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Review 综 述

运动、肠道菌群和 2 型糖尿病关系的研究进展

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摘　要：2 型糖尿病(type 2 diabetes mellitus, T2DM)是一种常见的代谢性疾病，然而其发病机制尚未有定论。研究发现，肠道菌群与 T2DM 密切相关，T2DM 导致某种特定的肠道菌群结构和代谢特征，从而导致疾病发生发展。运动是 T2DM 防治的有效手段，可逆转因 T2DM 而引发的肠道菌群紊乱，调节肠道代谢物，从而改善 T2DM。然而，运动对 T2DM 患者肠道菌群的影响仍存在许多问题亟须解决。此外，运动调控 T2DM 患者肠道菌群可与人体众多脏器关联，可通过多条肠道-肠外器官轴通路对 T2DM 产生效益。鉴于此，本文基于运动、肠道菌群和 T2DM 之间的关系，对 T2DM 肠道菌群特征以及运动对 T2DM 肠道菌群影响，并从肠道-器官轴角度对运动调控肠道菌群改善 T2DM 的机制进行综述，以期为进一步明确运动、肠道菌群和 T2DM 的关系提供参考。

关键词：运动；2 型糖尿病；肠道菌群；肠外器官轴

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Research advances in the relationship among exercise, gut microbiota, and type 2 diabetes mellitus

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Abstract: Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disease, yet its pathogenesis remains inconclusive. Recent studies have revealed a close relationship between the gut microbiota and T2DM, and specific gut microbiota structures and metabolic characteristics are associated with the onset and progression of T2DM. Exercise is an effective intervention for the prevention and management of T2DM, capable of reversing the dysbiosis induced by T2DM and regulating gut metabolites. However, the effects of exercise on the gut microbiota in T2DM patients still present many unresolved issues. Furthermore, the regulation of gut microbiota by exercise in T2DM patients is closely linked to multiple organs and can exert alleviation effects on T2DM *via* various gut-organ axis pathways. This paper reviews the characteristics of gut microbiota in T2DM and the effects of exercise on the gut microbiota in T2DM, with a particular focus on the mechanisms by which exercise regulates the gut microbiota to ameliorate T2DM *via* the gut-organ axis. This review aims to provide a reference for elucidating the relationship between exercise, gut microbiota, and T2DM.
Keywords: exercise; type 2 diabetes mellitus; gut microbiota; extraintestinal organ axis

据统计，我国 2 型糖尿病(type 2 diabetes mellitus, T2DM)患病率已达到 12.8%，而老年人口(60 岁以上)患病率高达 30%[1]，T2DM 已成为我国面临的重大公共卫生问题[2]。T2DM 涉及多种致病机制，受遗传、生活方式等混杂因素共同影响[3-4]。微生物组学技术的进步为 T2DM 的防治提供了新的视角，研究显示 T2DM 患者肠道菌群与正常健康个体存在显著差异[5-6]，称为肠道菌群紊乱。肠道菌群可直接分泌信号分子作用于 T2DM，或通过菌群代谢物间接影响 T2DM 发生发展[7]，肠道菌群已成为 T2DM 防治的重要靶点。

运动是 T2DM 防治的重要手段，它与肠道菌群之间的密切关系已得到广泛证实[8]，不仅能帮助 T2DM 患者重建健康的肠道微生态环境，还能直接增强患者体质[9-10]。以肠道菌群为运动干预靶点可能成为 T2DM 防治的新方向。然而，当前有关运动对 T2DM 患者肠道菌群的影响仍存在部分问题亟须解决，例如运动对肠道菌群影响的机制；不同运动方式对肠道菌群的影响差异；肠道菌群与运动响应之间的关系等，对这些问题的解决有助于为精准设定运动干预方案提供参考。另外，研究显示，肠道菌群可通过肠道与身体其他组织和器官功能相连接，称为肠道-肠外器官轴[11]，通过梳理肠道菌群与肠外器官轴通路的关系有助于更深入地理解肠道菌群与 T2DM 的关系，以及各器官之间的相互作用与联系。

1 肠道菌群与 T2DM

肠道菌群与 T2DM 密切相关。Larsen 等[12]首次证明了 T2DM 患者与正常个体的肠道菌群存在显著差异，这种差异通常被称为“肠道菌群失调”。据报道，正常个体肠道菌群主要由厚壁菌门(*Firmicutes*)、拟杆菌门(*Bacteroidetes*)、变形菌门(*Proteobacteria*)、放线菌门(*Actinobacteria*)和梭杆菌门(*Fusobacteria*)等组成，占肠道菌群总数的 90%以上[13]。研究显示，T2DM 会导致患者厚壁菌门丰度升高，而拟杆菌门丰度降低[14]；厚壁菌门/拟杆菌门比值(*Firmicutes*/*Bacteroidetes*, F/B)升高是 T2DM 的重要特征[15-16]，与血糖紊乱密切相关[17]。此外，肠道菌群失调也在其他分类水平上体现。T2DM 引发的肠道菌群紊乱主要表现为短链脂肪酸(short-chain fatty acids, SCFAs)产生菌丰度降低，如乳杆菌属(*Lactobacillus*)、双歧杆菌属(*Bifidobacterium*)和普氏栖粪杆菌(*Faecalibacterium prausnitzii*)等[12,18]，还有研究发现嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)在 T2DM 患者中丰度降低，该菌群对于维持葡萄糖稳态具有重要作用[19]。与此同时，有害菌和条件致病菌极易在肠道中定殖。埃希氏菌属(*Escherichia*)是 T2DM 重要标志物，它和韦荣氏球菌属(*Veillonella*)可通过代谢物介导促炎因子释放[20]；活泼瘤胃球菌(*Ruminococcus gnavus*)和扭链瘤胃球菌(*Ruminococcus torques*)也在 T2DM 患者肠道中富集，它们可合成具有鼠李糖架构的复合葡萄多糖，诱导 Toll 样受体 4 使促炎因子释放[21-22]。当前实证研究中，常将 T2DM 患者病状，如糖脂代谢和炎症指标等，与肠道菌群变化相关联，以探索肠道菌群与机体病状的潜在关系。Leite 等[23]发现大肠埃希氏菌(*Escherichia coli*)和白细胞介素 6 (interleukin-6, IL-6)之间呈较强的正相关关系，并发现厚壁菌门与炎性因子 γ 干扰素之间呈显著正相关关系[23]；Karlsson 等[24]的研究显示，拟杆菌属(*Bacteroides*)和加氏乳杆菌(*Lactobacillus gasseri*)与胰岛素和糖化血红蛋白呈负相关关系；余杭林等[25]研究发现，扭链瘤胃球菌、活泼瘤胃球菌和韦荣氏球菌属与空腹血糖呈显著正相关关系；Adachi 等[26]发现梭菌属(*Clostridium*)和乳杆菌属与甘油三酯和总胆固醇之间密切关联。综上所述，T2DM 可导致患者肠道菌群失调，具体表现为菌群多样性降低、有益菌丰度减少、有害菌丰度提升，以及条件致病菌丰度的异常变化。上述关联性结果可为 T2DM 与肠道菌群的关系提供参考，然而，肠道菌群与 T2DM 的关系并非简明单一，仅凭少数菌群丰度变化无法定义 T2DM 肠道菌群特征[27]，当前仍缺乏部分罕见菌群的相关报道，有待进一步完善。

2 肠道菌群代谢物与 T2DM

2.1 短链脂肪酸(short-chain fatty acids, SCFAs)

肠道菌群代谢物是肠道菌群和人体串联的关键介质，SCFAs 是肠道菌群的重要代谢物，在调节机体代谢活动中具有重要作用。SCFAs 主要由肠道菌群发酵不可消化的碳水化合物(如膳食纤维)产生，其中乙酸、丙酸和丁酸占据了 SCFAs 总量的约 95%[28]。如前所述，T2DM 引发的肠道菌群失调可导致 SCFAs 产生菌丰度降低，进而造成 SCFAs 含量减少[24]。SCFAs 可促进胰岛素分泌并保护 β 细胞[29]，尤其是丙酸，可抑制细胞凋亡、促进胰岛 β 细胞增殖，并减少向胰岛 α 细胞分化来增加 β 细胞数量，从而增加胰岛素释放[30-31]。SCFAs 还具有抗炎作用，丁酸可以通过缓解脂肪细胞和巨噬细胞相互

作用抑制炎症信号从而调节炎症平衡[32-33]。此外，SCFAs 还可激活肠道糖异生和改善线粒体功能[34]。

2.2 胆汁酸(bile acids, BAs)

BAs 代谢紊乱是 T2DM 的发病机制之一。BAs 以胆固醇为原料在肝脏中合成，在信号传导、糖脂代谢以及调节炎症平衡等方面发挥重要作用[35]。肠道菌群密切参与 BAs 代谢过程，肠道菌群紊乱将扰乱人体肝脏 BAs 代谢[36]，导致初级和次级 BAs 比例失衡，影响 BAs 相关受体激活，进而加剧 T2DM[37]。法尼醇 X 受体(farnesoid X receptor, FXR)和 G 蛋白偶联受体 5 (takeda G protein-coupled receptor 5, TGR5)是 BAs 对患者糖脂代谢进行调节的关键受体，BAs 可通过激活上述 2 种受体而对 T2DM 产生改善效果[38-39]。

2.3 氧化三甲胺(trimethylamine N-oxide, TMAO)

食物(如红肉、蛋类和鱼)中的胆碱、肉碱或甜菜碱可被肠道菌群代谢为三甲胺，随后通过肝脏转化为 TMAO。一项基于 2 694 名参与者的研究表明，在中国人群中，血浆 TMAO 浓度与 T2DM 存在正相关关系[40]。Meta 分析显示，TMAO 水平与 T2DM 风险增加呈正相关，血浆中 TMAO 每增加 5 μmol/L，T2DM 患病率增加 54%[41]。TMAO 可下调胆固醇和胆汁酸代谢，并损害巨噬细胞[42]。Chen 等[43]研究显示，TMAO 可通过激活蛋白激酶 R 样内质网激酶的表达，从而导致代谢功能障碍和高血糖；TMAO 还可引起转化生长因子-β1 及其下游分子 α-平滑肌肌动蛋白水平升高，导致肾纤维化，并促进白细胞介素-1β (interleukin-1β, IL-1β)释放而导致肾脏炎症。

2.4 脂多糖(lipopolysaccharide, LPS)

研究显示，SCFAs 含量在 T2DM 患者肠道中降低将导致“肠漏”，即肠道屏障功能降低[44]，这会导致有害菌和病原体大量进入肠道，LPS 是革兰氏阴性细菌外膜的主成分，被认为是引发 T2DM 全身性低度炎症的重要促炎分子，屏障功能降低将导致 LPS 含量在肠道中升高[45]。研究显示，LPS 的过度积累可与 TLR4 结合激活 NF-κB 表达，驱动促炎因子释放，从而加剧患者的全身低度炎症和胆固醇代谢紊乱[20,46]。

2.5 其他代谢物

除了上述代谢物外，还有研究报道了其他肠道代谢物对 T2DM 的潜在影响。研究显示，肠道菌群可将色氨酸(一种必需芳香族氨基酸)转化为吲哚、吲哚-3-丙酸等衍生物[47-48]，吲哚可调节胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1)分泌，从而改善胰岛素抵抗和调节炎症[49]；吲哚-3-丙酸可对胰岛 β 细胞产生保护作用，与 T2DM 风险降低有关[50]。另外，肠道菌群发酵膳食纤维产生琥珀酸，能激活肠道糖异生，进而改善葡萄糖稳态[51]。Zhang 等[52]研究发现，肠道菌群可代谢鞣花酸衍生物产生乌罗利丁 A (urolithin A)，此物质可对机体线粒体功能和肌肉功能产生有益影响。Vangipurapu 等[53]通过长期随访发现，肌酸、尿酸盐、黄脲酸盐、黄嘌呤等代谢物与 T2DM 风险增加显著相关。

综上所述，肠道菌群代谢物变化涉及机体多种代谢途径变化，可预测 T2DM 发病风险。然而，当前研究尚无法解释菌群代谢物与 T2DM 的因果关系和机制，有待进一步探索。

3 运动干预 T2DM 患者肠道菌群的研究进展

3.1 运动对 T2DM 患者肠道菌群及其代谢物的影响

运动是肠道健康和肠道菌群稳态的促进

剂。Clarke 等[54]对比了爱尔兰职业橄榄球运动员与普通个体的肠道菌群特征，首次发现了运动与肠道菌群的关联，相比普通个体，运动员肠道中呈现出更高水平的菌群多样性，提示高水平菌群多样性与健康结局密切关联。Shalon 等[55]研究表明，保持一定水平的肠道菌群多样性是维持菌群共生关系和肠道菌群稳态的基础，这对于肠道微生态环境具有重要意义。研究显示，运动可以增加人体肠道菌群多样性[56-57]，增强菌群间的共生关系网络[58]。此外，运动还可逆转由 T2DM 造成的肠道菌群组成失衡。动物试验显示，8 周游泳运动降低了 T2DM 小鼠的 F/B 值，并改善了胰岛素抵抗[59]。类似的结果也在人体实验中得到证实，Motiani 等[60]发现运动显著增加了 T2DM 患者拟杆菌门菌群丰度，降低了梭菌属和布劳特氏菌属(*Blautia*)丰度，与此同时，肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)等促炎因子水平也随之降低。研究显示，梭菌属和布劳特氏菌属在 T2DM 前期和 T2DM 患者肠道中显著富集，它们在全身免疫反应中起重要作用，可增加促炎细胞因子释放[61-62]。另外，运动引发的肠道菌群变化同样可改变患者肠道代谢特征[63]。Yu 等[64]对高脂饮食小鼠分别施加有氧运动和口服丁酸补充剂干预，结果显示，2 种干预方式都改善了小鼠的代谢功能障碍和不良炎症反应，有氧运动增加了 6 种丁酸产生菌丰度，如拟杆菌属、罗斯拜瑞氏菌属(*Roseburia*)、普雷沃氏菌属(*Prevotella*)等，提示运动可通过提升 SCFAs 产生菌的丰度,从而提升患者肠道中 SCFAs 含量。然而，Komaroff[27]认为，单一菌群并不能有效解释宿主病理状态的变化，肠道菌群对机体健康的影响可能涉及众多复杂的潜在机制。当前鲜有研究探讨菌群间的相互作用对机体健康的影响，未来研究应关注菌群间的相互作用，这有助于深入理解肠道菌群与人体健康的关联。

3.2 运动对肠道屏障功能和全身低度炎症的影响

肠道菌群及其代谢物与人体肠道屏障功能和慢性炎症密切相关，肠道屏障是一个动态系统，受肠道菌群组成和细胞间连接活动的控制。如前所述，T2DM 将导致“肠漏”，其主要特征为病原体入侵，破坏宿主免疫系统而引发炎症。Pasini 等[65]通过 6 个月耐力运动显著改善了 T2DM 患者的肠道菌群紊乱、血糖水平以及低度炎症，值得注意的是，运动干预后受试者肠道上皮细胞的连接更加紧密。研究实证，丁酸可以促进肠道上皮细胞增殖分化[66]，还可激活紧密连接蛋白[如封闭蛋白(occludin)]表达从而修复和加强肠道上皮细胞之间的紧密连接，增强肠道屏障功能[67]。此外，Yan 等[68]研究报道，丁酸可调节中性粒细胞迁移，从而有效抑制炎性因子释放，改善肠道屏障功能。以上结果均有助于防止有害菌和病原体通过肠壁渗透进入血液循环。LPS 是引发促炎因子表达的重要物质，肠道屏障功能的增强可直接降低肠道 LPS 含量。Gao 等[69]的研究证实，有氧运动可作用于肠道菌群及其代谢物，从而下调肝脏 LPS 结合蛋白、炎症因子和肝脏 LPS/TLR4/NF-κB 信号通路的表达，进而改善不良炎症反应。

3.3 运动剂量与 T2DM 患者肠道菌群的关系

随着运动处方的科学化发展，运动干预方式也随之呈现出多样化趋势。运动的剂量-效益关系得到广泛关注，尤其是在慢性病运动防治领域。运动剂量包含运动强度、持续时间、方式、频率等剂量要素，合理调控运动剂量要素是实现科学制定运动方案以提高运动效益的重要手段[70]。吴志建等[71]利用 Meta 分析表明，不同运动剂量对 T2DM 患者不同健康结局指标

存在效益差异，同样，不同运动剂量对 T2DM 患者的影响差异也在其肠道菌群中体现。动物实验显示，4 周高强度游泳运动降低了小鼠肠道菌群多样性，并造成肠道菌群紊乱[72]。然而，Denou 等[73]对高脂饮食小鼠施加高强度间歇运动，其结果表明运动提升了菌群多样性，并发现拟杆菌属在运动组小鼠肠道中富集。由此可见，不同运动强度对肠道菌群产生的影响存在差异，甚至产生完全相反的影响。Hill 等[74]研究显示，剧烈的过量运动会引起胃肠功能紊乱，胃肠长时间缺血、缺氧以及机械振荡被认为可直接破坏肠道菌群结构和稳态。Karl 等[75]的研究以 5:1 的工作休息比对 73 名士兵进行北极越野行军训练(极高强度训练)，发现士兵肠道中拟杆菌属丰度下降，血清促炎细胞因子浓度上升，由此推测，高强度运动并不会破坏肠道菌群稳态，而是超出个体所能承受的运动强度会对肠道菌群产生负面影响。除此之外，运动方式的差异也将对肠道菌群产生不同的影响，Torquati 等[76]对比了中等强度持续训练和高强度间歇训练对 T2DM 患者肠道菌群的影响，结果显示，2 种运动方式均可提升患者肠道中丁酸产生菌丰度，并在中等强度持续训练组发现了更多种类有益菌的丰度提升，这一结果在另一项系统综述中也得到证实[57]，提示肠道菌群对持续性运动具有更好的响应。另外，不同运动方式还将导致肠道菌群代谢特征差异，Zhang 等[77]将 20 名 T2DM 患者随机分为太极拳组和快步走组，代谢组学结果显示，太极拳干预与患者氨基酸代谢密切相关，而快步走与调节激素合成相关。然而，尽管当前研究证据证实了不同运动方式对肠道菌群的影响差异，但仍无法排除运动强度要素在实验中产生的偏倚，未来应基于更完善的实验设计对其进行验证。综上所述，当前研究已初步证实运动剂量对肠道菌群的影响差异，但运动剂量涉及众多要素，当前研究证据多数基于不完善的实验设计所得出，并缺乏深入探索，有待进一步补充证据。

3.4 运动调控 T2DM 患者肠道菌群可能机制

目前，运动影响肠道菌群的机制尚未有定论，研究显示，T2DM 代谢紊乱可导致胃肠蠕动减慢，进而延长肠道转运时间(intestinal transit time, ITT)[78]，ITT 被认为是影响肠道菌群定殖的可能因素[79]。研究显示，当 ITT 缩短，有利于复制时间较短的菌群在肠道中定殖，如瘤胃球菌属(*Ruminococcus*)和拟杆菌属等 SCFAs 产生菌，而不利于复制时间较长的菌群(多为有害菌)定殖[80-81]。然而，当前尚未有研究证实运动能通过改变 T2DM 患者 ITT 而影响肠道菌群定殖，这一假设仍有待进一步证实。另外，肠道菌群组成的变化可能与机体内环境相关。研究显示，运动可增加肠道中的含氧量，这可能会抑制某些厌氧菌的生长[82]。此外，运动可改变人体肠道 pH 值，研究显示，肠道 pH 值降低有利于乳酸杆菌等有益菌定殖[83]。这些证据显示，运动可能通过调节人体肠道环境而调控肠道菌群组成，这有利于益生菌在肠道中定殖而产生长期效益。上述可知，运动对肠道菌群的影响可能源于机体对运动的应激反应和机体内环境的改变，但当前尚缺乏充足的证据，未来有待进一步证实。

3.5 肠道菌群与 T2DM 运动响应

个体在进行运动干预后所出现的机体运动能力、生理学、形态学等变化被称为运动响应，运动干预后相关指标出现显著改善的个体，称为运动响应者，反之则为运动不响应者。大量证据表明，肠道菌群与 T2DM 运动响应密切相关[84]。Cheng 等[85]的研究显示，肠道菌群特征可以预测患者对于运动干预的响应程度；Liu

等[86]研究发现，相比于运动响应者，运动不响应者肠道中溶木聚糖拟杆菌(*Bacteroides xylanisolvens*)和沙氏别样杆菌(*Alistipes shahii*)成倍增加；运动响应者肠道中口腔链球菌(*Streptococcus oralis*)增加，并且其肠道菌群结构表现出更强的SCFAs合成和支链氨基酸分解的能力[87]。田浩冬等[58]发现，青春双歧杆菌(*Bifidobacterium adolescentis*)、克里斯滕森氏菌属(*Christensenella*)、毛螺菌属(*Lachnospira*)等益生菌在运动响应者的肠道中显著富集，并具有稳固的共存关系，而运动不响应者的肠道菌群在运动后未发生显著变化，提示肠道菌群共存关系被视为运动响应的重要条件。由上可知，T2DM 的运动不响应现象与肠道菌群密切相关，尽管当前已经发现部分菌群在运动响应中的可能作用，但T2DM运动响应与肠道菌群的关系研究仍处于空白阶段，有待进一步补充证据。

4 运动调控肠道菌群改善T2DM的肠道-器官轴通路

肠道菌群与人体众多脏器紧密联系，可通过多种肠道-器官轴通路相互作用对人体健康状态产生影响，如肠-肝轴等，以肠道-器官轴通路视角探讨T2DM运动防治有助于更好地理解肠道菌群与各脏器之间的联系以及运动效益的机制。本研究总结了肠道菌群介导运动治疗T2DM的几种可能的生物轴通路。

4.1 肠-肌轴(gut-muscle axis)

肠-肌轴是指肠道菌群对人体肌肉组织的关联，并通过肠道和肌肉组织之间的相互作用对人体健康状态进行调节[87-88]。肠道菌群可作用于肌肉组织促进肌因子释放，肌肉细胞分泌的IL-6是重要的肌因子。运动可诱导血清IL-6急性升高，在免疫反应中发挥促炎、抗炎和修复等作用[89-90]。研究显示，普雷沃氏菌和拟杆菌属与IL-6含量密切相关[91]，Rebecca等[92]的研究将LPS注射的受试者分为运动组、IL-6注射组和对照组，其结果表明，相比于对照组，运动组和IL-6注射组接种3 h后血清IL-6均显著升高，且TNF-α显著降低，运动介导的IL-6急性升高可抑制因LPS介导的TNF-α释放。此外，鸢尾素(irisin)也是重要的肌因子，可改善患者血脂代谢[93]，尽管当前尚未明晰它与肠道菌群相互作用的机制，但无法排除其与肠道菌群之间的密切联系。菌群代谢物也可作用于肌肉组织产生效益。Yang等[59]通过运动干预提升了T2DM小鼠肠道中拟杆菌丰度和SCFA含量，并改善了胰岛素抵抗，发现乙酸可与肌细胞上的G蛋白偶联受体43 (G-protein coupled receptor 43, GPR43)结合提高肌肉代谢和胰岛素敏感性[92]。随后，该研究又通过GPR 43拮抗剂抵消了运动对T2DM小鼠骨骼肌胰岛素抵抗改善，GPR43拮抗剂可抑制肌细胞p-IRS^{Tyr612}和p-AKT^{Ser473}活性，通过阻隔SCFAs与GPR43结合从而抵消运动效益[94]。此外，SCFAs还可通过激活结肠L细胞分泌GLP-1[95]，或通过抑制蛋白酪氨酸磷酸酶的活性增加肌肉胰岛素受体磷酸化而提高胰岛素敏感性[96-97]。另外，运动对肠道菌群调节还可反作用于机体运动能力。Scheiman等[98]将马拉松运动员粪便中分离出的非典型韦荣氏球菌(*Veillonella atypica*)移植到小鼠体内后显著提升了小鼠的运动表现，该菌株可将运动产生的乳酸转化为SCFAs底物和SCFAs，从而提高身体机能。

4.2 肠-脑轴(gut-brain axis)

肠-脑轴是指肠道与大脑以及神经系统之间的密切关系，肠道与大脑可通过神经、免疫

或内分泌相连接，从而调节机体功能[11]。肠-脑轴与 T2DM 胰岛素抵抗密切相关，动物实验表明，T2DM 的持续低度炎症会干扰肠道葡萄糖传感器，导致下丘脑对血糖的调控失灵[99]。研究显示，由肠道支配的迷走神经(vagus nerve, VNS)的传入神经在 T2DM 患者能量摄入和糖代谢中具有重要的调控作用[100]；Mazda 等[101]发现，5-羟色胺(5-hydroxytryptamine, 5-HT)可激活 VNS 传入神经末梢上的 5-HT3 受体，从而诱导特定脑核中的 c-Fos 表达，从而控制食欲。该过程可能通过肠神经系统(enteric nervous system, ENS)中的 VNS 传入神经，将局部肠道信号传递到中枢神经系统而实现。ENS 是人体重要的自主神经元集合，可调控胃肠道功能。研究显示，5-HT 对 ENS 具有显著的保护作用[102]。5-HT 是一种单胺类神经递质，运动可通过改变肠道菌群组成而促进机体色氨酸代谢，提升 5-HT 含量[103-104]。另外，SCFAs 在肠-脑轴中同样具有关键的信号传导作用，Chambers 等[105]通过对肥胖人群结肠输注丙酸盐，有效调节了患者食欲和体重。另有研究表明，运动还可抑制酰化生长素释放肽的表达，并增加 GLP-1 和酪酪肽(peptide YY)分泌，从而增加饱腹感[106-107]。GLP-1 既是激素，也是一种神经递质，肠道释放的 GLP-1 可与 VNS 传入神经末梢的 GLP-1 受体结合，将肠道信息传递到中枢神经系统而实现对机体调控[108]。综上所述，现有研究结论支持运动调节肠道菌群及其代谢物，进而通过肠-脑轴对机体产生调节作用，但目前缺乏运动调控肠道菌群作用于肠-脑轴调控的直接证据。此外，神经递质、肠道肽和菌群代谢物等均在肠-脑轴中具有重要作用，如 γ-氨基丁酸、多巴胺和 BAs 等[109]，然而，当前研究尚未完全明确这些物质在肠-脑轴中的作用和机制，均值得学者关注。

4.3 肠-肝轴(gut-liver axis)

肠-肝轴是指肠道与肝脏的密切关联，肠道和肝脏通过门静脉、胆道和体循环相互联系。肝脏是人体重要的脂质代谢器官，可通过多种酶化途径合成、分解及转运脂类物质，与 T2DM 密切相关[110]。T2DM 导致的肠道屏障受损，LPS 可通过门静脉进入肝脏，导致肝脏炎症而引发代谢紊乱[111]。如前所述，运动可调控肠道菌群从而改善肠道屏障功能，这可有效改善肝脏炎症。免疫球蛋白 A (immunoglobulin A, IgA)是黏膜免疫最重要的抗体，被视为抵御肠道病原体的第一道防线[112]，是肠-肝轴的重要调节因子。IgA 可调节肠道菌群和改善肠黏液功能来稳固肠道微生态系统[113]，研究表明将 γ-变形菌移植于 IgA 缺陷小鼠可导致肠道炎症和代谢紊乱[114]。动物实验显示，无菌小鼠中几乎不存在 IgA[115]，提示肝脏和肠道中 IgA 的合成依赖于肠道菌群。另外，肠道菌群还可调节肝脏 BAs 代谢。Carbajo-Pescador 等[116]的研究显示，有氧运动逆转了高脂饮食小鼠的肠道菌群紊乱，并增强了小鼠肠道屏障功能，从而恢复 BAs 稳态。运动可以调节 F/B 值并增加有益菌丰度，提升胆盐水解酶活性，促使牛磺酸和甘氨酸水解为初级 BAs，肠道菌群密切参与初级 BAs 向次级 BAs 的转化过程[117-118]。研究证实，BAs 还可通过激活 TGR5 促进肠道 L 细胞分泌 GLP-1[119]，服用高剂量 TGR5 激动剂可显著降低 T2DM 患者血糖水平[120]。FXR 是 BAs 的天然配体，Zhang 等[121]的研究显示，激活 FXR 表达可以增加肝糖原合成，显著改善糖尿病小鼠的高血糖和高脂血症。然而，BAs 和 FXR 的信号转导在 T2DM 中的作用非常复杂，当前研究还未能完全明确其机制，有待进一步研究。另外，SCFAs 也在肠-肝轴中发挥重要作用。丁酸可通过静脉进入

肝脏，调节糖脂代谢并提升胰岛素敏感性[122]。同样，肝脏还可合成胰岛素样生长因子-1，控制血糖并促进脂肪分解[83]。

5 总结与展望

运动、肠道菌群和 T2DM 三者密切相关，T2DM 可导致人体肠道菌群紊乱，当前研究认为，T2DM 将导致人体独特的肠道菌群特征，但当前尚未构建出较为成熟的 T2DM 肠道菌群模型。未来应进一步完善 T2DM 肠道菌群及其代谢特征模型，有助于为 T2DM 肠道菌群治疗靶点提供参考。

运动是改善 T2DM 肠道菌群紊乱的有效手段，运动可调控肠道菌群，从而有效防治 T2DM。不同运动方式会对肠道菌群产生不同的影响，但运动影响肠道菌群的机制尚未明晰，对其机制的研究有助于解释不同运动方式对肠道菌群的影响差异，进而依据个体差异制定运动方案。肠道菌群对 T2DM 的治疗效果涉及多条复杂的肠道-器官轴通路，且各器官轴均相互关联，然而，当前缺乏运动干预实验的直接证据，有待进一步验证。

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