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专论与综述

肠道菌群调控脂质代谢作用与机制的研究进展

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摘　要：近年来，肠道菌群对机体脂质代谢的调控机制成为研究热点。在肥胖小鼠或脂质代谢紊乱小鼠中，都存在肠道菌群的改变。通过粪菌移植、服用益生菌等方法可调节肠道菌群的平衡进而有效改善机体的脂质代谢紊乱。这篇综述中聚焦肠道菌群对脂质代谢的调控作用，并进一步从心血管系统疾病、神经系统疾病、非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)、肥胖和 2 型糖尿病(type 2 diabetes mellitus, T2DM)等脂质代谢紊乱疾病展开阐述，最后探索了肠道菌群调节脂质代谢紊乱的治疗前景。

关键词：肠道菌群；脂质代谢；肠道菌群代谢物

Advances in the role and mechanism of gut microbiota in regulating lipid metabolism

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Abstract: In recent years, the regulation mechanism of lipid metabolism by gut microbiota has become a focus of research. Changes in gut microbiota have been discovered in the mouse models of obesity and lipid metabolism disorders. Adjusting gut microbiota by fecal microbiota transplantation and probiotics can alleviate lipid metabolism disorders. This review focuses on the regulatory effect of gut microbiota on lipid metabolism and expounds the regulatory effects on cardiovascular diseases, nervous system diseases, non-alcoholic fatty liver disease, obesity, and type 2 diabetes mellitus. Finally, this paper explores the therapeutic prospects of regulating

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gut microbiota in the treatment of lipid metabolism disorders.
Keywords: gut microbiota; lipid metabolism; gut microbiota-derived metabolites

人体微生物的基因及其产物是先天固有的，可以在母体及子代中发生垂直转移，其中肠道菌群是人体最重要的四大微生物库之一[1]。在健康人体中，口腔和唾液中的微生物经过胃酸、消化酶及各种消化器官的层层筛选，最终留存在肠道，形成肠道菌群[2]。一个成年人的胃肠道大约存在 10–100 万亿个微生物，是自身体细胞数量的 10 倍之多[3]。这些微生物参与人体多种生理过程，主要在食物消化与营养吸收、免疫系统发育与功能成熟、抵抗外界致病菌与毒素，以及机体肿瘤的发生发展等方面发挥作用[4-5]。人体肠道菌群是动态变化的，不同年龄阶段、饮食、药物等均会影响肠道菌群的组成[6-9]。肠道微生物主要寄居在结肠和小肠远端，核心菌群由厚壁菌门(*Bacillota*)和拟杆菌门(*Bacteroidota*)组成[10]，其次是变形菌门(*Pseudomonadota*)、放线菌门(*Actinomycetota*)和疣微菌门(*Verrucomicrobiota*)[2,11]。肠道菌群失调可能会导致机体脂代谢紊乱，脂肪酸、甘油三酯(triglyceride, TG)和胆固醇等与血脂水平相关的指标异常，进而引发一系列代谢性疾病，如非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)、神经退行性疾病、动脉粥样硬化等[7,12]。如图 1 所示，脂代谢紊乱患者肠道的核心菌群丰度会发生改变。因此，全面了解人体肠道菌群调控脂质代谢的作用与机制对于脂代谢紊乱相关疾病的治疗具有重要意义。

1 肠道菌群代谢物对脂质代谢的调节机制

1.1 短链脂肪酸

短链脂肪酸(short chain fatty acid, SCFA)是人体无法消化的碳水化合物经肠道菌群发酵在结肠中产生的代谢产物[7]，主要包括甲酸、乙酸、丙酸、丁酸和戊酸，其中乙酸、丙酸、丁酸尤其是乙酸是肠道菌群的主要代谢产物[13]。乙酸盐由众多肠道细菌通过乙酰辅酶 A 从丙酮酸中产生，也可由产乙酸菌通过伍德-隆达尔代谢途径产生[14]。丙酸盐主要来自拟杆菌属(*Bacteroides*)、毛螺菌科(*Lachnospiraceae*)[15]，丁酸盐由普氏栖粪杆菌(*Faecalibacterium prausnitzii*)、直肠真杆菌(*Agathobacter rectalis*)、罗斯拜瑞氏菌属(*Roseburia*)等菌群的代谢产物[16]。肠道菌群产生的 SCFA 由肠道层层吸收后通过 β 氧化作用转换成乙酰辅酶 A，在机体脂质代谢、脂肪生成、糖异生和胆固醇合成等方面发挥着重要作用[17-18]。SCFA 也是一种信号分子，通过激活细胞膜上的游离脂肪酸受体(free fatty acid receptor, FFAR)/G 蛋白偶联受体(G-protein-coupled receptor, GPR)调节胰高血糖素肽(glucagon-like peptide-1, GLP-1)的分泌以及机体脂肪的合成，进而改善脂肪组织和肝脏中的糖脂代谢[19-20]。SCFA 参与多个信号通路的调节，一方面 SCFA 调控肝脏脂质代谢相关酶如脂肪酸合成酶(fatty acid synthase, FAS)和乙酰辅酶 A 羧化酶(acetyl CoA carboxylase, ACC)的转录，激活解偶联蛋白 2 (uncoupling protein 2, UCP2)/腺苷单磷酸活化蛋白激酶[adenosine 5′-monophosphate (AMP)-activated protein kinase, AMPK]/ACC 信号通路，促进线粒体脂肪酸氧化[21]；另一方面，SCFA 还可促进过氧化物酶体增殖物激活受体 γ 辅助激活因子 1α (peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α)的表达，激活 AMPK 信号通路，促进脂肪酸氧化、抑制脂肪生成[22]。此外，SCFA 还

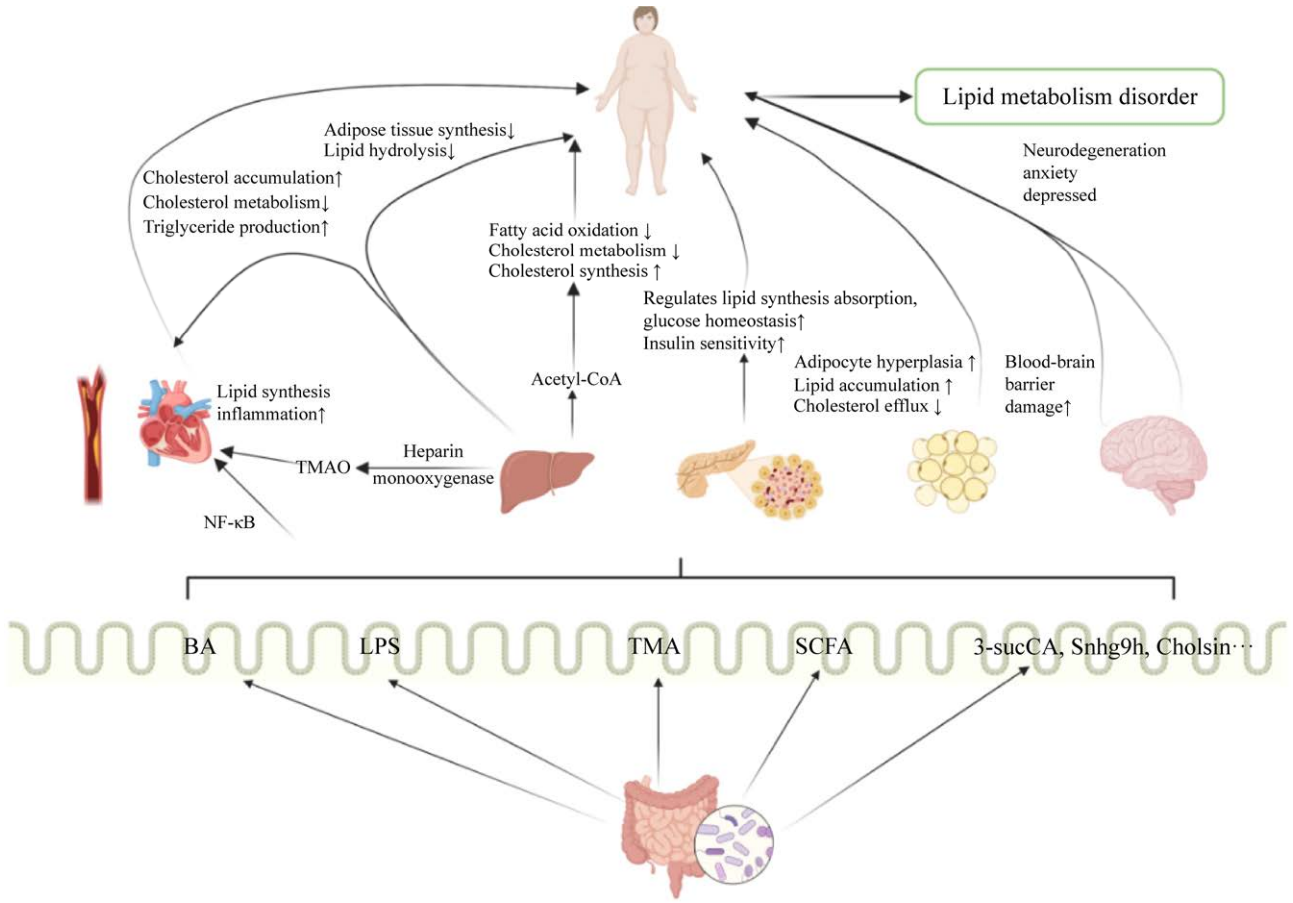

图 1　肠道菌群调控脂质代谢的机制　TMAO：氧化三甲胺；BA：胆汁酸；LPS：脂多糖；TMA：三甲胺；SCFA：短链脂肪酸。肠道微生物群通过胆固醇合成、脂质累积、脂肪细胞增生，以及机体炎症反应等途径调控心血管系统、神经系统、非酒精性脂肪肝、肥胖、糖尿病等病理生理过程。

Figure 1　The mechanism of intestinal flora regulating lipid metabolism. TMAO: Trimethylamine N-oxide; BA: Bile acid; LPS: Lipopolysaccharide; TMA: Trimethylamine; SCFA: Short chain fatty acid; Gut microbiota regulates pathophysiological processes such as cardiovascular system, nervous system, non-alcoholic fatty liver disease, obesity and type 2 diabetes mellitus through cholesterol synthesis, lipid accumulation, adipocyte proliferation and inflammatory response.

可通过下调肝脏脂肪生成基因主要调节因子固醇调节元件结合蛋白 1c (sterol regulatory element binding protein-1c, SREBP-1c)的表达进而抑制肝脏脂肪酸合成[23]。总体而言，SCFA 在机体脂质代谢方面发挥积极作用。

1.2　胆汁酸

胆汁酸(bile acid, BA)是胆汁的主要功能成分，在肝脏合成，并由胆囊储存，随后经肠道释放发挥作用[24]。胆固醇的分解代谢是 BA 合成的主要来源[25]，人体每天大约有 500 mg 的胆固醇经肝脏作用转化成 BA[26]，BA 主要有 5 种形式，分别是共轭胆汁酸(conjugated bile acid, CBA)、原胆汁酸(cholic acid, CA)、鹅去氧胆汁酸(chenodeoxycholic acid, CDCA)、次级胆汁酸脱氧胆酸(deoxycholic acid, DCA)和石胆酸(lithocholic acid, LCA)组成[24]。在摄入食物后，

BA 被释放到小肠，参与膳食脂肪的消化吸收[27]。大约 95%的 BA 经回肠重吸收后再由肝脏重新分泌，这是维持机体葡萄糖、脂质和能量代谢稳态的重要生理机制[28]。海氏梭菌(*Clostridium hylemonae*)[29]、双歧杆菌属(*Bifidobacterium*)[30]、嗜酸乳杆菌(*Lactobacillus acidophilus*)[31]、乳肠球菌(*Enterococcus lactis*)[32]等肠道菌群通过分泌胆盐水解酶(bile salt hydrolase, BSH)对初级胆汁酸进行解偶联以及去羟基化、氧化脱氢后形成次级胆汁酸，进而调控 BA 稳态，阻碍信号传导，干扰机体脂质代谢[33]。

BA 是参与糖脂代谢的重要信号分子，主要通过存在于肝脏、肠道、肌肉、棕色脂肪、中枢和外周神经系统的法尼醇 X 受体(farnesoid X receptor, FXR)[34]、G 蛋白偶联胆汁酸受体 1 (G protein-coupled bile acid receptor 1, GPBAR1)/胆汁酸 G 蛋白偶联受体 5 (Takeda G protein-coupled receptor 5, TGR5)[27]等受体激活参与脂质和碳水化合物代谢、能量代谢及炎症基因的表达。BA 通过刺激 FXR 活化抑制脂肪合成和促进脂质水解[35]，高脂饮食可以增加小鼠体内普拉梭菌(*Faecalibaculum*)和瘤胃球菌属(*Ruminococcus*)的相对丰度，进而升高 CA、CDCA 和 DCA 的含量，减少胆汁酸合成并通过 FXR 增加胆固醇积累，调节脂质代谢；CDCA 通过激活 FXR-小异二聚体配体(small heterodimer partner, SHP)通路，使 SREBP-1c 及脂质表达相关基因下调[36-37]。BA 与 TGR5 结合可以改善胰岛素及葡萄糖耐量、降低血浆脂质代谢相关指标并改变肝脂肪变性等[38]。TGR5 主要通过以下 3 个途径发挥作用：首先通过激活环腺苷酸(cyclic adenosine monophosphate, cAMP)依赖性甲状腺激素激活酶碘甲腺原氨酸脱碘酶 II (type 2 iodothyronine deiodinase, DIO2)将无活性的甲状腺激素 T4 转换成有活性的 T3，增加脂肪组织的产热作用[39]。其次，它通过释放 GLP-1 调节机体葡萄糖代谢和能量平衡[40]，抑制巨噬细胞核转录因子 κB (nuclear factor kappa-B, NF-κB)信号传导，减少泡沫细胞形成和降低脂质负荷，抑制动脉粥样硬化形成[41]。

1.3 氧化三甲胺

肠道中的膳食脂肪如肉碱、磷胆碱或胆碱经肠道菌群的作用转化为三甲胺(trimethylamine, TMA)，随后进入门静脉循环经肝黄素单加氧酶(flavin-containing monooxy genase, FMO)形成氧化三甲胺(trimethylamine N-oxide, TMAO)[42]。TMAO 及其相关前体物质可影响肝脏线粒体的肉碱穿梭系统，并抑制 BA 合成与运输、阻碍肝胰岛信号传导，进而减弱肝细胞氧化脂肪酸的能力，导致脂质沉积的发生[35]。在临床研究中，膳食磷脂酰胆碱代谢物 TMAO 被证实为心血管风险的独立预测因子[42]。实验证明，饮食中的胆碱和肠道菌群在三甲胺的生产及氧化、增强巨噬细胞胆固醇积累和泡沫细胞形成中具有关键作用[43]。在动物模型中发现，特异性敲除肝脏 FMO3 的小鼠中动脉粥样化面积有所减少，脂质和胆固醇代谢水平有所改善[44]。另有研究显示，肠道内益生菌定殖可以降低血清中 TMA 和 TMAO 的水平，调节 BSH 活性，促进 BA 和胆固醇代谢，减少肝脂代谢[35,45]。

1.4 促炎细菌衍生因子：脂多糖

脂多糖(lipopolysaccharide, LPS)是革兰氏阴性菌细胞膜上的内毒素，并通过激活特定模式识别受体(pattern recognition receptor, PRR)家族中的 Toll 样受体(Toll-like receptor, TLR)发挥活性，诱发炎症，对微生物和感染因子发出防御信号；Toll 样受体 4 (Toll-like receptor 4, TLR4)相关受体广泛分布在免疫、肝脏、脂肪细胞中[7]，通过诱导炎症反应导致脂质代谢异常[46]，抑制 LPS 诱导的炎症反应可抑制胰岛素抵抗和脂质

堆积，改善脂质代谢[35]。LPS 诱导促炎因子的释放，激活免疫和炎症反应，促进动脉硬化进展和斑块形成[47]，并且显著降低小鼠巨噬细胞内 ATP 结合盒转运蛋白 A1 (ATP-binding cassette transporter A1, ABCA1)蛋白，减少胆固醇流出[48]。高脂饮食可导致肠道内含有 LPS 的细菌丰度增加，诱导肿瘤坏死因子 α (tumor necrosis factor alpha, TNF-α)和 NF-κB 信号通路的激活[49]。LPS 及 TNF-α 是抑制脂肪组织褐变的细胞凋亡信号调节激酶 1 (apoptosis signal regulating kinase-1, ASK1)的激活剂，可抑制高脂饮食小鼠脂肪组织褐变，从而减少能量消耗，导致代谢性疾病[50]。此外，LPS 还通过刺激巨噬细胞分泌相关细胞因子诱导半胱天冬酶-3 (caspase-3, CASP3)的激活，从而抑制肠道对脂肪酸的吸收[51]。

1.5 其他物质

近年来，除肠道菌群代谢物之外，还有一些肠源性物质备受关注。研究显示，肠道菌群下调小肠上皮细胞中长链非编码 RNA 基因 Snhg9 表达、进而抑制脂质代谢中心调节剂过氧化物酶体、增殖物激活受体 γ (peroxisome proliferators-activated receptor γ, PPARγ)活性来调控脂质代谢[52]。一种新发现的肠源性激素 cholesin 可以与 G 蛋白偶联受体 146 (G-protein-coupled receptor146, GPR146)结合，抑制肝脏中胆固醇合成，降低循环中的胆固醇水平，调节脂质代谢，为治疗高胆固醇血症和动脉粥样硬化提供新方案[53]。3-琥珀酰化胆酸(3-succinylated cholic acid, 3-sucCA)是一种管腔限制性代谢物，它可通过重塑肠道菌群，尤其是扩大嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)种群，延缓小鼠肝脏相关代谢疾病发展[54]。

上述研究提示，SCFA、BA、TMAO、LPS 等肠道菌群代谢物和脂质代谢相关基因 Snhg9、肠源性激素等物质通过胆固醇合成、脂质累积、脂肪细胞增生及机体炎症反应等多种途径影响机体脂质代谢(图 1)。

2 肠道菌群调控脂质代谢在多种疾病中的作用

2.1 心血管疾病

血液中的脂质水平升高是导致心血管疾病的关键因素，肠道菌群与小鼠及人类血液和组织中的脂质代谢和脂质水平密切相关[7]。动脉粥样硬化患者脂质代谢改变可能与口腔和肠道中细菌分类群及血浆胆固醇水平相关[55]。心血管相关疾病的患者其体内大肠杆菌(*Escherichia coli*)、志贺氏菌属(*Shigella*)、鲁杰氏菌属(*Ruegeria*)相对丰度增加，厌氧菌(*Anaerotrumcus*)、副萨特氏菌属(*Parasutterella*)、欧尔森氏菌属(*Olsenella*)相对丰度减少[47]。将从人体粪便分离出的青春双歧杆菌(*Bifidobacterium adolescentis*)应用于喂养高脂饮食的小鼠后，小鼠血脂谱恢复到正常水平[56]，双歧杆菌通过胆固醇同化、参与 BA 代谢等方式来降低血浆中胆固醇[57]。研究中发现，拟杆菌目(*Bacteroidales*)、毛螺菌科(*Lachnospiraceae*)、颤螺菌目(*Oscillospirales*)这 3 种肠道菌与糖化血红蛋白、高密度脂蛋白、胆固醇和 TG 有关联[58]。此外，LPS 增加巨噬细胞中 TG 的浓度[59]，TMAO 是胆固醇积累和动脉泡沫细胞形成的关键，二者与动脉粥样硬化等心血管疾病高度相关。低丰度的生物活性脂质如内源性大麻素(endocannabinoid, eCB)，通过肠道菌群和益生菌调节心血管相关疾病的结局[60]。综上，肠道菌群和宿主脂质代谢及心血管疾病的发展之间的联系可以确定，肠道菌群通过改变肠道菌群代谢物、血脂水平等途径调节机体脂质代谢，间接减少肥胖、2 型糖尿病等疾病带来的心脏负担以及动脉粥样硬化、心肌梗死等心血管疾病的发生。

2.2 神经系统疾病

肠道菌群结构的变化对神经系统相关疾病起着至关重要的作用，肠道微生物群可以通过微生物群-肠-脑轴影响大脑功能和行为。研究显示，脑-肠-菌群轴是神经退行性疾病发生发展中不可忽视的因素，肠道菌群的改变使肠道屏障的通透性增加、免疫激活，引发全身炎症反应，破坏血脑屏障，促进神经损伤发展，最终导致神经退行性病变[61]。载脂蛋白 E (apolipoprotein E, ApoE)是一种主要的胆固醇载体，在维持外周和大脑的脂质平衡方面起着重要的作用[62]，是阿尔茨海默病(Alzheimer disease, AD)最重要的遗传因素，近来的研究发现，肠道菌群的构成与 ApoE 的等位基因相关联，其中乳杆菌科(*Lactobacillaceae*)受 ApoE 基因型的影响最大，瘤胃球菌属(*Ruminococcus*)的增加与 ApoE2 相关[63]。铁死亡作为神经退行性疾病 AD 和帕金森病的主要发病机制，其特征之一是不受限制的脂质过氧化积累[64]，而肠道菌群通过其微生物组成、生物学功能及代谢物对铁死亡发挥调节作用，如肠道微生物调节肠道 pH 优化膳食铁的生物利用等[65]。有研究显示癫痫发作时脂质过氧化增加且总抗氧化能力降低[66]，患者体内出现双歧杆菌属(*Bifidobacterium*)和乳杆菌属(*Lactobacillus*)相对丰度的下降[67]，调节肠道菌群的构成可以抑制癫痫大鼠海马体的氧化应激和炎症反应，进而抑制癫痫发作[68]。另有研究发现，嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)可能与高胆固醇饮食诱发抑郁症的发展密切相关[69]。肠道菌群代谢产生的乳酸可以激活 G 蛋白偶联受体 81 (G-protein-coupled receptor 81, GPR81)，它是一种内源性乳酸受体，通过调节脂肪分解导致脂质代谢紊乱来诱导焦虑样行为，可为焦虑症靶向治疗提供参考[70]。以上研究结果表明肠道菌群可以通过干扰大脑中脂质代谢、调控相关基因表达、调节铁死亡等途径影响大脑的行为和功能。

2.3 非酒精性脂肪肝

非酒精性脂肪肝通常伴随着肝细胞中堆积过多的脂肪和胰岛素抵抗[1]。相关研究显示，非酒精性脂肪肝患者存在明显的肠道菌群构成及丰度的变化，主要报道有变形菌门(*Pseudomonadota*)、乳杆菌属(*Lactobacillus*)、埃希氏菌属(*Escherichia*)、普雷沃氏菌属(*Prevotella*)、链球菌属(*Streptococcus*)、粪球菌属(*Coprococcus*)、粪杆菌(*Faecalibacterium*)、瘤胃球菌属(*Ruminococcus*)、嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)等改变[71-73]。最近一项研究发现，相较于乳脂饮食，富含硬脂酸的饮食改善小鼠体内糖脂代谢紊乱，并增加嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)的数量，而将富含硬脂酸饮食小鼠的肠道微生物转移到喂食乳脂饮食小鼠中，乳杆菌属(*Lactobacillus*)的若干种菌株有所增加，有效防止肥胖、葡萄糖稳态受损和肝脂肪变性[74]。肠道菌群代谢物通过调节脂质代谢促进非酒精性脂肪肝的发展，其中 BA 是调节脂质代谢的重要信号分子[75]，肠道菌群通过 BA 的重要受体 FXR 依赖性机制控制脂质和脂蛋白代谢，该机制涉及调节肝脏脂肪生成、脂蛋白分泌、血浆清除和肠道胆固醇吸收[76]。SCFA 可以减少脂肪组织中的脂肪堆积，而非酒精性脂肪肝患者体内的 SCFA 生成菌减少[77]，增加了内脏脂肪堆积的风险[78]。此外，肠道菌群的变化会影响细胞膜磷脂成分的胆碱代谢改变，有研究发现膳食胆碱在肠道微生物的作用下转化为有害代谢物三甲胺进而引发肝细胞炎症[79]。肠道菌群及相关代谢产物对于非酒精性脂肪肝的发生发

展具有重要意义，通过增加患者体内的益生菌含量或调节相关代谢产物的生成可有效扭转非酒精性脂肪肝的进程。

2.4 肥胖

肥胖是指长期的能量摄入超出能量消耗导致人体脂肪组织过度蓄积[80-81]，通常以身体质量指数(body mass index, BMI)作为评判标准，将 BMI>28.0 kg/m^2 定义为肥胖。肥胖影响消化、心血管、内分泌等各大系统功能的正常运行，极大地增加了脂肪肝、2 型糖尿病、心血管疾病等慢性病发病风险，导致生活质量和预期寿命下降，已成为不容忽视的公共危机。研究表明，某些肠道微生物群有助于收集能量并增加宿主脂肪储存[82]。将野生小鼠的肠道菌群移植到无菌小鼠体内后，无菌小鼠身体脂肪量增加，肝脏 TG 水平和胰岛素抵抗急剧增加[83]。肥胖患者瘤胃球菌属(*Ruminococcus*)、罗斯拜瑞氏菌属(*Roseburia*)相对丰度升高，嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)、肠杆菌(*Enterobacter* sp.)、多形拟杆菌(*Bacteroides thetaiotaomicron*)、梭菌(*Clostridium* sp.)等益生菌相对丰度降低[84]。此外，肠道微生物群可下调肠道中空腹诱导脂肪因子(fasting induced adipose factor, FIAF)表达，从而抑制脂肪组织中的脂蛋白脂肪酶。FIAF 激活含有脂蛋白的三酰基甘油分解成游离脂肪酸，供肌肉和脂肪组织使用；因此，抑制 FIAF 表达可促进脂肪细胞中 TG 沉积[83]。总体来看，肠道菌群的组成和丰度对于机体脂肪储存和能量积累具有重要作用，肠道菌群紊乱会促使机体代谢紊乱，促进肥胖的发生发展。

2.5 糖尿病

2 型糖尿病(type 2 diabetes mellitus, T2DM)是以进行性胰岛 β 细胞功能障碍和胰岛素抵抗为特点的糖脂代谢疾病。近年来，脂肪细胞胰岛素抵抗和炎症已确定为 T2DM 发展的重要因素。脂肪分解增加、游离脂肪酸水平升高以及中间脂质代谢物的积累会进一步增加葡萄糖输出，降低外周葡萄糖利用率并损害 β 细胞功能。同时多项研究提示脂质代谢紊乱是 T2DM 发病的重要因素，并且认为脂质代谢水平可作为 T2DM 控制血糖的预测指标，可用 TG/高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)的比率来预测 10 年内 T2DM 的发展[85]。通过对比健康人与 T2DM 患者发现，T2DM 患者体内柔嫩梭菌(*Clostridium leptum*)、乳杆菌(*Lactobacillus* sp.)、肠杆菌(*Enterobacter* sp.)、肠球菌(*Enterococcus* sp.)、志贺氏菌(*Shigella*)数量显著性升高，而双歧杆菌属(*Bifidobacterium*)、拟杆菌(*Bacteroides* sp.)、普氏栖粪杆菌(*Faecalibacterium prausnitzii*)数量明显低于健康人群[86-89]。在清除肠道菌群后，雄性小鼠葡萄糖代谢会得到改善[90]。长双歧杆菌(*Bifidobacterium longum*)和乳杆菌属(*Lactobacillus*)可上调机体 GLP-1 和白细胞介素-10 (interleukin 10, IL-10)表达，并抑制脂肪细胞中的脂质积累[91]。由拟杆菌(*Bacteroides* sp.)等菌群发酵膳食纤维产生的短链脂肪酸直接进入细胞或作用于跨膜受体，如 FFAR2、FFAR3，这些受体参与如脂肪酸氧化、葡萄糖代谢和炎症反应[92]，有助于改善 T2DM。此外，BA 在 T2DM 中也发挥着关键作用。富含梭菌的肠道菌群可以通过抑制肠道成纤维细胞生长因子 19 (fibroblast growth factor19, FCF19)的产生来促进 BA 的合成，进而 BA 激活 FXR 和 TGR5，调节脂质合成与吸收，从而改善葡萄糖稳态和胰岛素敏感性[93]。由此可见，无论是肠道微生物还是其代谢产物对 T2DM 的发生发展都具有关键性作用。

2.6 其他

肠道炎症性疾病是一种肠道慢性炎症性疾病，分为溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD)，发病机制尚不清楚，但肠道菌群的改变与其密切相关[94]。一种长链脂肪酸——棕榈油酸对重编程肠道微生物群结构并诱导炎症性肠病(inflammatory bowel disease, IBD)肠道损伤后的组织修复和稳态至关重要，显著上调嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)的生长，并抑制了有害的促炎细菌如梭杆菌属(*Fusobacterium*)的生长[95]。多囊卵巢综合征是一种常见的女性内分泌疾病，脂质代谢紊乱是其主要危险因素之一，患者常伴有血脂谱改变[96]，此类患者肠道菌群的 α 多样性降低，β 多样性和代谢产物发生改变，拟杆菌(*Bacteroides* sp.)、卟啉单胞菌属(*Porphyromonas*)、瘤胃球菌属(*Ruminococcus*)、乳杆菌属(*Lactobacillus*)等发生变化[97]。如图 2 所示，肠道菌群组成的改变与多系统疾病的脂质代谢相关，作用机制繁多，未来仍需进一步探索。

3 肠道菌群与脂代谢紊乱的治疗

现阶段肠道菌群已成为治疗脂质代谢异常的关键靶点。现有的治疗策略主要有改变饮食、益生菌和益生元、菌群移植、噬菌体疗法、抗生素治疗等[1]。益生菌如双歧杆菌、乳酸菌，益生元如低聚果糖和菊粉，以及合生元(两者的组合)在脂质代谢紊乱治疗中的应用已十分普遍，如双歧杆菌可以减少肥胖小鼠 PPARγ 的表达，减轻高脂肪饮食诱导的肥胖小鼠的体重和脂肪增加[98]；菊粉经肠道菌群发酵后产生短链脂肪酸，有效改善肥胖小鼠的血脂谱，降低小鼠体质量，治疗脂质代谢紊乱[99]。肠道微生物除细菌外，还包括以噬菌体为主的病毒，以宿主特异性方式特异性感染细菌并影响机体代谢，将低脂饮食小鼠的粪便病毒组移植到高脂肪饮食小鼠的肠道后，发现肥胖小鼠的体重增加变慢，并改善了葡萄糖耐量[100]。菌群移植是通过结肠镜检查、鼻胃管、灌肠等方式将健康人类供体粪便中的菌群传递给患者的手段，由于目前粪菌移植技术尚不成熟，供体的选择、治疗方案的标准化缺乏统一共识[101-102]，目前的研究多为动物实验，人体中的临床应用有限。

4 总结与展望

肠道菌群与脂质代谢之间具有十分密切的关系。一方面，肠道菌群通过肠道菌群代谢物和一些与肠道相关的物质等影响脂质稳态；另一方面，肠道菌群的构成和丰度也会干扰机体脂质合成与分解，两者可能通过影响胆固醇合成、脂质累积、脂肪细胞增生以及机体炎症反应等途径发挥作用，并对心血管系统、神经系统、肝脏相关脂代谢性疾病等多种疾病的病理生理过程产生影响。肠道菌群在脂质代谢领域的临床应用潜力巨大，但目前仍需要进一步的研究来明确不同菌群及其代谢产物对脂质代谢的具体影响机制和安全性。随着技术的进步和研究的深入，肠道菌群在脂质代谢疾病管理中的应用前景将更加明朗化。目前，国内外关于肠道菌群在代谢性疾病中的作用已有大量文献报道，但肠道菌群调节脂质代谢机制的报道仍不够准确全面。因此，在未来的研究中使用微生物测序分析、生物标志物筛选、代谢组学等手段来更好地了解肠道菌群调控脂质代谢的关键驱动因素，进而深入探讨肠道菌群调控脂质代谢的机制，对于人体代谢健康具有十分重要的意义。

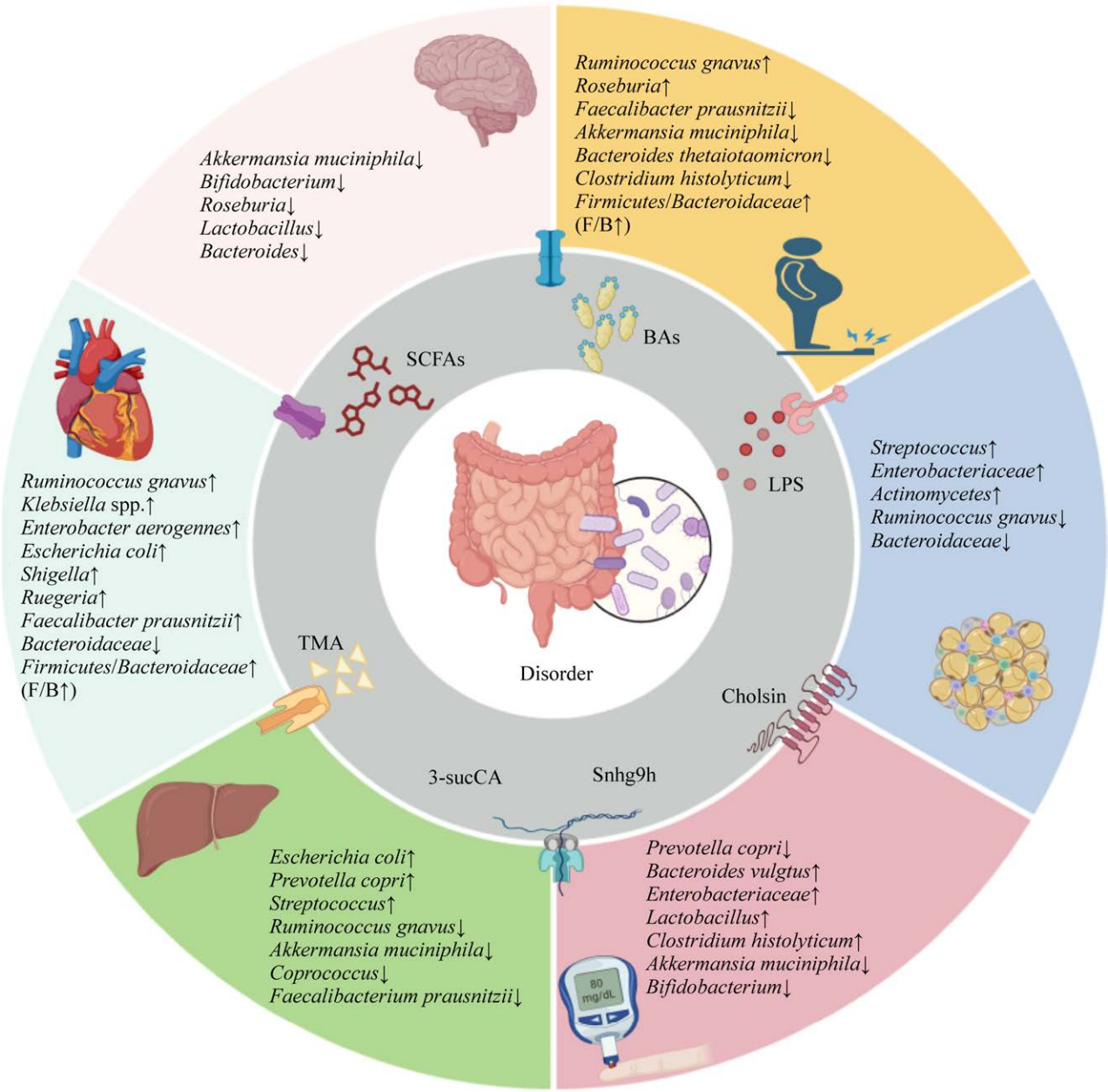

图 2　脂质代谢疾病肠道菌群紊乱特征　总结了多项涉及脂质代谢疾病中肠道菌群的变化情况，但不同研究之间的结果有所不同，本图并不全面涵盖所有已变化的菌群。

Figure 2　Characteristics of gut microbiota disorder in lipid metabolic diseases. The changes of gut microbiota in diseases involving lipid metabolism were summarized. However, results vary from study to study, and the chart does not fully cover all the changed microbiota.

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