细胞中血管内皮生长因子表达,促进血管生成,改善脉络膜新生血管^[21];通过表观遗传修饰影响组蛋白乙酰化水平,增强过氧化物酶体增殖物激活受体 γ 辅激活因子1 α 转录活性,提高线粒体生物合成效率进而调控炎症反应^[22-23]。低氧诱导因子1 α (hypoxia-inducible factor 1- α , HIF-1 α)是细胞响应低氧环境的核心调控因子,通过协调细胞对低氧的适应性反应,调控多种基因表达以维持氧稳态^[24]。肝脏作为乳酸重要代谢器官^[25],近期研究发现,乳酸可通过激活HIF-1 α 通路促进肝细胞分泌羧酸酯酶2(carboxylesterase 2, CES2),经囊泡运输激活脂肪组织脂联素通路,提示运动诱导的乳酸-CES2轴可能是代谢稳态调控的关键介质^[26]。此外,运动产

生的乳酸与苯丙氨酸在胞质非特异性二肽酶2催化下生成的N-乳酰苯丙氨酸被证实可以显著降低肥胖小鼠摄食量、体重,改善葡萄糖耐量^[27]。丙酮酸作为糖代谢的中间产物,也在脂肪和氨基酸代谢中发挥重要作用^[28]。研究发现,70%~80%最大重复次数(repetition maximum, RM)/次、10次/组、进行3~4组抗阻训练,可显著提升血清丙酮酸水平^[29-30]。在乳酸脱氢酶A(lactate dehydrogenase A, LDHA)的作用下,乳酸/丙酮酸比值维持在10左右,该比值在线粒体功能障碍时异常升高^[31]。此外丙酮酸代谢障碍不仅影响甲状腺功能减退患者的肌力和神经功能,还可能促进神经胶质瘤等肿瘤的发生^[32-33]。同时,外源性丙酮酸被发现可显著调控代谢。20名肥胖男性随机分为对照组(仅有有氧运动)和实验组(有氧运动+6 g/d丙酮酸),10周后,实验组体重、身体质量指数(body mass index, BMI)、体脂率和去脂体重均显著低于对照组^[34]。

与脂肪代谢相关的典型运动代谢标志物有酮体、肉碱等。酮体是肝细胞线粒体中脂肪酸 β 氧化的代谢产物,其合成途径受羧甲基二酰辅酶A合酶催化调控^[35]。运动可诱导体内酮体含量升高。运动既可通过上调氧化物酶体增殖物激活受体 α 的表达激活酮体生成酶的活性,又可通过上调成纤维细胞生长因子21表达促进酮体生成,还可通过抑制哺乳动物雷帕霉素靶蛋白复合物1通路增强生酮路径^[36]。17名男性健康志愿者在30 s极量冲刺后经代谢组检测发现尿酮体含量显著升高^[37];10名耐力运动员先后进行高强度间歇训练和能量消耗匹配的持续中等强度训练,血浆代谢组学分析均显示酮体显著升高^[38]。机体内的酮体具有双重代谢调节功能:一方面可作为糖原的替代能源物质,减少机体对糖原的依赖;另一方面通过抑制脂解酶活性及促进胰岛素分泌的形式调控脂代谢^[35, 39]。在耐力运动中,酮体浓度与血液pH值下降、ATP合成效率下降及中枢疲劳呈显著正相关,提示其可能作为代谢压力标志物^[40]。对14名肥胖成人(平均年龄56岁,平均BMI 32.8 kg/m²)研究发现,连续14 d餐前15 min服用12 g β 羟基丁酸能显著降低餐后血糖水平及全身炎症反应,并改善血管功能^[41]。同时临床研究发现,静脉输注3-羟丁酸(酮体的一种)使慢性心衰患者心输出量提升21%,射血分数提高8%^[42]。肉碱作为线粒体代谢枢纽,一方面通过形成酰基肉碱酯介导长链脂肪酸跨线粒体膜转

运, 维持膜电位稳定, 另一方面通过催化线粒体基质内乙酰基转移, 动态调节乙酰辅酶A/辅酶A比值, 激活丙酮酸脱氢酶复合体, 提升糖原分解代谢效率^[43]。耐力训练可显著提升体内肉碱水平^[44]。通过对13名健康受试者60 min跑步前后血浆代谢组分析发现, 中链酰基肉碱是中等强度运动的核心代谢标志物^[45]。同时, 肉碱补充可为健康带来众多良好效应。以70名百岁老人(100~106岁)为研究对象的试验发现, 2 g/d肉碱长期补充较对照组可增加3 kg瘦体重, 减少2.4 kg脂肪, 改善神经疲劳并提高认知功能^[46]。在一项包括263名健康男性参与者的研究中, 131名受试者口服含有肉碱的抗氧化剂后精子的体积、数量活力等显著高于安慰剂组^[47]。

与蛋白质代谢相关的典型运动代谢标志物有丙氨酸、肌酸等。丙氨酸作为骨骼肌氨转载体, 经谷丙转氨酶催化丙酮酸生成, 通过丙氨酸-葡萄糖循环在肝脏完成糖异生, 构成能量代谢核心环节^[48]。运动诱导体内丙氨酸含量升高。10名健康男性完成下肢抗阻训练(2个动作各4组, 每组10次, 70%1RM, 组间休息1 min)后, 血清代谢组学分析显示丙氨酸水平较运动前显著升高^[29]。丙氨酸是肌肽的前体物质, 通过补充丙氨酸可更有效提高肌肽水平^[49]。研究发现, 持续4周, 每天4~6 g丙氨酸剂量使肌肽浓度增加64%, 持续补充10周可增加80%^[49]。肌肽可以通过清除自由基延缓衰老进程, 在帕金森病及脑卒中模型中展现神经保护效应, 并可作为金属螯合剂调控铜锌代谢稳态减少细胞损伤等^[50]。肌酸是精氨酸等三种氨基酸经酶促反应合成的非蛋白氨基酸化合物, 可经肌酸激酶催化形成磷酸肌酸, 是磷酸原供能系统的核心分子, 其代谢特性支持6~8 s爆发性运动的能量需求, 是短时高强度运动的主要能量来源^[51]。25名业余跑步者在全程马拉松运动后, 血浆代谢组学发现肌酸水平升高93%^[52]。4名皮划艇运动员进行专项联合抗阻训练后同样发现了肌酸升高的现象^[53]。运动导致肌酸水平升高与AMP激活蛋白激酶(adenosine 5'-monophosphate-activated protein kinase, AMPK)激活密切相关。运动导致体内ATP与AMP比例发生变化, AMPK作为细胞能量传感器将通过协调糖脂代谢与线粒体功能调控能量平衡, 而磷酸肌酸系统在此过程中发挥能量缓冲作用, 导致肌酸浓度发生改变。同时, 肌酸作为常见营养补充剂, 可为机体带来众多健康效应, 如增加

肌肉质量和力量^[54]、促进骨骼重建^[55]、减缓肿瘤生长^[56]、提高认知功能^[57]。

1.2 代谢物的疾病预测价值

代谢紊乱是多种疾病的重要特征, 个体健康状况可通过体内代谢物得到精准呈现, 目前已在疾病早期预警、风险评估等领域发挥重要作用^[58]。比如, Buergel等^[59]在提取UK Biobank数据库中117 981名参与者的基线代谢组数据和24种疾病终点事件后, 设计了一个疾病风险预测神经网络模型。该模型可以根据168个循环代谢物特征对心血管疾病、糖尿病等24种疾病的发病风险进行分层。

心血管疾病(cardiovascular diseases, CVD)是一类疾病的总称。中国CVD患病率持续增高, 是我国城乡居民因病死亡的第一原因^[60]。目前已开展大量CVD相关的代谢组学研究, 不仅发现了众多新型生物标志物, 而且构建了CVD疾病风险预测模型^[61]。基于中国慢性病前瞻性研究(China kadoorie biobank, CKB), Holmes等^[62]对912例心肌梗死、1 146例缺血性卒中、1 138例脑出血患者及1 466名健康对照样本开展巢式病例对照研究。血浆代谢组学(225种代谢物)分析显示, 糖蛋白乙酰基、酮体、葡萄糖和二十二碳六烯酸与三种疾病显著相关。进一步, 将225个代谢物中的18个代谢物(可解释总体代谢物变化的95%)添加到已有的预测疾病的逻辑回归模型中后, 原有模型的受试者特征工作曲线下面积显著增加, 提示模型判别疾病风险能力提高。同样地, 在雅芳父母和儿童前瞻性队列研究和年轻芬兰人心血管风险研究中也发现糖蛋白乙酰基可以预测10年后罹患高血压的风险^[63]。此外, 研究发现, 甘露糖、苯丙氨酸、单不饱和脂肪酸、酰基肉碱等也与CVD发病风险密切相关, 其中酰基肉碱还可提高原有Framingham复发性冠心病评分的疾病风险预测能力^[64-66]。

糖尿病是一种以代谢紊乱为特征的疾病, 体内众多代谢物水平发生显著变化^[67]。中国糖尿病患者数量位列全球第一^[68]。基于CKB的一项病例队列研究中(病例组包括882名T2DM患者, 亚队列包括789名参与者, 其中有26名糖尿病患者), 研究者发现, 所检测的225种代谢物中有163种代谢物与T2DM独立相关, 比如支链氨基酸、甘油三酯和葡萄糖等^[69]。通过对54名正常个体和156名T2DM患者血浆进行靶向代谢组学分析后, 评估出酰基肉碱可能是糖尿病及其并发症的鉴别诊断的生

物标志物^[70]。在一项纳入了206名糖尿病患者和206名非糖尿病患者的大型病例对照研究中,确认了酰基肉碱可以为靶向预防、诊断和治疗糖尿病提供帮助^[71]。Sun等^[72]对来自北京和上海的2103名社区居民开展了平均随访时间为6年的前瞻性队列研究,分析基线血浆酰基肉碱含量与T2DM患病之间的关系,结果显示一组涉及线粒体脂质代谢失调的酰基肉碱与T2DM风险增加显著相关,进一步将选定的游离肉碱等25种酰基肉碱加入原有预测模型(预测因子为年龄、性别等12个指标)后,模型的曲线下面积由0.73增至0.89。类似地,Suvitaival等^[73]在107名T2DM患者和216名健康对照组进行脂质组学检测后,发现将溶血磷脂酰胆碱酰基C18:2、磷脂酰胆碱PC(32:1)、PC(34:2e)和PC(36:1)以及三酰甘油TG(17:1/18:1/18:2)加入原有模型(FINDRISC和/或代谢综合征变量)后,模型疾病预测能力均显著提高。酰基肉碱等代谢物在队列研究中展现出优于传统指标的预测价值,多代谢物联用、结合临床指标

及多组学数据,同样可显著提升对癌症、衰老及死亡风险的预测效能^[74-75]。

2 多组学视角下运动促进健康的代谢标志物

体内代谢物的含量受其吸收、转运、分解和合成等多途径的共同影响,这与其转运体或受体表达量、代谢酶表达量和活性密切相关。代谢组学技术能以无偏倚的方式测量单个样品中多达数百种代谢物^[13, 76]。基因组学、转录组学和蛋白质组学等所阐述的分子尽管反映的是复杂代谢网络的上游变化,却能与代谢组学互补,在发现运动促进健康的代谢标志物的同时揭示其背后可能机制,甚至提示潜在代谢物标志物线索。借助基因组检测技术,可以筛选到与运动表型相关的编码代谢物转运体、受体或酶的基因;借助转录组和蛋白质组检测技术,可以筛选在运动前后表达量发生变化的代谢物转运体、受体或酶(图1)。

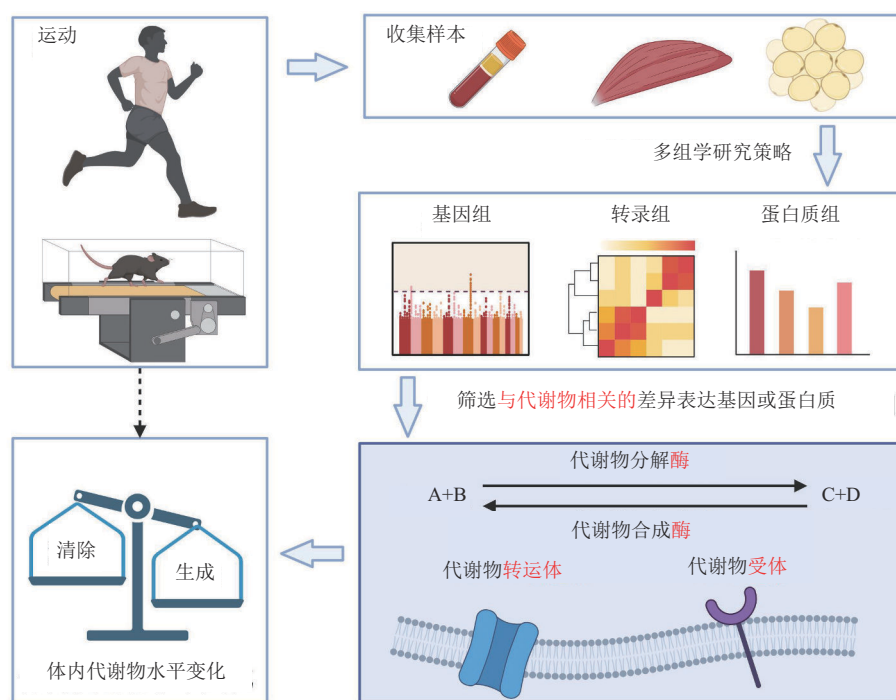


Fig. 1 Application of multi-omics for screening the potential exercise-related metabolites

图1 多组学在筛选潜在运动相关代谢物中的应用

2.1 基因组学视角下运动相关代谢物的发现与研究

遗传因素显著影响机体代谢物含量,使代谢物成为一个关键枢纽,串联起运动、健康与特定基因

位点之间的复杂关联^[77]。控制代谢物的基因具有显著的多效性和多基因性^[78]。2024年Karjalainen等^[78]完成了233个循环代谢数据的全基因组关联研究,发现所检测的代谢数据在全基因组范围内均

具有显著关联, 如循环肌酸与49个基因座具有显著关联。因此, 借助基因组学技术和全基因组关联研究, 研究者可以筛选与最大摄氧量、肌肉力量等运动表型相关的代谢物调控基因及遗传变异, 为运动代谢标志物的发现提供了线索。

当前运动基因组学被广泛应用于科学选材^[79]。值得注意的是, 运动基因组学关注的与耐力水平等运动表型相关的基因在运动健康促进领域也有重要的研究价值。比如, 最大摄氧量是评价机体有氧耐力的金标准, 2016年美国心脏协会建议将最大摄氧量列为人体第五大生命体征^[80]。规律运动人群的最大摄氧量会显著升高^[81], 且与T2DM、CVD等慢性非传染疾病也展现出了显著负相关关系^[82-83]。最大摄氧量具有很高的遗传度(0.59~0.66)^[84]。Bye等^[85]在3 470人的发现队列中筛选到了41个与最大摄氧量相关单核苷酸多态性(single nucleotide polymorphisms, SNPs), 并在718人的验证队列中完成了6个SNPs的验证。通过分析挪威北特伦德拉格健康研究第三队列(The third wave of the Nord-Trøndelag Health Study, HUNT3)中4 525名受试者的基因型和最大摄氧量的关系, 研究者发现了28个与最大摄氧量相关的SNPs^[86]。有趣的是, 该研究团队在此基础上开展了先前发现的与最大摄氧量相关的基因变体与糖尿病、CVD等疾病, 以及肌酐等临床检测指标的全表型组关联分析, 尝试探索最大摄氧量和疾病背后的共同遗传机制, 结果发现, 与较高最大摄氧量相关的卵泡刺激素受体基因的SNPs与血清肌酐水平呈显著正相关关系^[87]。血清肌酐是肌酸主要代谢产物, 血清肌酐含量降低会增加T2DM的发生风险^[88], 提示血清肌酐是一种潜在的运动代谢标志物。

2.2 转录组学视角下运动相关代谢物的发现与研究

运动可以对体内基因表达产生快速且显著的影响。Contrepois等^[9]收集36名平均年龄59岁的受试者在急性运动前和运动后2 min~1 h不同时间点的外周血单核细胞样本进行转录组测序, 发现急性运动引起了9 132个转录本的水平发生变化。转录组测序技术在运动健康领域广泛应用, 已有不同研究团队先后系统梳理运动转录组相关研究^[89-90]。

帕金森病是一种常见的神经退行性疾病, 伴有异常的糖代谢^[91]。与健康对照组相比, 患者脑脊液中升高的果糖、甘露糖可作为早期帕金森病诊

断的生物标志物^[92]。运动可以有效缓解帕金森病临床症状, 但其背后机制仍不清楚。在一项以帕金森病患者为研究对象的12周有氧运动干预研究中, 研究者分析了受试者循环白细胞转录组测序结果, 发现与运动前相比, 运动后有1 873个差异表达基因^[93]。京都基因和基因组数据库(Kyoto Encyclopedia of Genes and Genomes, KEGG)通路富集结果显示, 果糖和甘露糖代谢通路中诸多基因在运动后显著上调^[93]。其中, 山梨醇脱氢酶基因编码山梨醇脱氢酶, 催化山梨醇转化为果糖, *PFKFB3*编码果糖-2,6-二磷酸酶3, 催化果糖-2,6-二磷酸分解为果糖6磷酸, 果糖6磷酸随后进入糖酵解途径^[94]。山梨醇、果糖等作为渗透调节物质, 其异常积累会导致细胞渗透压失衡和功能受损^[95]。由此推测, 果糖和甘露糖代谢通路所涉代谢物或是运动改善帕金森病的潜在代谢标志物。肥胖等代谢性疾病是当前重大公共卫生问题, 运动是有效防治手段。特殊环境下的运动, 如低氧运动(源自竞技体育领域的高原训练)在防治代谢性疾病中展现出了独特的优势, 但其背后机制仍在探索之中^[96]。Glotov等^[97]收集7名精英女子速滑运动员在1 h高原速滑训练后的全血进行转录组测序, 通过对比先前已有的8个平原训练后的微阵列数据集, 发现了2个在特定类型细胞中表达显著上调的基因, 分别是*MARCI*和*PHOSPHOI*。其中, *PHOSPHOI*编码磷酸乙醇胺磷酸胆碱磷酸酶1, 催化磷酸胆碱分解为胆碱^[94]。在另一项研究中, 与胰岛素敏感性正常的肥胖患者相比, 胰岛素抵抗的肥胖患者和T2DM患者血清胆碱含量显著下降^[98]。此外, 胆碱可以通过食物进行外源性补充。在一项以健康中老年人作为研究对象的抗阻运动干预研究中, 通过控制胆碱(蛋黄形式)摄入量区分低、中、高胆碱摄入量组, 12周运动干预后, 低胆碱摄入量组受试者腿部和胸部肌肉力量收益显著低于中、高胆碱摄入量组^[99]。因此, 胆碱可能是一种运动促进代谢健康的标志物。

2.3 蛋白质组学视角下运动相关代谢物的发现与研究

蛋白质组是动态变化的蛋白质分子集合, 其组成随生物体生理状态及外界刺激发生系统性改变。近年来蛋白质组学技术在运动科学领域应用广泛(表1), 其中, 部分研究提供了潜在运动代谢标志物的线索。

5名健康年轻未经训练的男性受试者提供了其

Table 1 List of representative proteomics research associated with exercise

表1 与运动相关的蛋白质组学研究列表

	作者 (年份)	研究对象	运动方案	蛋白质组学研究结果
人体研究	Hoffman等 ^[100] (2015)	4名24~27岁未经训练的健康男性, 自身前后对照	高强度运动, 9~11 min	骨骼肌磷酸化蛋白质组学, AMPK等562个蛋白质的共1 004个磷酸化蛋白质表达发生显著改变
	Whitham等 ^[101] (2018)	11名健康男性, 平均年龄27岁, 自身前后对照	耐力训练, 1 h	血浆囊泡蛋白质组, 糖酵解相关酶等322个蛋白质表达发生显著改变
	Contrepois等 ^[9] (2020)	21名男性, 15名女性, 年龄范围40~75岁, 平均BMI为28.4 kg/m ² , 自身前后对照	症状限制心肺运动测试	血浆靶向和非靶向蛋白质组, 髓过氧化物酶 (myeloperoxidase, MPO) 等49个蛋白质表达在急性运动后发生变化
	Deshmukh等 ^[102] (2021)	5名健康年轻未经训练的男性受试者, 自身前后对照	耐力训练, 12周	股外侧肌慢肌纤维和快肌纤维蛋白质组, NADH脱氢酶等237个慢肌纤维蛋白和G6P脱氢酶等172个快肌纤维蛋白在运动后表达显著变化
	Robbins等 ^[103] (2021)	HERITAGE队列中654名健康久坐成年人, 平均年龄34.8岁, 55.2%女性, 自身前后对照	耐力训练, 20周	血浆蛋白组, 胞外-5'-核苷酸酶 (ecto-5'- nucleotidase, NT5E) 等102种血浆蛋白与运动前后最大摄氧量变化值显著相关
	Blazev等 ^[104] (2022)	8名平均年龄26.3岁的未经训练的健康年轻男性	耐力、冲刺、抗阻训练干预, 间隔至少10 d	骨骼肌磷酸化蛋白质组学, LDHA等1 573个蛋白质的共5 486个磷酸化蛋白质表达发生显著改变
	Ahn等 ^[105] (2024)	16名超重肥胖成年人, 其中8人为久坐不动组8人为运动组, 各组男女各4人	无干预	腹部皮下脂肪组织蛋白质组, 与久坐不动受试者相比, 在运动组受试者中有脂肪酸合成酶 (fatty acid synthase, FASN) 等158个蛋白质表达显著变化
动物研究	Horowitz等 ^[106] (2020)	18月龄老年小鼠和7月龄成年小鼠, 对照组为未经训练小鼠	耐力训练, 6周	血清蛋白质组, 糖基磷脂酰肌醇特异性磷脂酶D1 (glycosylphosphatidylinositol specific phospholipase D1, GPLD1) 等12个蛋白质在两个年龄组中表达均显著变化
	Nelson等 ^[107] (2020)	3月龄雌性小鼠, 对照组为未经训练小鼠	单次力竭耐力训练	骨骼肌磷酸化蛋白质组, 1 752个磷酸化蛋白质表达发生显著改变
	De Miguel等 ^[108] (2021)	3月龄小鼠, 对照组为同窝不训练小鼠	转轮运动, 28 d	血浆蛋白质组, 簇集素 (clusterin, CLU) 等49个蛋白质表达发生显著改变
	Peng等 ^[109] (2022)	2月龄雄性大鼠, 对照组为未经训练大鼠	耐力训练, 3周	骨髓上清蛋白质组, 网钙蛋白2 (reticulocalbin 2, RCN2) 等443个蛋白质表达显著变化
	Wei等 ^[26] (2023)	雄性小鼠, 对照组为未经训练大鼠	耐力训练, 1周	血浆蛋白组, 赖氨酰氧化酶样蛋白1 (lysyl oxidase like protein 1, LOXL1) 等181个分泌蛋白质表达显著变化
	MoTrPAC Study Group等 ^[110] (2024)	6月龄雌性和雄性Fischer 344大鼠, 对照组为未经训练大鼠	耐力训练, 8周	心脏、腓肠肌、皮下白色脂肪组织等7个组织的蛋白质组和磷酸化蛋白质组等, 腓肠肌、心脏和肝脏的蛋白质表达丰度和翻译后修饰差异显著
	Amar等 ^[111] (2024)	6月龄雌性和雄性Fischer 344大鼠, 对照组为未经训练大鼠	耐力训练, 8周	心脏、腓肠肌、皮下白色脂肪组织等7个组织中的线粒体相关蛋白质组和磷酸化蛋白质组等, 17 β -羟基类固醇脱氢酶10 (17 β -hydroxysteroid dehydrogenase type 10, HSD17B10) 等513个线粒体蛋白表达发生变化, 占所有线粒体蛋白的38%
	Many等 ^[112] (2024)	6月龄雌性和雄性Fischer 344大鼠, 对照组为未经训练大鼠	耐力训练, 8周	皮下白色脂肪组织蛋白质组和磷酸化蛋白质组, 以蛋白质组学结果为例, 雄性大鼠中有溶质载体家族25成员15 (solute carrier family 25 member 15, SLC25A15) 等18个在所有时间点均差异表达的蛋白质, 雌性大鼠中有类黏蛋白1 (orosomucoid 1, Orm1) 等5个在所有时间点均差异表达的蛋白质

12周耐力训练前后股外侧肌样本, 研究者分离样本中的慢肌纤维和快肌纤维进行蛋白质组学检测, 结果发现, 在慢肌纤维中有237个蛋白质表达显著改变, 在快肌纤维中有172个蛋白质表达显著改变。进一步对差异表达蛋白的分析发现65%以上的蛋白质与代谢相关, 比如参与脂肪酸代谢的长链脂肪酸辅酶A连接酶1和烯酰辅酶A水合酶1、参与肉碱和肌酐代谢的肌酸激酶脑型亚基^[102]。不同的运动训练方式会产生不同的健康效应。Blazev等^[104]设计随机交叉实验, 分析了耐力训练、冲刺训练和抗阻训练后骨骼肌磷酸蛋白质组的差异, 结果发现, 乳酸脱氢酶A (lactate dehydrogenase A, LDHA) 等1573个蛋白质的共5486个磷酸化蛋白质表达发生显著改变。同时为确定与代谢适应相关的磷酸化蛋白质位点, 研究者对每个磷酸化蛋白质与乳酸等代谢物进行了相关分析, 发现LDHA3 (Y39) 与血浆乳酸含量显著负相关、GYS1 (S469) 与骨骼肌糖原含量显著负相关、DHCR7 (S14) 与血浆脂肪酸显著负相关等, 这些数据为机体运动代谢适应和运动代谢物标志物变化提供了可能的解释。类似的研究思路也可用于挖掘新的运动代谢标志物。6月龄雄性Fischer 344大鼠, 耐力训练干预1、2、4和8周后收集皮下白色脂肪组织进行蛋白质组学检测, 结果发现了溶质载体家族25成员15 (solute carrier family 25 member 15, SLC25A15) 等18个在所有时间点均差异表达的蛋白质。SLC25A15是线粒体转运体家族成员, 在尿素循环代谢和精氨酸合成等生物过程中发挥重要作用^[113]。研究中发现的耐力训练后脂肪组织中SLC25A15表达上调, 提示精氨酸等合成加强。与此一致的是, 有研究显示, 高心肺耐力水平人群体内的精氨酸水平显著高于低心肺耐力水平人群^[114]。同时, 补充精氨酸在CVD等多种疾病的防治中也展现出了一定临床价值, 这提示运动可能通过控制SLC25A15来调控精氨酸水平, 进而削弱疾病风险^[115]。此外, 在疾病群体中观察到的血尿素氮升高与糖尿病风险增加具有显著正相关关系, 提示尿素或是运动促进健康的候选代谢标志物^[116]。在运动促进脑健康领域的研究中, Horowitz等^[106]通过蛋白质组学技术分析老年和成年小鼠在运动后血浆蛋白差异谱, 结果在两个年龄组中同时发现糖基磷脂酰肌醇特异性磷脂酶D1 (glycosylphosphatidylinositol specific phospholipase D1, GPLD1) 等12个差异表达蛋白。GPLD1是一种由肝脏分泌的磷脂酶, 该

酶可切割磷脂酰肌醇二酸的酰基链参与磷脂代谢平衡调控, 同时作为磷脂酯酶催化磷脂酸酯的降解反应, 它与运动改善神经元功能相关, 直接注射GPLD1至久坐小鼠体内, 可模拟运动对大脑的保护作用, 包括神经发生增加和认知功能提升^[106]。推测, 运动可以通过控制机体GPLD1的表达来调节磷脂酰肌醇代谢通路, 影响细胞膜相关信号转导和脂质动态平衡进而改善神经元功能。

需要注意的是, 在应用多组学策略筛选运动相关代谢物时, 不同组学技术存在其特定的优势与局限性。基因组学提供遗传基础, 优势在于高通量、低成本的全基因组扫描能力, 可系统鉴定遗传变异, 但受限于基因表达调控层级, 无法直接反映蛋白质动态^[117-118]; 转录组学揭示动态调控, 其凭借单碱基分辨率优势, 能精准捕捉低丰度转录本和可变剪接事件, 但对翻译效率及RNA稳定性要求很高, 且存在样本易降解的技术瓶颈^[119-120]; 蛋白质组学验证功能终点, 直接检测蛋白质表达及修饰状态, 与表型关联性最强, 但受制于技术灵敏度, 低丰度蛋白质检测仍面临重复性差、成本高的挑战^[121-124]。进一步, 随着表观基因组学、肠道微生物组学等新兴技术的发展, 运动健康研究维度也得到拓展。如抗阻运动通过显著降低脂肪组织PPAR γ 基因启动子区甲基化水平, 上调脂联素分泌, 改善胰岛素抵抗^[125-126], 耐力训练诱导骨骼肌肉碱棕酮酰转移酶1A基因低甲基化, 促进线粒体 β 氧化能力提升^[125, 127], 耐力训练上调肝脏沉默调节蛋白1表达, 通过组蛋白H4第16位赖氨酸 (H4K16) 去乙酰化抑制固醇调节元件结合蛋白1c基因, 减少脂肪生成^[127-128], 运动干预后肠道中嗜黏蛋白阿克曼菌 (*Akkermansia muciniphila*) 丰度增加3.2倍, 其携带的Amuc_1100基因表达上调近6倍, 可促进乙酸生成并改善脂肪氧化等^[128-129]。综上所述, 组学技术已成为运动促进健康领域开展研究工作的常用技术, 并且正快速由“单一组学”向“多组学联用”发展^[130-132]。跨组织、多维度的组学技术联用将有助于构建一个完整的运动代谢网络, 但同时也对基因组—代谢组、蛋白质组—代谢组等关联分析技术提出了更高的要求^[133]。

3 总结与展望

多组学技术的发展极大促进了乳酸等传统运动代谢标志物与N-乳酰苯丙氨酸等新型运动代谢标志物的发现鉴定与功能解析。运动对机体的影响是

多维度、多层次的,其系统调控机制解析是目前领域研究热点。

运动代谢标志物是生物体在基因与运动联合作用下整体代谢反应的表征,因此,基于整合生物学理论,利用多组学联合研究策略可以在鉴定代谢标志物的同时提供机制研究线索,如基因组-代谢组、蛋白质组-代谢组、基因组-蛋白质组-代谢组等多组学联用。目前,基因组已筛选出大量与运动表型相关的遗传标记,转录组与蛋白质组发现了众多调控代谢物的关键蛋白质和基因,进一步整合代谢组分析数据,将可以精准揭示运动过程中的能量代谢规律和深层机制。但目前该领域存在着多组学数据整合不足、运动干预方案和样本采集程序标准化欠缺、运动促进健康的异质性,以及代谢组学技术存在动态监测能力不足、样本处理和分析方法不同导致的结果差异等问题,有待进一步标准化,建议:

a. 技术应用方面,研发基于质谱探针等微创动态监测设备,实时追踪运动中代谢物变化,加速单细胞组学、空间组学等前沿技术与运动研究的交叉融合,从细胞异质性和微环境相互作用等角度出发解析机制;b. 在分析方法选择上,推荐优先采用飞行时间质谱和傅里叶变换离子回旋共振质谱等高分辨率实时监测技术,以提升代谢物动态变化的检测灵敏度和分析精度;c. 运动方案设计中,整合惯性传感器、表面肌电等设备,结合周期训练等理论方法,建立健康收益最大化的精准运动干预模型;d. 数据分析方面,借助人工智能与计算机技术的发展,将基于数据驱动策略的智能算法整合到多组学数据分析中。

参 考 文 献

- [1] Sato Y, Nagasaki M, Nakai N, *et al.* Physical exercise improves glucose metabolism in lifestyle-related diseases. *Exp Biol Med* (Maywood), 2003, **228**(10): 1208-1212
- [2] Docherty S, Harley R, McAuley J J, *et al.* The effect of exercise on cytokines: implications for musculoskeletal health: a narrative review. *BMC Sports Sci Med Rehabil*, 2022, **14**(1): 5
- [3] Stensvold D, Viken H, Steinshamn S L, *et al.* Effect of exercise training for five years on all cause mortality in older adults-the Generation 100 study: randomised controlled trial. *BMJ*, 2020, **371**: m3485
- [4] 樊春海,程蜀琳.运动转化医学:从分子生物力学管窥主动健康. *体育科学*, 2024, **44**(1): 3-11, 20
Fan C H, Cheng S L. *China Sport Sci*, 2024, **44**(1): 3-11, 20
- [5] Guijas C, Montenegro-Burke J R, Warth B, *et al.* Metabolomics activity screening for identifying metabolites that modulate phenotype. *Nat Biotechnol*, 2018, **36**(4): 316-320
- [6] 侯江涛,郑洁,韩雨梅.代谢组学在运动实践中的应用. *体育科技文献通报*, 2022, **30**(11): 241-244
Hou J T, Zheng J, Han Y M. *Bull Sport Sci Technol*, 2022, **30**(11): 241-244
- [7] Liu Z, Liu M, Fan M, *et al.* Metabolomic-proteomic combination analysis reveals the targets and molecular pathways associated with hydrogen sulfide alleviating NAFLD. *Life Sci*, 2021, **264**: 118629
- [8] Lupberger J, Croonenborghs T, Suarez A A R, *et al.* Combined analysis of metabolomes, proteomes, and transcriptomes of hepatitis C virus-infected cells and liver to identify pathways associated with disease development. *Gastroenterology*, 2019, **157**(2): 537-551.e9
- [9] Contrepois K, Wu S, Moneghetti K J, *et al.* Molecular choreography of acute exercise. *Cell*, 2020, **181**(5): 1112-1130.e16
- [10] Qi S, Li X, Yu J, *et al.* Research advances in the application of metabolomics in exercise science. *Front Physiol*, 2023, **14**: 1332104
- [11] Sakaguchi C A, Nieman D C, Signini E F, *et al.* Metabolomics-based studies assessing exercise-induced alterations of the human metabolome: a systematic review. *Metabolites*, 2019, **9**(8): 164
- [12] Schraner D, Kastenmüller G, Schönfelder M, *et al.* Metabolite concentration changes in humans after a bout of exercise: a systematic review of exercise metabolomics studies. *Sports Med Open*, 2020, **6**(1): 11
- [13] Khoramipour K, Sandbakk Ø, Keshteli A H, *et al.* Metabolomics in exercise and sports: a systematic review. *Sports Med*, 2022, **52**(3): 547-583
- [14] Brooks G A. The science and translation of lactate shuttle theory. *Cell Metab*, 2018, **27**(4): 757-785
- [15] Jamnick N A, Pettitt R W, Granata C, *et al.* An examination and critique of current methods to determine exercise intensity. *Sports Med*, 2020, **50**(10): 1729-1756
- [16] Sato S, Dyar K A, Treebak J T, *et al.* Atlas of exercise metabolism reveals time-dependent signatures of metabolic homeostasis. *Cell Metab*, 2022, **34**(2): 329-345.e8
- [17] Brooks G A. Lactate as a fulcrum of metabolism. *Redox Biol*, 2020, **35**: 101454
- [18] 魏亚茹,刘妍妍,周桐希,等.利用血乳酸评定短道速滑项目运动员无氧能力的研究. *沧州师范学院学报*, 2022, **38**(1): 94-98
Wei Y R, Liu Y Y, Zhou T X, *et al.* *J Cangzhou Norm Univ*, 2022, **38**(1): 94-98
- [19] 刘阳,张赛,董高芳,等.高强度间歇训练通过支配内脏脂肪的交感神经活动促进白色脂肪组织棕色化. *中国体育科技*, 2020, **56**(2): 15-23
Liu Y, Zhang S, Dong G F, *et al.* *China Sport Sci Technol*, 2020, **56**(2): 15-23
- [20] Petersen C, Nielsen M D, Andersen E S, *et al.* MCT1 and MCT4 expression and lactate flux activity increase during white and brown adipogenesis and impact adipocyte metabolism. *Sci Rep*, 2017, **7**(1): 13101

- [21] Song J, Lee K, Park S W, *et al.* Lactic acid upregulates VEGF expression in macrophages and facilitates choroidal neovascularization. *Invest Ophthalmol Vis Sci*, 2018, **59**(8): 3747-3754
- [22] Cai X, Ng C P, Jones O, *et al.* Lactate activates the mitochondrial electron transport chain independently of its metabolism. *Mol Cell*, 2023, **83**(21): 3904-3920.e7
- [23] Zhang D, Tang Z, Huang H, *et al.* Metabolic regulation of gene expression by histone lactylation. *Nature*, 2019, **574**(7779): 575-580
- [24] Wang G L, Jiang B H, Rue E A, *et al.* Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O₂ tension. *Proc Natl Acad Sci USA*, 1995, **92**(12): 5510-5514
- [25] Carneiro L, Asrih M, Repond C, *et al.* AMPK activation caused by reduced liver lactate metabolism protects against hepatic steatosis in MCT1 haploinsufficient mice. *Mol Metab*, 2017, **6**(12): 1625-1633
- [26] Wei W, Riley N M, Lyu X, *et al.* Organism-wide, cell-type-specific secretome mapping of exercise training in mice. *Cell Metab*, 2023, **35**(7): 1261-1279.e11
- [27] Li V L, He Y, Contrepois K, *et al.* An exercise-inducible metabolite that suppresses feeding and obesity. *Nature*, 2022, **606**(7915): 785-790
- [28] 王翔, 魏源. 丙酮酸补充与运动能力. 北京体育大学学报, 2002, **25**(2): 207-210
Wang X, Wei Y. J Beijing Univ Phys Educ, 2002, **25**(2): 207-210
- [29] Berton R, Conceição M S, Libardi C A, *et al.* Metabolic time-course response after resistance exercise: a metabolomics approach. *J Sports Sci*, 2017, **35**(12): 1211-1218
- [30] Valério D F, Berton R, Conceição M S, *et al.* Early metabolic response after resistance exercise with blood flow restriction in well-trained men: a metabolomics approach. *Appl Physiol Nutr Metab*, 2018, **43**(3): 240-246
- [31] 马振菁, 邓思珊, 刘洪旭, 等. 血清丙酮酸水平和乳酸/丙酮酸比值在线粒体病筛查中的作用. 国际检验医学杂志, 2010, **31**(12): 1396-1397
Ma Z J, Deng S S, Liu H X, *et al.* *Int J Lab Med*, 2010, **31**(12): 1396-1397
- [32] Buchanan J L, Taylor E B. Mitochondrial pyruvate carrier function in health and disease across the lifespan. *Biomolecules*, 2020, **10**(8): 1162
- [33] Löding S, Antti H, Sjöberg R L, *et al.* Blood based metabolic markers of glioma from pre-diagnosis to surgery. *Sci Rep*, 2024, **14**(1): 20680
- [34] Cho H J, Paik I Y, Kim J S, *et al.* The effect of pyruvate intake and aerobic exercise on the change of serum parameters and body composition in obese men. *Korean J Sport Sci*, 2019, **30**(2): 223-235
- [35] Puchalska P, Crawford P A. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab*, 2017, **25**(2): 262-284
- [36] 刘俊, 娄淑杰. 高强度间歇训练(HIIT)可能通过改变小鼠 mTORC1、PPAR α 和 FGF21 表达诱导肝酮体生成. 生理学报, 2024, **76**(2): 224-232
Liu J, Lou S J. *Acta Physiol Sin*, 2024, **76**(2): 224-232
- [37] Pechlivanis A, Papaioannou K G, Tsalis G, *et al.* Monitoring the response of the human urinary metabolome to brief maximal exercise by a combination of RP-UPLC-MS and (1)H NMR spectroscopy. *J Proteome Res*, 2015, **14**(11): 4610-4622
- [38] Peake J M, Tan S J, Markworth J F, *et al.* Metabolic and hormonal responses to isoenergetic high-intensity interval exercise and continuous moderate-intensity exercise. *Am J Physiol Endocrinol Metab*, 2014, **307**(7): E539-E552
- [39] Rojas-Morales P, Tapia E, Pedraza-Chaverri J. β -Hydroxybutyrate: a signaling metabolite in starvation response. *Cell Signal*, 2016, **28**(8): 917-923
- [40] White A M, Johnston C S, Swan P D, *et al.* Blood ketones are directly related to fatigue and perceived effort during exercise in overweight adults adhering to low-carbohydrate diets for weight loss: a pilot study. *J Am Diet Assoc*, 2007, **107**(10): 1792-1796
- [41] Walsh J J, Neudorf H, Little J P. 14-day ketone supplementation lowers glucose and improves vascular function in obesity: a randomized crossover trial. *J Clin Endocrinol Metab*, 2021, **106**(4): e1738-e1754
- [42] Nielsen R, Møller N, Gormsen L C, *et al.* Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. *Circulation*, 2019, **139**(18): 2129-2141
- [43] Stephens F B, Constantin-Teodosiu D, Greenhaff P L. New insights concerning the role of carnitine in the regulation of fuel metabolism in skeletal muscle. *J Physiol*, 2007, **581**(Pt 2): 431-444
- [44] Parstorfer M, Poschet G, Brüning K, *et al.* Exercise-induced effects on the metabolome of endurance and strength-trained athletes in comparison with sedentary subjects: a pilot study. *Physiol Rep*, 2025, **13**(3): e70206
- [45] Lehmann R, Zhao X, Weigert C, *et al.* Medium chain acylcarnitines dominate the metabolite pattern in humans under moderate intensity exercise and support lipid oxidation. *PLoS One*, 2010, **5**(7): e11519
- [46] Malaguarnera M, Cammalleri L, Gargante M P, *et al.* L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr*, 2007, **86**(6): 1738-1744
- [47] Lahimer M, Gherissi O, Ben Salem N, *et al.* Effect of micronutrients and L-carnitine as antioxidant on sperm parameters, genome integrity, and ICSI outcomes: randomized, double-blind, and placebo-controlled clinical trial. *Antioxidants (Basel)*, 2023, **12**(11): 1937
- [48] Felig P. Amino acid metabolism in man. *Annu Rev Biochem*, 1975, **44**: 933-955
- [49] Blancquaert L, Everaert I, Derave W. Beta-alanine supplementation, muscle carnosine and exercise performance. *Curr Opin Clin Nutr Metab Care*, 2015, **18**(1): 63-70
- [50] Boldyrev A A, Stvolinsky S L, Fedorova T N, *et al.* Carnosine as a natural antioxidant and geroprotector: from molecular

- mechanisms to clinical trials. *Rejuvenation Res*, 2010, **13**(2/3): 156-158
- [51] Trombley P Q, Horning M S, Blakemore L J. Interactions between carnosine and zinc and copper: implications for neuromodulation and neuroprotection. *Biochemistry (Mosc)*, 2000, **65**(7): 807-816
- [52] Lewis G D, Farrell L, Wood M J, *et al*. Metabolic signatures of exercise in human plasma. *Sci Transl Med*, 2010, **2**(33): 33ra37
- [53] Coelho W S, Viveiros de Castro L, Deane E, *et al*. Investigating the cellular and metabolic responses of world-class canoeists training: a sportomics approach. *Nutrients*, 2016, **8**(11): 719
- [54] Dolan E, Artioli G G, Pereira R M R, *et al*. Muscular atrophy and sarcopenia in the elderly: is there a role for creatine supplementation. *Biomolecules*, 2019, **9**(11): 642
- [55] Candow D G, Forbes S C, Chilibeck P D, *et al*. Effectiveness of creatine supplementation on aging muscle and bone: focus on falls prevention and inflammation. *J Clin Med*, 2019, **8**(4): 488
- [56] Cordingley D M, Cornish S M, Candow D G. Anti-inflammatory and anti-catabolic effects of creatine supplementation: a brief review. *Nutrients*, 2022, **14**(3): 544
- [57] Xu C, Bi S, Zhang W, *et al*. The effects of creatine supplementation on cognitive function in adults: a systematic review and meta-analysis. *Front Nutr*, 2024, **11**: 1424972
- [58] Qiu S, Cai Y, Yao H, *et al*. Small molecule metabolites: discovery of biomarkers and therapeutic targets. *Signal Transduct Target Ther*, 2023, **8**(1): 132
- [59] Buerger T, Steinfeldt J, Ruyoga G, *et al*. Metabolomic profiles predict individual multidisease outcomes. *Nat Med*, 2022, **28**(11): 2309-2320
- [60] 国家心血管病中心, 中国心血管健康与疾病报告编写组. 中国心血管健康与疾病报告 2023 概要. *中国循环杂志*, 2024, **39**(7): 625-660
National Center for Cardiovascular Diseases, The Writing Committee of the Report on Cardiovascular Health and Diseases in China. *Chin Circ J*, 2024, **39**(7): 625-660
- [61] 程思, 庞元捷, 吕筠, 等. 代谢组学在心血管代谢疾病病因研究中的应用进展. *中华流行病学杂志*, 2023, **44**(1): 157-164
Cheng S, Pang Y J, Lyu J, *et al*. *Chin J Epidemiol*, 2023, **44**(1): 157-164
- [62] Holmes M V, Millwood I Y, Kartsonaki C, *et al*. Lipids, lipoproteins, and metabolites and risk of myocardial infarction and stroke. *J Am Coll Cardiol*, 2018, **71**(6): 620-632
- [63] Chiesa S T, Charakida M, Georgiopoulos G, *et al*. Glycoprotein acetyls: a novel inflammatory biomarker of early cardiovascular risk in the young. *J Am Heart Assoc*, 2022, **11**(4): e024380
- [64] Mardinoglu A, Stančáková A, Lotta L A, *et al*. Plasma mannose levels are associated with incident type 2 diabetes and cardiovascular disease. *Cell Metab*, 2017, **26**(2): 281-283
- [65] Würtz P, Havulinna A S, Soininen P, *et al*. Metabolite profiling and cardiovascular event risk: a prospective study of 3 population-based cohorts. *Circulation*, 2015, **131**(9): 774-785
- [66] Rizza S, Copetti M, Rossi C, *et al*. Metabolomics signature improves the prediction of cardiovascular events in elderly subjects. *Atherosclerosis*, 2014, **232**(2): 260-264
- [67] Chen Z Z, Gerszten R E. Metabolomics and proteomics in type 2 diabetes. *Circ Res*, 2020, **126**(11): 1613-1627
- [68] Xu Y, Lu J, Li M, *et al*. Diabetes in China part 1: epidemiology and risk factors. *Lancet Public Health*, 2024, **9**(12): e1089-e1097
- [69] Bragg F, Kartsonaki C, Guo Y, *et al*. Circulating metabolites and the development of type 2 diabetes in Chinese adults. *Diabetes Care*, 2022, **45**(2): 477-480
- [70] Li X, Li Y, Liang Y, *et al*. Plasma targeted metabolomics analysis for amino acids and acylcarnitines in patients with prediabetes, type 2 diabetes mellitus, and diabetic vascular complications. *Diabetes Metab J*, 2021, **45**(2): 195-208
- [71] Hosseinkhani S, Arjmand B, Dilmaghani-Marand A, *et al*. Targeted metabolomics analysis of amino acids and acylcarnitines as risk markers for diabetes by LC-MS/MS technique. *Sci Rep*, 2022, **12**(1): 8418
- [72] Sun L, Liang L, Gao X, *et al*. Early prediction of developing type 2 diabetes by plasma acylcarnitines: a population-based study. *Diabetes Care*, 2016, **39**(9): 1563-1570
- [73] Suvitaival T, Bondia-Pons I, Yetukuri L, *et al*. Lipidome as a predictive tool in progression to type 2 diabetes in Finnish men. *Metabolism*, 2018, **78**: 1-12
- [74] Chen Y, Wang B, Zhao Y, *et al*. Metabolomic machine learning predictor for diagnosis and prognosis of gastric cancer. *Nat Commun*, 2024, **15**(1): 1657
- [75] Zhang S, Wang Z, Wang Y, *et al*. A metabolomic profile of biological aging in 250, 341 individuals from the UK Biobank. *Nat Commun*, 2024, **15**(1): 8081
- [76] 黄彩华, 归予恒, 林东海. 代谢组学: 运动人体科学研究的新工具. *体育科学*, 2011, **31**(9): 77-84
Huang C H, Gui Y H, Lin D H. *China Sport Sci*, 2011, **31**(9): 77-84
- [77] Lin C, Xia M, Dai Y, *et al*. Cross-ancestry analyses of Chinese and European populations reveal insights into the genetic architecture and disease implication of metabolites. *Cell Genom*, 2025, **5**(4): 100810
- [78] Karjalainen M K, Karthikeyan S, Oliver-Williams C, *et al*. Genome-wide characterization of circulating metabolic biomarkers. *Nature*, 2024, **628**(8006): 130-138
- [79] Ahmetov I I, Fedotovskaya O N. Current progress in sports genomics. *Adv Clin Chem*, 2015, **70**: 247-314
- [80] Ross R, Blair S N, Arena R, *et al*. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American heart association. *Circulation*, 2016, **134**(24): e653-e699
- [81] 邱淑敏, 陈佩杰, 张春华. 有氧锻炼对久坐不动生活方式的健康人群最大摄氧量的影响: Meta 分析. *中国运动医学杂志*, 2010, **29**(1): 14-17
Qiu S M, Chen P J, Zhang C H. *Chin J Phys Med*, 2010, **29**(1): 14-17
- [82] 高天, 王星, 石培文, 等. 有氧能力在慢性病风险预测和管理中的研究进展. *中国预防医学杂志*, 2025: 1-8
Gao T, Wang X, Shi P W, *et al*. *Chin Prev Med*, 2025: 1-8

- [83] Ung G A, Nguyen K H, Hui A, *et al.* Impact of cardiorespiratory fitness and diabetes status on cardiovascular disease and all-cause mortality: an NHANES retrospective cohort study. *Am Heart J Plus*, 2024, **42**: 100395
- [84] 何子红, 胡扬. 运动与健康的基因组学和代谢组学研究进展. *生理科学进展*, 2014, **45**(4): 257-262
He Z H, Hu Y. *Prog Physiol Sci*, 2014, **45**(4): 257-262
- [85] Bye A, Klevjer M, Ryeng E, *et al.* Identification of novel genetic variants associated with cardiorespiratory fitness. *Prog Cardiovasc Dis*, 2020, **63**(3): 341-349
- [86] Klevjer M, Nordeidet A N, Hansen A F, *et al.* New genetic determinants of VO₂ max-level identified by GWAS: The HUNT Study. *Cardiovasc Res*, 2022, **118**(Supplement_1): cvac066.013
- [87] Nordeidet A N, Klevjer M, Wisløff U, *et al.* Exploring shared genetics between maximal oxygen uptake and disease: the HUNT study. *Physiol Genomics*, 2023, **55**(10): 440-451
- [88] Song D K, Hong Y S, Sung Y A, *et al.* Association of serum creatinine levels and risk of type 2 diabetes mellitus in Korea: a case control study. *BMC Endocr Disord*, 2022, **22**(1): 4
- [89] Sun L, Luan J, Wang J, *et al.* GEPREPA comprehensive data atlas of RNA-seq-based gene expression profiles of exercise responses. *J Sport Health Sci*, 2024, **14**: 100992
- [90] Pan L, Ai S, Shi X, *et al.* ExerGeneDB: a physical exercise-regulated differential gene expression database. *J Sport Health Sci*, 2025, **14**: 101027
- [91] Chen L, Wang C, Qin L, *et al.* Parkinson's disease and glucose metabolism impairment. *Transl Neurodegener*, 2025, **14**(1): 10
- [92] Trezzi J P, Galozzi S, Jaeger C, *et al.* Distinct metabolomic signature in cerebrospinal fluid in early Parkinson's disease. *Mov Disord*, 2017, **32**(10): 1401-1408
- [93] Hu Y, Zhang K, Zhang T, *et al.* Exercise reverses dysregulation of T-cell-related function in blood leukocytes of patients with Parkinson's disease. *Front Neurol*, 2019, **10**: 1389
- [94] Ogata H, Goto S, Sato K, *et al.* KEGG Kyoto encyclopedia of genes and genomes. *Nucleic Acids Res*, 1999, **27**(1): 29-34
- [95] 李玲君, 张月鑫, 崔毓桂. 山梨醇代谢旁路及其在生殖领域研究进展. *国际生殖健康/计划生育杂志*, 2019, **38**(4): 313-317
Li L J, Zhang Y X, Cui Y G. *J Int Reprod Health/Family Plan*, 2019, **38**(4): 313-317
- [96] 王茹, 王婕娉, 王汝雯, 等. 低氧运动对代谢性疾病的潜在影响机制. *上海体育大学学报*, 2025, **49**(2): 29-45
Wang R, Wang J P, Wang R W, *et al.* *J Shanghai Univ Sport*, 2025, **49**(2): 29-45
- [97] Glotov A S, Zelenkova I E, Vashukova E S, *et al.* RNA sequencing of whole blood defines the signature of high intensity exercise at altitude in elite speed skaters. *Genes (Basel)*, 2022, **13**(4): 574
- [98] Al-Sulaiti H, Diboun I, Agha M V, *et al.* Metabolic signature of obesity-associated insulin resistance and type 2 diabetes. *J Transl Med*, 2019, **17**(1): 348
- [99] Lee C W, Lee T V, Galvan E, *et al.* The effect of choline and resistance training on strength and lean mass in older adults. *Nutrients*, 2023, **15**(18): 3874
- [100] Hoffman N J, Parker B L, Chaudhuri R, *et al.* Global phosphoproteomic analysis of human skeletal muscle reveals a network of exercise-regulated kinases and AMPK substrates. *Cell Metab*, 2015, **22**(5): 922-935
- [101] Whitham M, Parker B L, Friedrichsen M, *et al.* Extracellular vesicles provide a means for tissue crosstalk during exercise. *Cell Metab*, 2018, **27**(1): 237-251.e4
- [102] Deshmukh A S, Steenberg D E, Hostrup M, *et al.* Deep muscle-proteomic analysis of freeze-dried human muscle biopsies reveals fiber type-specific adaptations to exercise training. *Nat Commun*, 2021, **12**(1): 304
- [103] Robbins J M, Peterson B, Schraner D, *et al.* Human plasma proteomic profiles indicative of cardiorespiratory fitness. *Nat Metab*, 2021, **3**(6): 786-797
- [104] Blazev R, Carl C S, Ng Y K, *et al.* Phosphoproteomics of three exercise modalities identifies canonical signaling and C¹⁸ORF25 as an AMPK substrate regulating skeletal muscle function. *Cell Metab*, 2022, **34**(10): 1561-1577.e9
- [105] Ahn C, Zhang T, Yang G, *et al.* Years of endurance exercise training remodel abdominal subcutaneous adipose tissue in adults with overweight or obesity. *Nat Metab*, 2024, **6**(9): 1819-1836
- [106] Horowitz A M, Fan X, Bieri G, *et al.* Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. *Science*, 2020, **369**(6500): 167-173
- [107] Nelson M E, Parker B L, Burchfield J G, *et al.* Phosphoproteomics reveals conserved exercise-stimulated signaling and AMPK regulation of store-operated calcium entry. *EMBO J*, 2020, **39**(8): e104246
- [108] De Miguel Z, Khoury N, Betley M J, *et al.* Exercise plasma boosts memory and dampens brain inflammation via clusterin. *Nature*, 2021, **600**(7889): 494-499
- [109] Peng H, Hu B, Xie L Q, *et al.* A mechanosensitive lipolytic factor in the bone marrow promotes osteogenesis and lymphopoiesis. *Cell Metab*, 2022, **34**(8): 1168-1182.e6
- [110] MoTrPAC Study Group, Analysts L, Group M S. Temporal dynamics of the multi-omic response to endurance exercise training. *Nature*, 2024, **629**(8010): 174-183
- [111] Amar D, Gay N R, Jimenez-Morales D, *et al.* The mitochondrial multi-omic response to exercise training across rat tissues. *Cell Metab*, 2024, **36**(6): 1411-1429.e10
- [112] Many G M, Sanford J A, Sagendorf T J, *et al.* Sexual dimorphism and the multi-omic response to exercise training in rat subcutaneous white adipose tissue. *Nat Metab*, 2024, **6**(5): 963-979
- [113] 毛莹莹, 陈倩, 姬辛娜, 等. SLC25A15 基因复合杂合突变致 HHH 综合征 1 例报告并文献复习. *临床儿科杂志*, 2019, **37**(10): 794-797
Mao Y Y, Chen Q, Ji X N, *et al.* *J Clin Pediatr*, 2019, **37**(10): 794-797
- [114] 林家仕, 费小小. 不同 CRF 水平的 MS 风险因素人群血浆代谢物差异. *体育科学研究*, 2024, **28**(5): 46-55
Lin J S, Fei X X. *Phys Sci Res*, 2024, **28**(5): 46-55

- [115] Giri S, Varshney K K, Srivastava R. Therapeutic potential and prospects of L-arginine in various diseases and its clinical intervention. *Curr Drug Ther*, 2024, **19**(5): 529-545
- [116] Du J, Zhang W, Niu J, *et al.* Association between blood urea nitrogen levels and the risk of diabetes mellitus in Chinese adults: secondary analysis based on a multicenter, retrospective cohort study. *Front Endocrinol (Lausanne)*, 2024, **15**: 1282015
- [117] Green E D, Guyer M S. Charting a course for genomic medicine from base pairs to bedside. *Nature*, 2011, **470**(7333): 204-213
- [118] Galluzzi L, Vitale I, Michels J, *et al.* Systems biology of cisplatin resistance: past, present and future. *Cell Death Dis*, 2014, **5**(5): e1257
- [119] Leonelli S, Smirnov N, Moore J, *et al.* Making open data work for plant scientists. *J Exp Bot*, 2013, **64**(14): 4109-4117
- [120] 祁云霞, 刘永斌, 荣威恒. 转录组研究新技术: RNA-Seq 及其应用. *遗传*, 2011, **33**(11): 1191-1202
Qi Y X, Liu Y B, Rong W H. *Hereditas*, 2011, **33**(11): 1191-1202
- [121] Graf A, Dragosits M, Gasser B, *et al.* Yeast systems biotechnology for the production of heterologous proteins. *FEMS Yeast Res*, 2009, **9**(3): 335-348
- [122] Di Meo A, Pasic M D, Yousef G M. Proteomics and peptidomics: moving toward precision medicine in urological malignancies. *Oncotarget*, 2016, **7**(32): 52460-52474
- [123] Capati A, Ijare O B, Bezabeh T. Diagnostic applications of nuclear magnetic resonance-based urinary metabolomics. *Magn Reson Insights*, 2017, **10**: 1178623X17694346
- [124] Couvillion S P, Zhu Y, Nagy G, *et al.* New mass spectrometry technologies contributing towards comprehensive and high throughput omics analyses of single cells. *Analyst*, 2019, **144**(3): 794-807
- [125] Barrón-Cabrera E, Ramos-Lopez O, González-Becerra K, *et al.* Epigenetic modifications as outcomes of exercise interventions related to specific metabolic alterations: a systematic review. *Lifestyle Genom*, 2019, **12**(1/2/3/4/5/6): 25-44
- [126] Clemente-Suárez V J, Martín-Rodríguez A, Redondo-Flórez L, *et al.* New insights and potential therapeutic interventions in metabolic diseases. *Int J Mol Sci*, 2023, **24**(13): 10672
- [127] Ishikawa V N, Gontijo G M, Ichikawa A I T, *et al.* Major metabolic and metabolomic aspects of nutrition in the gut microbiota and sports performance: a systematic review. *Int J Nutrol*, 2023, **16**(2): 1-12
- [128] Tang H, Huang Y, Yuan D, *et al.* Atherosclerosis, gut microbiome, and exercise in a meta-omics perspective: a literature review. *PeerJ*, 2024, **12**: e17185
- [129] Zhang C, Zhao L. Strain-level dissection of the contribution of the gut microbiome to human metabolic disease. *Genome Med*, 2016, **8**(1): 41
- [130] Tanaka M, Wang G, Pitsiladis Y P. Advancing sports and exercise genomics: moving from hypothesis-driven single study approaches to large multi-omics collaborative science. *Physiol Genomics*, 2016, **48**(3): 173-174
- [131] Wei W, Raun S H, Long J Z. Molecular insights from multiomics studies of physical activity. *Diabetes*, 2024, **73**(2): 162-168
- [132] Katz D H, Lindholm M E, Ashley E A. Charting the molecular terrain of exercise: energetics, exerkines, and the future of multiomic mapping. *Physiology (Bethesda)*, 2025, **40**(2): 185-202
- [133] Hoffman N J. Omics and exercise: global approaches for mapping exercise biological networks. *Cold Spring Harb Perspect Med*, 2017, **7**(10): a029884

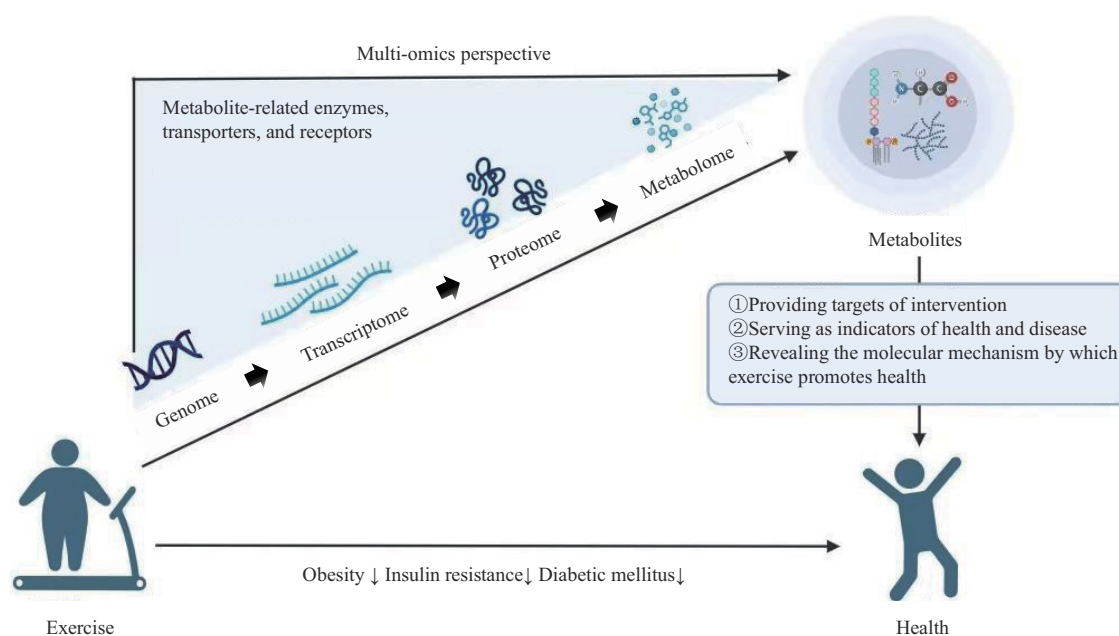
Molecular Mechanisms of Exercise in Promoting Health: a Multi-omics Analysis of Metabolic Biomarkers

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Graphical abstract



Abstract The molecular mechanisms underlying the health-promoting effects of exercise remain to be fully elucidated. As a bridge between genetics, exercise and phenotype, metabolites can be detected in high throughput through metabolomics, offering valuable insights into mechanism elucidation and disease prediction. Metabolic homeostasis is intricately regulated by various factors, including enzyme activity and transporters. Integration of multiple omics technologies such as genomics, transcriptomics, and proteomics enables the comprehensive elucidation of the metabolic network modulated by exercise interventions and facilitates the identification of key metabolic markers. This review summarizes the current research advancements, biological functions, discovery methods, and applications of exercise-induced multi omics metabolic markers, furnishing a theoretical foundation for understanding the mechanisms of exercise-induced health benefits and enabling precision interventions. Relevant literatures from 2000 to 2025 were systematically retrieved from databases including PubMed, CNKI and other databases with the keywords such as “multi-omics”, “metabolic biomarkers”, “exercise”, “health”. Subsequently, the identified literature was meticulously screened to meet the specified criteria and was subsequently incorporated into the study. (1) Exercise induces profound alterations in metabolite levels within the body, with particular emphasis on markers associated with sugar, lipid, and protein metabolism being extensively

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investigated. As an intensity marker, lactate is implicated in the regulation of fat browning (UCP-1), angiogenesis (VEGF), mitochondrial function (PGC-1 α) and metabolic homeostasis (HIF-1 α /CES2). Following resistance training, pyruvate levels increase, and an aberrant pyruvate to lactate ratio (approximately 10) may indicate mitochondrial dysfunction. Supplementation with pyruvate has been shown to reduce weight and lipid levels. Ketone bodies regulate metabolism by inhibiting lipolytic enzyme activity and promoting insulin secretion. Plasma ketone body concentrations rise after high-intensity exercise, with levels positively associated with central fatigue. Carnitine levels elevate post-endurance training, and supplementation with carnitine has been linked to increased lean body mass and enhanced cognitive function in older individuals. Serum alanine levels rise following resistance training and, as a precursor of carnosine, supplementation can elevate carnosine concentration by 80%, exerting antioxidant and neuroprotective effects. Creatine, a pivotal molecule in phosphagen energy supply, exhibits a 93% increase in plasma levels post-marathon, with its metabolism intricately related to AMPK activation. (2) Metabolites play a crucial role in disease prediction, particularly in the context of cardiovascular disease where 18 metabolites including glycoprotein acetyl and ketone bodies have been shown to enhance the performance of prediction models. Similarly, in diabetes research, acylcarnitine and other metabolites can improve prediction model efficacy. The combination of multiple metabolites has been found to substantially enhance predictive capabilities for various conditions such as cancer, aging, and other risks, surpassing the predictive power of traditional indicators. (3) Genomics investigations have unveiled the genetic underpinnings of exercise-related metabolites. VO₂max, a significant exercise phenotype with heritability estimates ranging from 0.59 to 0.66, exhibits a negative correlation with the susceptibility to diabetes and cardiovascular disease. SNPs associated with VO₂max, such as variants in the *F5HR* gene, are positively linked to serum creatinine levels. Reduced creatinine levels have been associated with an elevated risk of T2DM. These findings suggest that creatinine serves as a potential marker of exercise metabolism. (4) Transcriptomic studies have elucidated the molecular mechanisms by which exercise modulates metabolites. Acute exercise induces rapid alterations in the expression profiles of 9 132 transcripts. Exercise elicits upregulation of genes involved in the fructose/mannose metabolic pathway (such as *SORD*, *PFKFB3*), suggesting these metabolites may serve as pivotal mediators in the beneficial effects of exercise on Parkinson's disease. Altitude training enhances the expression of the *PHOSPHOI* gene, which encodes an enzyme facilitating choline synthesis. Choline deficiency has been linked to insulin resistance. Choline supplementation has been shown to augment the effects of resistance training, underscoring the significance of choline as a key marker in exercise-mediated metabolic health promotion. (5) Proteomic analyses have unveiled the key mechanisms through which exercise modulates metabolism. Endurance training induces significant alterations in myofibrillar expression, with 237 slow muscles and 172 fast muscles proteins showing differential regulation, of which 65% are associated with metabolism, including *ACSL1* and *ECHS1*. Various training modalities elicit distinct phosphorylation modifications, exemplified by the negative correlation between LDHA3 phosphorylation and lactate levels. Endurance training upregulates *SLC25A15* expression in adipose tissue, enhancing arginine synthesis. The post-exercise elevation of plasma GPLD1 levels mimics the neuroprotective effects of exercise on the brain. These findings present novel targets for investigating exercise-related metabolic markers. The application of multi omics technologies has expedited the identification and mechanistic analysis of both established and novel sports-related metabolic markers like lactate. Integrated multi omics strategies (*e. g.*, genome-metabolome) enable the simultaneous examination of metabolic markers and their regulatory mechanisms, facilitating the discovery of exercise-related genetic markers and pivotal regulatory proteins. However, challenges persist, including inadequate data integration and a lack of standardization. Future endeavors should focus on developing dynamic monitoring tools, integrating state-of-the-art approaches such as single-cell/spatial omics, and leveraging AI algorithms for optimized analysis to construct precise predictive models for maximizing health benefits in exercise.

Key words multi-omics, metabolic biomarkers, exercise, health

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