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Review 综述

肥胖特征肠菌的跨疾病调控机制及诊疗新策略

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摘　要：肥胖及其相关代谢性疾病的全球发病率持续上升，已成为重大公共卫生问题。肠道菌群在肥胖的发生发展过程中扮演着关键角色，其组成和功能紊乱与肥胖及其相关并发症直接相关。本文综述了肥胖的遗传、神经内分泌、慢性炎症以及肠道菌群代谢轴等病理机制，重点梳理了脱硫弧菌、巨单胞菌等条件致病菌和乳酸杆菌、嗜黏蛋白阿克曼氏菌等益生菌对肥胖的正、负调控机制，总结了肥胖特征性肠菌在糖尿病、代谢功能障碍相关脂肪性肝病、心血管疾病和高血压发生中的驱动机制，创新性地提出了肥胖疾病的肠菌演变假说，并展望了未来肥胖特征性肠菌的研究趋势以及疾病早期诊断技术的开发前景。本文将为肥胖及相关代谢性疾病的早期诊断和精准干预提供新策略，有助于推动个性化诊疗的发展。

关键词：肥胖；肠道菌群；代谢性疾病；早期诊断

Obesity-associated gut microbiota: cross-disease regulatory mechanisms and novel diagnostic/therapeutic strategies

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Abstract: The global prevalence of obesity and its associated metabolic disorders keeps rising,

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presenting a major challenge to public health. The gut microbiota plays a pivotal role in obesity onset and development, and its dysbiosis and dysfunction are closely associated with obesity and its complications. This review synthesizes the pathological mechanisms underlying the heredity, neuroendocrine, chronic inflammation, and the gut microbiota-metabolism axis of obesity. Then, we explore the positive and negative regulatory effects of opportunistic pathogens (e. g., *Desulfovibrio* spp., *Megamonas* spp.) and putative beneficial bacteria (e. g., *Lactobacillus* spp., *Akkermansia muciniphila*) on obesity. Furthermore, we summarize the mechanisms by which these signature gut microbes drive the development of obesity-related conditions, including type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease, cardiovascular diseases, and hypertension. We firstly propose a gut microbiota trajectory hypothesis to delineate the interrelationships between these representative gut microbial signatures and the onset and progression of obesity and its complications. Finally, the review discusses future research directions and the potential for developing early diagnostic technologies based on these microbial signatures. Collectively, this work aims to provide novel strategies for the early diagnosis and precision intervention of obesity and related metabolic disorders, thereby advancing the development of personalized therapeutics.

Keywords: obesity; gut microbiota; metabolic diseases; early diagnosis

近年来，肥胖(obesity)及其相关代谢性疾病的全球发病率持续攀升[1]，已成为不容忽视的全球性公共卫生挑战。Turnbaugh 等[2]的研究揭示了肠道菌群在肥胖及其相关代谢性疾病发生、发展中的关键作用。本课题组前期已深入探讨了肠道菌群与宿主间的互作机制，并阐释了多种药物经肠道菌群代谢后防治疾病的分子调控机制[3-5]。然而，肥胖特征性肠道菌群与肥胖诱发其他疾病之间的相关性尚未得到系统总结，且基于靶向特征肠菌开发疾病早期诊断技术的理论依据尚不成熟。本文分析了肠道菌群在肥胖及相关代谢性疾病中的作用机制，探讨肥胖特征肠菌与重大代谢性疾病进展的相互关系，并提出通过监测肥胖特征肠菌来预测重大疾病风险的新思路，以期为肥胖及相关代谢性疾病的早期筛查和治疗提供新的策略。

1 肥胖及其相关重大疾病现状

1.1 肥胖的发病趋势

肥胖表现为脂肪组织的过度积累，世界卫生组织采用体重指数(body mass index, BMI)进行定义，其中 BMI≥25 kg/m^2 为超重，BMI≥30 kg/m^2 为肥胖[6]。据 2025 年 Lancet 发布的流行病学研究，全球约 50% 的成年人超重，17%–22% 处于肥胖状态，且女性肥胖率通常高于男性。美国目前肥胖率最高，近 42% 的成人肥胖，其中严重肥胖(BMI≥40)人群占比达 9%[7]。我国肥胖发病趋势也不容乐观，成人超重率达 51%，肥胖人群年均增长率 4%，远超全球平均水平(1.8%)，预计到 2030 年中国成人超重和肥胖人数将超过 5 亿[8]。为此，2024 年 6 月，国家卫生健康委等 16 个部门联合开展了为期 3 年的“体重管理年”活动，标志着我国防治肥胖工作已上升至国家战略层面。

1.2 肥胖病理机制研究

肥胖是一种因能量摄入超过消耗导致的慢性代谢性疾病，其发生是多因素共同作用的结果，与遗传背景、生活习惯、自然环境等密切相关。基于进化论，研究者提出了节俭基因假说、遗传漂变假说、产热能力假说和元炎症假说等，从不同角度解释了肥胖的进化起源[9]。具

体而言，肥胖的发病机制主要包括遗传表型异质性机制[10]、神经内分泌紊乱机制[11-12]、慢性炎症刺激机制[13]和肠道菌群代谢轴机制[14]等。

1.2.1 肥胖的遗传背景和代谢表型异质性

肥胖具有高度异质性的遗传基础，包括单基因和多基因突变。目前已发现超过 20 个可导致严重早发性肥胖的单基因突变，以及约 1 000 个与常见多基因肥胖相关的单核苷酸多态性[15]。代谢健康型肥胖(metabolically healthy obesity, MHO)与代谢不健康型肥胖(metabolically unhealthy obesity, MUO)患者因脂肪组织分布和脂质代谢的差异，其心血管代谢表型也存在显著不同。MHO 个体皮下脂肪组织扩展性更好，脂肪组织炎症更低，脂肪生成基因表达更高[16]。此外，肥胖表型还呈现性别差异，女性倾向于女性型肥胖(gynoid-type obesity)，而男性更多表现为男性型肥胖(android-type obesity)[17]。在同一 BMI 水平下，女性体脂率一般高于男性[18]，这与性激素调控有关，雌激素促进皮下脂肪储存，而睾酮促进内脏脂肪积累[17]。雌激素通过增加抗脂解的 α2A-肾上腺素受体(α2A-adrenergic receptors)的数量降低脂解反应、促进皮下脂肪的积累[19]。睾酮则通过诱导肝激酶 B1/AMP 活化蛋白激酶(liver kinase B1/AMP-activated protein kinase, LKB1/AMPK)信号通路促进葡萄糖的摄取并抑制肝脏糖异生[20]。Moldovan 等[21]的转录组学研究表明，女性肥胖与 Wnt 信号传递(Wnt signaling)通路异常显著相关，而男性肥胖更多与线粒体损伤和游离脂肪酸代谢紊乱相关。在疾病发展方面，女性肥胖更易伴随心血管-肾脏-代谢综合征风险，而男性肥胖与 2 型糖尿病(diabetes mellitus type 2, T2DM)关联更强[22]。

1.2.2 神经内分泌异常引发肥胖

神经内分泌异常可通过影响神经元功能和代谢相关激素平衡等途径引发肥胖；除胰岛素信号通路外，瘦素(leptin)、饥饿素(ghrelin)和抵抗素(resistin)等激素分泌紊乱也直接影响食欲和糖稳态[23]。遗传性和获得性下丘脑损伤、能量稳态的神经调控失衡易导致“下丘脑性肥胖”[24]，表现为下丘脑弓状核(arcuate nucleus of hypothalamus)的摄食神经元刺鼠相关肽(agouti-related peptide, AgRP)和抑食神经元阿黑皮素原(proopiomelanocortin, POMC)功能失衡，进而引发能量代谢失调[25]。此外，神经免疫内分泌网络也通过调控炎症反应参与肥胖进展[26]。

1.2.3 慢性低丰度炎症导致代谢紊乱

Ajoolabady 等[27]研究发现，内质网应激诱导的“终端未折叠蛋白反应”可激活炎症通路，与炎症的交互作用形成了肥胖发生的正反馈循环。脂肪细胞肥大和增生导致脂肪组织缺氧和应激，游离脂肪酸刺激免疫细胞上的 Toll 样受体 4 (Toll-like receptor 4, TLR4)激活炎症信号通路[28]，致使 M2 型巨噬细胞向 M1 型转变，TLR4 敲除小鼠可抵抗高脂饮食诱导的肥胖[29]。此外，肿瘤坏死因子 α (tumor necrosis factor α, TNF-α)上调后阻断脂肪细胞的胰岛素信号传导，将加剧代谢紊乱[30-31]。

1.2.4 肠道微生态影响肥胖进程

Gasmi 等[32]的研究证实，高脂饮食可导致肠道微生物群失调，显著增加肠道通透性，促使脂多糖(lipopolysaccharide, LPS)进入循环系统引发代谢性内毒素血症，进而加剧全身炎症反应和胰岛素抵抗[33]。肠道菌群代谢产物通过 G 蛋白偶联受体 43 (G protein-coupled receptor 43, GPR43)、Takeda G 蛋白偶联受体 5 (Takeda G protein-coupled receptor 5, TGR5)受体激动剂、过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor, PPARγ)等信号通路调节糖脂代谢，是肠道菌群串联宿主代谢轴的主要途径[34]。

1.3 肥胖诱发的重大疾病

1.3.1 肥胖诱发重大疾病的临床数据

流行病学证据表明，肥胖是多种代谢性疾病的关键风险因素。Yao 等[35]纳入 27 万成年人

的大规模前瞻性队列研究证实，BMI 升高与代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)、2 型糖尿病、高脂血症/脂代谢紊乱、痛风等疾病的发生风险呈显著正相关。

肥胖可解释高达 36% 的 T2DM 病例[35]。最新全球数据显示，高 BMI 值贡献了超过 55% 的 T2DM 已知死亡风险[36]。同时，超过 80% 的 T2DM 患者伴有肥胖，而代谢健康的肥胖患者仅占肥胖者的 10%−30%，Magkos 等[37]临床随机对照试验表明，体重减轻 5% 可大幅改善肝脏和脂肪组织胰岛素抵抗。

肥胖人群中的 MASLD 患病率高达 75%，肥胖是其最重要的危险因素之一[38]。中国北方成年人的横断面研究数据表明，肥胖也是血脂异常的重要驱动因素之一，肥胖人群高甘油三酯血症的患病率是体重正常人群的 1.8 倍[39]。

肥胖也是心力衰竭(heart failure, HF)的重要独立危险因素[40-42]。内脏脂肪堆积促进心力衰竭的发生和发展[43-44]。BMI 与 HF 风险呈剂量依赖性，BMI 每增加一个单位，男性和女性的 HF 风险分别增加 5% 和 7%[45]。

肥胖与高血压的相互关联已被广泛证实[46-47]。Hall 等[48]在权威研究中指出，以内脏脂肪堆积为特征的超重是原发性高血压的主要危险因素，肥胖对其风险贡献率高达 65%−75%。

虽然肥胖与多种疾病发生发展存在高度关联性，但目前肥胖诱发其他疾病的风险预测模型尚不成熟，缺乏前瞻性评估的潜在靶标。

1.3.2 肥胖诱发重大疾病的机制研究

胰岛素抵抗是导致代谢紊乱的核心驱动力，直接扰乱葡萄糖和脂质代谢，导致血脂异常与 MASLD，表现为脂解与脂氧化失衡[49]。其次，脂肪组织巨噬细胞暴露于过量脂质，激活核因子 κB (nuclear factor kappa B, NF-κB)等炎症通路，加剧胰岛素抵抗与脂代谢紊乱[50]。此外，脂肪细胞肥大导致脂联素等脂肪因子分泌失调，破坏脂质稳态[51]。脂肪过度累积引发的脂肪转运感知紊乱和糖脂代谢调控失衡，如分化抗原 36 (cluster of differentiation 36, CD36)、AMPK、PPARγ 等表达异常，导致循环系统中游离脂肪酸增加和脂肪异位堆积[52-53]。肥大的脂肪细胞释放过量游离脂肪酸，抑制胰岛素信号通路，脂肪组织分泌促炎因子加重胰岛素抵抗[54]。

肥胖患者脂代谢紊乱后，高密度脂蛋白胆固醇水平降低，小而密低密度脂蛋白生成增加，导致高甘油三酯血症，从而显著增加动脉粥样硬化的风险[55]。

内脏脂肪组织(visceral adipose tissue, VAT)和心外膜脂肪组织(epicardial adipose tissue, EAT)通过旁分泌作用释放炎症因子、脂质介质和细胞外囊泡，直接导致心肌炎症和氧化应激[41]。此外，肥胖引发高血压的病理机制关键在于肾素-血管紧张素-醛固酮系统过度激活[56]，肾脏的钠重吸收和钾排泄增加，终致血压升高[48,56-57]。

2 肠道菌群与肥胖发生相互关系

2.1 肠道菌群简介

肠道菌群是宿主胃肠道内由细菌、真菌等构成的极其复杂的数百万亿微生物群落，其组成多样性由饮食、宿主遗传和环境因素等多种因素共同塑造[58]。肠道菌群(本文特指肠道细菌)并非静态存在，其组成处于波动状态，人类健康肠道菌群中芽孢杆菌门(*Bacillota*，曾用名 *Firmicutes*)、拟杆菌门(*Bacteroidota*，曾用名 *Bacteroidetes*)、放线菌门(*Actinomycetota*，曾用名 *Actinobacteria*)和假单胞菌门(*Pseudomonadota*，曾用名 *Proteobacteria*)占 98% 以上。不同物种之间的肠菌丰度存在一定差异。在健康成年人中，*Bacillota* 通常占 30%−70%，具有分解复杂碳水化合物能力[59]；*Bacteroidota* 占 20%−60%，参与宿主碳水化合物的发酵、含氮物质的利用及胆汁酸和其他类固醇的生物转化，也是多糖水解酶的重要来源[59]。肠道菌群

通过代谢调节、免疫调控、神经干预、生态位竞争等机制深度参与机体生理病理过程，对人体健康产生巨大影响[59-62]。

2.2 肠道菌群紊乱与肥胖

肠道菌群在肥胖发生发展中起关键作用，其组成和多样性在肥胖个体与健康人群间存在显著差异。菌群通过调节脂质/碳水化合物代谢、激素水平和营养物质合成影响能量平衡[63-65]。2006 年，Turnbaugh 等[2]首次发现肥胖(ob/ob)小鼠肠道中 *Bacillota* 菌门比例升高 50%，而 *Bacteroidota* 菌门降低 30%；将肥胖小鼠菌群移植给无菌小鼠后，受体小鼠脂肪组织在 2 周内增加 60%，且脂肪酸合成基因表达上调，证明了肥胖表型可经菌群传递，建立了菌群与肥胖的因果关联。同年，Ley 等[66]进一步发现肥胖人群存在菌门水平失衡(*Bacteroidota*/*Bacillota* 比例下降)，而 *Bacillota* 富集的碳水化合物活性酶可提高膳食能量提取效率，提出了“菌群代谢基因补充假说”，目前已被广泛验证。

2012 年 Cho 等[67]在动物模型中证实，幼年小鼠低剂量的抗生素暴露导致 *Bacteroidota*/*Bacillota* 比例下降，*Pseudomonadota* 丰度显著升高，直接驱动脂肪积累和代谢紊乱。肥胖个体中肠道菌群改变呈现性别差异，肥胖男性中梭杆菌门(*Fusobacteriota*)富集，而肥胖女性的 *Actinomycetota* 菌门丰度更高[68]。2013 年，Cotillard 等[69]在临床研究发现，肠道菌群基因丰富度低(<48 万微生物基因)的肥胖患者体重反弹风险增高 51%，而膳食纤维干预可提升肠道菌群多样性，并降低 0.3 BMI/月，凸显肠道菌群多样性在肥胖个性化治疗中的价值。近年来，Wang 等[70]利用孟德尔随机化进一步明确了菌群与肥胖的量化关联，即双歧杆菌科(*Bifidobacteriaceae*)、双歧杆菌目(*Bifidobacteriales*)、放线菌纲(*Actinomycetes*)和放线菌门在验证数据集中显示与体脂百分比显著相关。*Bacillota* 丰度与 BMI 呈正相关[71]。2023 年，Li 等[72]首次锁定阿克曼氏菌属(*Akkermansia*)、肠杆菌属(*Enterobacter*)和丁酸单胞菌属(*Butyricimonas*)为儿童肥胖的关键菌属，其中 *Akkermansia* 可抵抗儿童肥胖风险。

更多证据表明，提升肠道菌群多样性、精准改造肠道菌群微生态均可有效减少肥胖的发生[73-75]。因此肠道菌群的精准解析为肥胖及相关疾病诊疗提供决策参考。

2.3 肠道菌群参与能量代谢的机制

肠道菌群通过短链脂肪酸(short-chain fatty acids, SCFAs)信号轴、胆汁酸代谢轴、表观遗传调控、免疫-代谢交叉调控等机制参与能量代谢过程，具体潜在机制如图 1 所示。

2.3.1 多糖-菌群-短链脂肪酸介导肠分泌

肠道菌群可将小肠难以吸收的多糖发酵转化为 SCFAs，如乙酸、丙酸和丁酸。SCFAs 不仅可为肠道细胞提供 5%−10% 的能量供应，还能激活G 蛋白偶联受体 41 (G protein-coupled receptor 41, GPR41)和 GPR43 受体，进而诱导胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1)和酪酪肽(peptide tyrosine-tyrosine, PYY)的分泌，并抑制下丘脑食欲中枢神经肽 Y (neuropeptide Y, NPY)/刺鼠相关肽(agouti-related peptide, AgRP)神经元的活性[76]。Kimura 等[77]的研究证实，GPR43 敲除小鼠即使饲喂高纤维饮食仍会出现脂肪过度积累的情况，这表明 GPR43 介导的信号通路对维持能量平衡至关重要。丁酸可通过上调肉碱棕榈酰基转移酶 1A (carnitine palmitoyltransferase 1A, CPT1A)的表达水平促进脂肪酸的氧化代谢[78]。

2.3.2 菌群-胆汁酸代谢轴的双向调控

肝脏合成的胆汁酸经胆囊释放至小肠，胆汁酸可抑制肠道菌群过度增殖，而肠道菌群则通过表达 7α-脱羟酶将初级胆汁酸转化为次级胆汁酸，从而改变胆汁酸组成，最终影响法尼酯 X 受体(farnesoid X receptor, FXR)/TGR5 信号通路。代表性的次级胆汁酸，如脱氧胆酸(deoxycholic acid, DCA)、石胆酸(lithocholic acid, LCA)，能

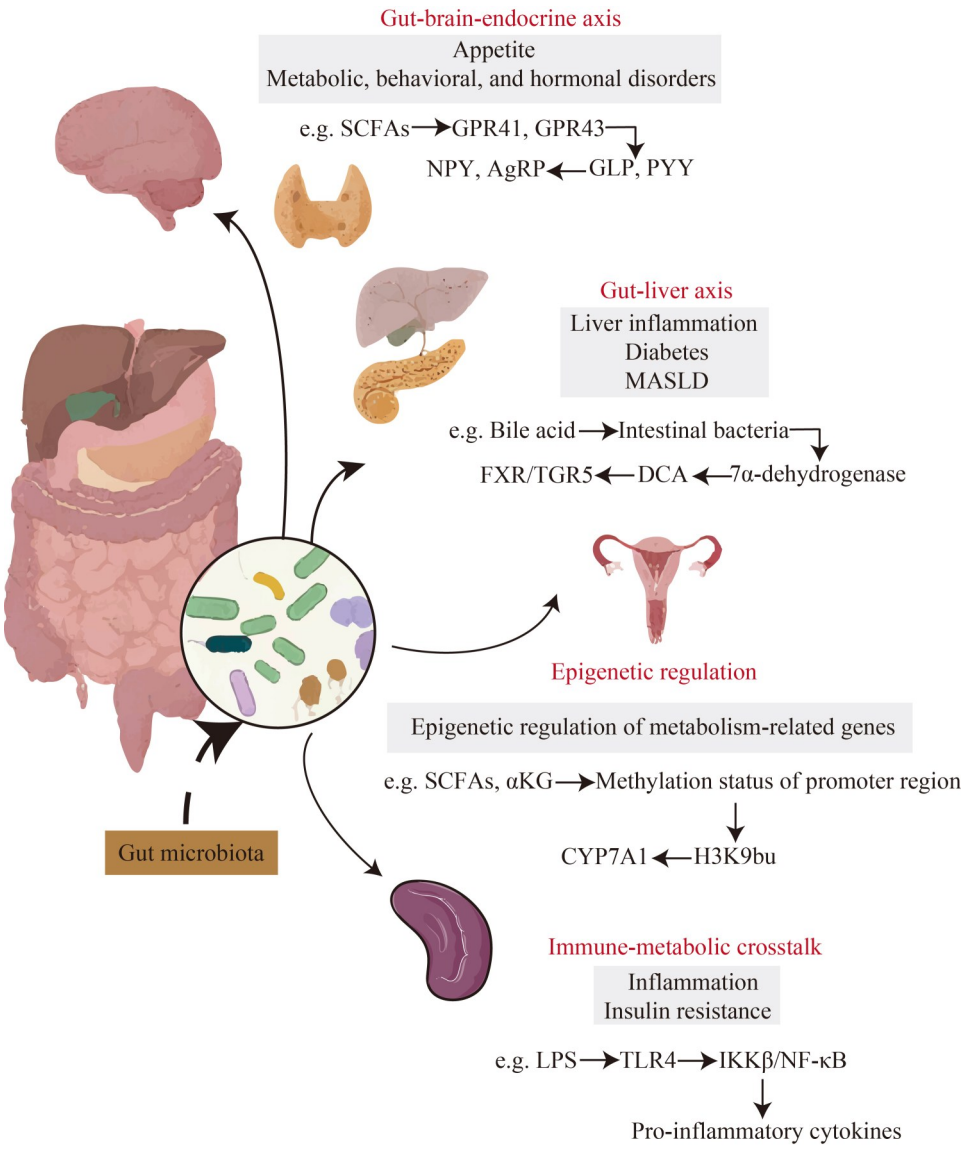

图1　肠道菌群的跨器官调控机制示意图

Figure 1　Schematic diagram of the cross-organ regulatory mechanism of gut microbiota.

激活肠道 TGR5 受体并增强 GLP-1 分泌，促进白色脂肪褐变，增强褐色脂肪产热[79]。此外，DCA 还可激活 FXR，抑制固醇调节元件结合蛋白-1c (sterol regulatory element binding protein-1c, SREBP-1c)的表达，减少肝脏脂质新生。Mudaliar 等[80]的临床研究证实，奥贝胆酸作为 FXR 激动剂可使 MASLD 患者甘油三酯水平降低，改善胰岛素敏感性，减少脂肪堆积。

2.3.3　表观遗传调控代谢相关基因

肠道菌群通过代谢产物介导的多维度表观遗传调控，影响宿主糖脂代谢基因[81]。在短链脂肪酸中，丁酸盐可通过抑制组蛋白脱乙酰酶(histone deacetylase, HDAC)增加组蛋白乙酰化水平，激活 PPARγ 等基因的表达以调节脂质代谢与能量平衡[82]；SCFAs、α-酮戊二酸(α-ketoglutaric acid, αKG)等可通过调节 DNA 甲基化和去甲基化直接调控基因启动子区的甲基化

状态，改变细胞色素 P450 (cytochrome P450, CYP450)基因及糖代谢基因的转录[83]。除经典的乙酰化修饰外，SCFAs 可诱导组蛋白丁酰化(H3K9bu)、丙酰化(H3K23pr)等新型修饰，通过改变染色质状态调控脂质吸收相关基因的表达[84]。6-甲基腺嘌呤(N6-methyladenosine, m6A) RNA 修饰受肠道菌群调节，其异常会通过影响细胞色素 P450 等代谢酶的翻译效率干扰葡萄糖代谢稳态和胰岛素信号通路[85-86]。在跨器官网络中，肠-脑轴内的色氨酸衍生物经 DNA 甲基化调控下丘脑 POMC 基因，进而影响食欲[87]。

2.3.4 免疫-代谢交叉调控

肠道菌群可调控 TLR4/MyD88 信号通路，从而影响代谢炎症。高脂饮食会导致革兰氏阴性菌增殖，大量 LPS 会透过破损的肠黏膜进入血液循环，激活 NF-κB 信号通路，促进多种促炎因子的释放，引发肝脏慢性炎症反应，诱发胰岛素抵抗[88]。菌群还可调节 Th17/Treg 平衡，进而影响代谢，其中分段丝状菌可诱导 Th17 细胞分化，加剧炎症及代谢紊乱[89]。

3 肥胖特征肠菌研究进展

越来越多的证据表明，人体中存在与肥胖紧密关联的特征肠道细菌(简称肥胖特征肠菌)，脆弱拟杆菌(*Bacteroides fragilis*)、丹毒丝菌科(*Erysipelotrichaceae*)、脱硫弧菌属(*Desulfovibrio*)、巨单胞菌属(*Megamonas*)等条件致病肠道细菌可通过代谢调控、炎症激活及肠-脑轴干扰等途径促进脂肪积累和肥胖生成，而乳杆菌属(*Lactobacillus*)、双歧杆菌属(*Bifidobacterium*)、嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)、多形拟杆菌(*Bacteroides thetaiotaomicron*)等肠道细菌则是抑制肥胖的重要力量，其与肥胖的关系如表 1 所示[90-99]

表1 肥胖特征肠菌及相关机制

Table 1 Obesity-associated gut microbiota and related mechanisms

拉丁名称 Bacterium name	氧气依赖度 Oxygen dependence	肥胖相关性 Obesity-dependency	作用机制 Action mechanism
Bacteroides fragilis	Anaerobe	Positive correlation	Expressing bile salt hydrolase to promote lipid absorption[90-91]
Erysipelotrichaceae	Facultative anaerobe	Positive correlation	Disrupting intestinal barrier integrity and triggering systemic inflammation[92]
Desulfovibrio (*Desulfovibrio desulfuricans*)	Anaerobe	Positive correlation	Producing H_2S to interfere the mitochondrial respiratory chain and promote hepatic lipid deposition[93]
Megamonas (*Megamonas rupellensis*)	Anaerobe	Positive correlation	Expressing hydrolase (ioIG) to reduce inositol levels, and further promoting intestinal lipid absorption[94]
Lactobacillus (*Lactobacillus rhamnosus*)	Facultative anaerobe	Negative correlation	Generating short-chain fatty acids to activate intestinal GPR41/43 receptors[95]
Bifidobacterium (*Bifidobacterium longum*)	Anaerobe	Negative correlation	Improving intestinal barrier and inflammation[96]
Akkermansia muciniphila	Anaerobe	Negative correlation	Producing outer membrane protein Amuc-1100 or extracellular vesicles for repairing intestinal barrier and inhibiting inflammation[97-98]
Bacteroides thetaiotaomicron	Obligate anaerobe	Negative correlation	Metabolite regulation, microbial interactions[99]

3.1 潜在致胖肠菌

3.1.1 脆弱拟杆菌

脆弱拟杆菌(*Bacteroides fragilis*)是人类肠道核心共生菌之一，主要大量定殖于结肠，*Bacteroides fragilis* 与肥胖的关系具有菌株特异性和环境依赖性，它既可通过某些代谢途径促进肥胖发展，也可通过调节菌群组成和宿主代谢产生保护作用。一方面，*Bacteroides fragilis* 可通过调节胆汁酸代谢诱发肥胖相关代谢疾病，其表达的胆盐水解酶(bile salt hydrolase, BSH)已被证实是肥胖相关代谢疾病的潜在药物靶点[100]。另一方面，一株 *Bacteroides fragilis* 被证实可通过产生 SCFAs 和调节白介素-10 (interleukin 10, IL-10)等细胞因子改善糖代谢[101]。脆弱拟杆菌对肥胖的摇摆作用可能与肠道营养状态相关，具体机制仍有待进一步挖掘。

3.1.2 丹毒丝菌科

丹毒丝菌科(*Erysipelotrichaceae*)是肠道常见细菌。Wang 等[102]的临床研究证实，肥胖受试者的肠道菌群中 *Erysipelotrichaceae* 的丰度增加与腰围增大等肥胖表型呈正相关。高脂饮食干预可显著增加 *Erysipelotrichaceae* 的相对丰度[93]。从微生物代谢层面研究发现，*Erysipelotrichaceae* 表达丰富的胆汁酸水解酶 BSH，能将结合型胆汁酸转化为游离型胆汁酸，从而增强膳食脂肪的乳化与吸收[103]。此外，*Erysipelotrichaceae* 丰度上调可增加肠道通透性，促进 LPS 入血，激活炎症通路，导致肥胖和胰岛素抵抗[104-105]。因此 *Erysipelotrichaceae* 的 BSH 过量表达或可作为肥胖的干预靶点。

3.1.3 脱硫弧菌

脱硫弧菌属(*Desulfovibrio*)是硫酸盐还原菌的代表菌属，其在肥胖个体肠道中的丰度显著升高，且与体重呈正相关[106-107]。该菌可通过多种途径促进肥胖。首先，*Desulfovibrio* 具有产生硫化氢(hydrogen sulfide, H_2S)的能力，可抑制细胞色素 C 氧化酶活性，降低线粒体能量代谢效率，导致脂质积累，过量的 H_2S 靶向肠道 L 细胞，抑制其线粒体呼吸链复合物 IV 功能并诱发内质网应激，减少 GLP-1 分泌，引发糖代谢紊乱[94]。其次，该菌属增加肠道通透性，加速 LPS 易位，引发慢性炎症并加剧胰岛素抵抗[108]。Qi 等[93]的研究证实，代谢综合征患者肠道 *Desulfovibrio* 的丰度显著升高，且与血清 GLP-1 水平呈负相关。限制含硫氨基酸摄入可降低 *Desulfovibrio* 的丰度，从而逆转肝脏脂肪变性[109]。综上所述，*Desulfovibrio* 的丰度可作为肥胖干预的潜在靶点。

3.1.4 罗谢尔巨单胞菌

罗谢尔巨单胞菌(*Megamonas rupellensis*)属于 *Bacillota* 菌门，在肥胖人群中显著富集，与多基因风险协同促进肥胖发生[110]。Wu 等[94]最新的中国人群队列研究表明，在肥胖受试者的肠道微生物组中发现了以巨单胞菌为主导的肠型样聚类，其丰度显著高于正常体重对照组，该结果在以色列、英国/美国、丹麦和荷兰的 4 个外部宏基因组数据集中得到了验证，表明 *Megamonas* 属与肥胖表型显著关联；研究还发现多基因易感性和 *Megamonas* 属对肥胖的易感性具有累加效应，表明 *Megamonas* 可能与遗传因素共同促进肥胖；*Megamonas rupellensis* 或异源表达肌醇降解基因(*iolG*)的大肠杆菌，均通过降解肌醇解除宿主肠道内源性肌醇对脂质吸收的抑制作用，导致肥胖率大幅增加。*Megamonas* 有望作为肥胖精准干预的靶点，具有巨大的临床应用潜力。

3.2 对肥胖有抑制作用的肠道细菌

3.2.1 传统益生菌

乳杆菌属(*Lactobacillus*)和双歧杆菌属(*Bifidobacterium*)是传统益生菌，可调节肠道菌群、代谢产物、免疫系统和肠道屏障功能，发挥促进能量平衡的作用。肥胖个体中长双歧杆菌(*Bifidobacterium longum*)和两歧双歧杆菌(*Bifidobacterium bifidum*)的丰度显著降低，口服

上述 2 种菌株后，肥胖个体的内脏脂肪组织指数、BMI 及血清甘油三酯水平均明显改善[111]。类似地，*Lactobacillus* 可通过抑制肠道脂质吸收减少脂肪积累[112]，灌胃约翰逊氏乳杆菌(*Lactobacillus johnsonii*)可预防高脂饮食诱导的肥胖和高脂血症[113]。补充 *Bifidobacterium longum* APC1472 可显著降低饮食诱导肥胖小鼠的体重，还可降低超重/肥胖患者的 BMI[114]。此外，*Bifidobacterium* 与 *Lactobacillus* 等有益菌可促进肠道巨噬细胞向抗炎 M2 型极化，减轻肠道炎症反应，调节肠道上皮细胞功能，改善葡萄糖耐受性和脂肪堆积[115]。发酵乳杆菌(*Lactobacillus fermentum*)通过增强脂肪组织线粒体氧化磷酸化能力增加能量消耗，从而改善葡萄糖代谢[116]。补充益生菌防治肥胖具有广阔的应用市场。

3.2.2 嗜黏蛋白阿克曼氏菌

嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)是一种定殖于肠道黏液层的革兰氏阴性菌，于 2004 年首次从人类粪便中分离并命名[117]。早期研究主要关注其与肠道屏障功能的关联。2013 年，研究者首次揭示了该菌在代谢疾病中的作用，补充活体 *Akkermansia muciniphila* 可逆转高脂饮食诱导的小鼠代谢紊乱，改善脂肪堆积和胰岛素抵抗，并增强肠道屏障完整性[118]。后续研究进一步阐明了其改善代谢综合征的机制，发现该菌属可通过调节内源性大麻素系统减轻炎症和促进肠道分泌抗菌肽 Reg3γ[119]。值得注意的是，在动物模型中巴氏灭活的 *Akkermansia muciniphila* 比活菌展现出更显著的代谢改善效果[120]，其作用机制部分归因于外膜蛋白 Amuc-1100，该蛋白可通过调控 Toll 样受体 2 (Toll-like receptor 2, TLR2)信号通路，直接改善脂肪组织炎症和糖代谢[121-122]。此外，*Akkermansia muciniphila* 显著增加棕色脂肪组织中线粒体解偶联蛋白 1 (uncoupling protein 1, UCP1)的表达，并调节肠道激素(如 GLP-1)分泌，增加能量消耗[123-124]。与甜菜碱联用可增强其定殖效率，进一步抑制高脂饮食小鼠的体重增长[125]。*Akkermansia muciniphila* 在肥胖和 T2DM 患者中的丰度显著降低[126]，补充 *Akkermansia muciniphila* (AKK-WST01)可减轻肥胖相关表型并改善糖代谢[75]。*Akkermansia muciniphila* 有望成为功能明确的新一代益生菌，用于缓解肥胖及多种代谢性疾病。

3.2.3 多形拟杆菌

多形拟杆菌(*Bacteroides thetaiotaomicron*)作为一种核心肠道共生菌，其丰度变化与肥胖及相关代谢疾病密切相关。Hu 等[127]的临床研究表明，该菌相对丰度与肥胖及动脉粥样硬化性心血管疾病参数呈显著负相关，且饮食干预后其丰度增加常伴随代谢改善。Wen 等[128]的动物实验进一步证实了其因果作用，在肥胖小鼠模型中增加 *Bacteroides* (含 *Bacteroides thetaiotaomicron*)的丰度可减轻肥胖、胰岛素抵抗及脂质积累。单一定殖 *Bacteroides* 的小鼠也显示肠道 CD36 表达下调与葡萄糖代谢改善[129]。其抗肥胖机制主要涉及代谢物调控、免疫调节、微生物互作等多通路协同。*Bacteroides thetaiotaomicron* 通过发酵复杂多糖(果胶)产生丙酸等 SCFAs[130-131]，通过抑制肠道炎症改善代谢[132]；多形拟杆菌特有的 BT_0416 酶可将胆固醇转化为胆固醇硫酸盐，维持胆固醇稳态(该酶缺失可导致代谢紊乱)[133]；该菌还可提升肠道叶酸水平，改善肝脏脂肪变性[134]。*Bacteroides thetaiotaomicron* 分泌的膜外囊泡通过拮抗病原体侵袭载脂蛋白 L9a/b (apolipoprotein L9a/b, Apo L9a/b)蛋白介导的免疫反应维持肠道稳态[135]。此外，该菌还通过单糖供给影响色氨酸代谢竞争，调控吲哚衍生物水平[136]，其荚膜多糖介导的噬菌体逃避策略可能增强其在肥胖菌群中的定殖优势[137]。综上所述，*Bacteroides thetaiotaomicron* 通过多维度机制缓解肥胖，但特定多糖利用位点功能及膜外囊泡免疫调节等深层机制仍需深入解析[134]。

4 肥胖特征肠菌与相关代谢疾病的关系

4.1 特征肠菌与糖尿病

肥胖特征肠菌与糖尿病的发生密切相关。Wu 等[138]通过对千余例患者的队列研究发现，糖尿病前期患者肠道内产丁酸肠菌丰度降低与胰岛素抵抗呈强相关性，该指标或可用于指示糖尿病的发展进程。青春双歧杆菌(*Bifidobacterium adolescentis*)能发酵膳食纤维生成丁酸，刺激 GLP-1 分泌，有效减少胰岛素抵抗[139]。*Akkermansia muciniphila* 不仅可通过 Amuc-1100 外膜蛋白拮抗 TLR2 信号通路，抑制炎症反应，还可促进肠道黏液生成和抗菌肽 Reg3γ 的分泌抑制其他潜在有害菌增长，降低 LPS 水平，遏制糖尿病的发生[140]。本课题组 Zheng 等[141-142]前期证实，壳寡糖、桑叶提取物 1-脱氧野尻霉素等多种活性组分可通过富集 *Akkermansia mucinphilia* 发挥糖尿病防治疗效。此外，Wang 等[143]研究证实，中药复方首荟通便方能调控 *Akkermansia* 及支链氨基酸代谢通路，提升胰岛素敏感性。Shih 等[144]临床研究表明，难治型 T2DM 人群粪便菌群中 *Akkermansia* 丰度较常规 T2DM 人群更低，且与糖化血红蛋白呈负相关，这表明 *Akkermansia* 的缺乏或可成为糖尿病特征肠菌之一。相反，肥胖型糖尿病患者肠道内 *Desulfovibrio* 水平显著高于单纯肥胖个体[145]，其丰度与胰岛素敏感性呈强烈负相关[146]。采用高膳食纤维干预的糖尿病患者，症状改善的同时也伴随着 *Desulfovibrio* 水平的降低，这进一步提示了该菌与糖尿病发生发展的密切关系[147]。

4.2 特征肠菌与代谢功能障碍相关脂肪性肝病

肝脏作为菌群代谢物的首要暴露器官，直接受肠道菌群代谢产物调控。MASLD 患者中 *Akkermansia mucinphilia* 丰度明显下调[148]，定殖 *Akkermansia mucinphilia* 可促进腺苷钴胺的合成、减少神经酰胺的积累，最终缓解 MASLD[149]。人参皂苷 Rh4 等多种天然化合物被证实可增加 *Akkermansia mucinphilia* 的丰度，从而改善 MASLD[150]。*Bacteroides thetaiotaomicron* 的膜外囊泡可能抑制志贺氏菌(*Shigella*)等病原菌的毒力基因表达，间接保护肠道屏障功能，减少肠源性肝损伤[151]。Zhou 等[152]的青少年队列研究首次揭示了 *Megamonas* 丰度与肥胖、MASLD 呈正相关，动物粪菌移植实验证实高丰度的 *Megamonas* 可直接诱导肝脏脂肪沉积和胰岛素抵抗。Lin 等[153]在肥胖伴 MASLD 儿童中发现懒惰脱硫弧菌(*Desulfovibrio piger*)的丰度显著增加，这支持了 *Desulfovibrio* 在 MASLD 发病中的诱发作用。此外，食物中含硫成分可促进硫代谢菌的增殖(如 *Desulfovibrio*)，增加 MASLD 的患病风险[154]。

4.3 特征肠菌与心血管疾病

菌群-胆汁酸-胆固醇轴是调控血脂稳态的核心。*Erysipelotrichaceae* 可能激活炎症通路加剧血管内皮功能障碍，从而导致冠状动脉微血管重塑障碍和心肌灌注不足[155]。Wang 等[156]的观察性研究和孟德尔随机化分析显示，*Desulfovibrio* 丰度升高与心血管疾病风险增加呈正相关，尤其是其硫酸盐还原活性可能影响脂代谢、降低 APoA1/ApoB 比例，促进动脉粥样硬化。Fujihara 等[157]病例报告发现，*Desulfovibrio desulfuricans* 可导致感染性动脉瘤，提示该菌可能通过直接感染血管组织参与心血管疾病的发生。此外，*Desulfovibrio* 具有与生物膜形成的特性，可能加剧血管内皮的损伤[158]。*Akkermansia mucinphilia* 通过调节色氨酸代谢产物(吲哚-3-丙酸)激活心脏核受体调控的能量代谢信号通路，从而改善线粒体功能，对心血管损伤具有保护作用[159]。寒冷暴露会降低 *Akkermansia mucinphilia* 丰度，增加心房纤颤易感性，补充 *Akkermansia mucinphilia* 可调节肠道菌群-代谢物网络，降低冷诱导的心房纤颤风险[160]。

4.4 特征肠菌与高血压

特征肠菌可通过菌群-代谢物-宿主轴参与血压调控[161-165]。近年来，多项研究揭示了特定肠道细菌与高血压发生发展之间的潜在联系。对于抑制肥胖的特征肠菌，*Akkermansia muciniphila* 和 *Bifidobacterium* 的丰度增加与血压下降显著相关，其作用机制可能涉及抗炎途径(减少 LPS 和三甲基胺氧化物(trimethylamine oxide, TMAO)等促炎物质)及 SCFAs 等代谢产物调节的代谢和免疫应答[161-162]。Fan 等[163]动物实验表明 *Desulfovibrio* 丰度水平与收缩压呈负相关，可能通过硫酸盐还原代谢影响肠道 H_2S 水平，而 H_2S 具有血管舒张作用，但其具体机制仍需进一步研究。值得注意的是，虽缺乏直接证据证明 *Bacteroides thetaiotaomicron* 能改善高血压，但作为拟杆菌属的一员，其潜在作用可能涉及胆汁酸代谢等途径。作为益生菌，*Lactobacillus rhamnosus* 能通过产生 SCFAs 激活 GPR41/43 等受体，抑制肾素分泌或调节免疫反应，从而发挥降血压作用[164-165]。

4.5 特征肠菌与疾病预测

近年来，大量重磅研究正在构建肠道菌群与疾病谱之间的映射模型，有望实现重大疾病的早期预测。常规方法中单独使用微生物类群预测健康结局的效果有限，整合表型变量后能显著提升预测能力[166]。尤其是采用机器学习技术可更高效地处理肠道菌群的高度变异性，识别肥胖的总体特征[167]。Jian 等、Vals-delgado 等[168-169]研究表明，肠道菌群基线特征可解释约 25% 的体脂变化，提示其具有预测体脂波动的潜力。Nychas 等[170]基于 1 206 例中国人群的多组学分析表明，肠道菌群特征(*Prevotella*/*Bacteroides* 属比例)对 MASLD、肥胖和 T2DM 的预测准确率达 80% 以上。丁酸盐合成通路基因的缺失被认为是代谢紊乱的早期预警指标[136]。冠心病患者中肠道菌群组成联合传统生物标志物能更早预测 T2DM 发病风险。浙江大学倪艳教授构建了首个专注于肥胖相关代谢疾病(肥胖、T2DM、MASLD)的肠道微生物分析网络服务器(Web Server)，整合标准化分析、跨数据集验证和创新评分系统，显著提升了微生物标志物的可靠性和可重复性，有望为机制研究、临床诊断及干预策略开发提供高效工具[171]。

5 总结与展望

近年来，肠道菌群与肥胖的互作机制研究取得了突破性进展。靶向肠道菌群被认为是防治疾病的重要策略，通过促进益生菌增长、遏制有害菌增殖、整体替换肠道菌群的思路不断凸显肠道菌群在生物医学中的重要地位。综上所述，作者所在团队提出“肥胖疾病的肠菌演变假说”，认为肥胖诱导其他不同疾病的发生概率与肠道菌群的差异息息相关，以肥胖为基础的特征肠菌包括 *Desulfovibrio*、*Megamonas*、*Erysipelotrichaceae* 等条件致病菌和 *Lactobacillus*、*Bifidobacterium*、*Akkermansia muciniphila*、*Bacteroides thetaiotaomicron* 等益生菌。在此基础上，部分有益菌或条件致病菌丰度持续偏离，会分化衍生不同疾病，一部分向糖尿病演变，一部分向代谢功能障碍相关脂肪性肝病发展，另外还有可能进展为心血管疾病或高血压疾病。如 *Akkermansia* 益生菌缺乏程度与糖尿病进展呈高度负相关，而 *Megamonas* 的高丰度与 MASLD 呈正相关。*Erysipelotrichaceae* 等菌组成与心血管疾病指向性较强。上述结论仍有待于深入的多组学研究验证。

未来，肥胖特征肠菌的丰度变化或将成为重大疾病的早期诊断指标，识别关键肠菌对于疾病的早期诊断具有重要意义，有望实现肥胖及相关代谢疾病的早期预警和精准诊断，以便在疾病尚未表现出明显症状时及时采取干预措施。此外，基于肠道菌群的诊断方法还可能为个性化和精准治疗方案的制定提供依据，以提高临床疗效。

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