中国科学: 生命科学 2021 年 第 51 卷 第 4 期: 375 ~ 383
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS

评 述

肠道微生物及其代谢产物与宿主脂质代谢研究进展

龚赛明[1], 马杰[1], 李凤娜[2], 李铁军[2], 刘刚[3], 谭碧娥[1], 黄兴国[1], 尹杰[1*], 印遇龙[1,2]

1. 湖南农业大学动物科学技术学院, 长沙 410128;
2. 中国科学院亚热带农业生态研究所, 长沙 410125;
3. 湖南农业大学生物科学技术学院, 长沙 410128
* 联系人, E-mail: yinjie2014@126.com

收稿日期: 2020-12-02; 接受日期: 2021-01-07; 网络版发表日期: 2021-02-24
中国科协青年人才托举工程(批准号: 2019-2021QNRC001)、国家自然科学基金(批准号: U20A2055)和湖南省优秀青年基金(批准号: 2020JJ3023)资助

摘要 近年来, 肠道微生物与宿主脂质代谢研究受到国内外的广泛关注. 首先, 肠道微生物多样性和组成在脂肪代谢紊乱动物模型、肥胖患者中均发生显著改变, 而利用粪菌移植、益生菌以及营养干预重塑肠道菌群结构可以调控宿主脂质代谢. 本文重点介绍了肠道微生物与宿主脂代谢的联系, 并从短链脂肪酸、胆汁酸、氨基酸、内毒素和微生物节律等方面探讨了肠道微生物调控宿主脂代谢的潜在机制, 以期为脂质代谢引起的疾病提供干预靶点.

关键词 肠道微生物, 脂质代谢, 肥胖

肠道微生物的数量庞大, 人体肠道中寄生的微生物总数量高达10^{14}级, 这与人体中全部细胞的总数量几乎一致[1]. 肠道微生物已被视为机体整体构成中至关重要的一部分, 甚至具有与内分泌器官相似的功能, 对宿主生理代谢起到重要的调节作用[2,3]. 肠道中微生物的失调能对宿主代谢和生理生化反应产生影响, 过程涉及肠道屏障完整性、大脑饱腹感和胰岛素抵抗以及胆汁酸代谢等, 最终导致宿主代谢紊乱[4]. 通过补充益生菌平衡肠道微生物菌群, 可以有效调节食物摄入和食欲以及代谢功能, 并改善宿主代谢状态[5]. 同时, 粪菌移植也表明, 微生物对宿主代谢能产生影响, 并且在改善肠道微生态紊乱方面优于单一的益生菌[6]. 此外, 肠道微生物具有许多宿主自身所不具备的代谢功能, 例如分解宿主不能消化的纤维, 其代谢产物能被肠上皮细胞识别和利用, 作为信号分子调控宿主生理代谢. 本文将讨论肠道微生物与宿主脂质代谢的相互联系, 总结当前肠道菌群影响宿主脂质代谢的研究进展.

1 肠道微生物和脂质代谢

肠道菌群平衡有助于人类健康, 而肠道微生物被

引用格式: 龚赛明, 马杰, 李凤娜, 等. 肠道微生物及其代谢产物与宿主脂质代谢研究进展. 中国科学: 生命科学, 2021, 51: 375–383
Gong S M, Ma J, Li F N, et al. Recent advances in the interaction between gut microbiota/metabolites and host lipid metabolism (in Chinese). Sci Sin Vitae, 2021, 51: 375–383, doi: 10.1360/SSV-2020-0396

破坏可能导致多种常见代谢疾病的发生, 包括肥胖、2型糖尿病、非酒精性脂肪肝、心脏代谢疾病和营养不良等[7]. 肥胖的发生主要受遗传、环境、饮食、运动等影响, 但是近30年的研究发现, 肠道微生物广泛参与宿主脂肪代谢和肥胖的发生、发展[8]. 通过比较无菌小鼠和普通小鼠对高脂日粮的响应, 发现无菌小鼠对高脂日粮存在抵抗作用, 但微生物重塑可导致无菌小鼠肥胖[9,10], 由此证实, 肠道微生物是影响机体脂肪沉积的重要因子. 肠道微生物与脂质代谢的关系主要表现在两个方面: 首先, 肠道微生物组成在肥胖患者或者肥胖动物模型中变化显著. 大量研究证实, 肠道中含量最丰富的Firmicutes和Bacteroidetes菌门在肥胖或高脂日粮模型中变化显著, 因此Firmicutes与Bacteroidetes丰度比值明显升高而可视为肥胖的微生物标志信号[11]. 本文总结了临床上关于肥胖研究中变化的微生物, 以期为后续关键微生物介导宿主脂质代谢以及益生菌的筛选研究提供参考(表1)[12~38]. 其次, 通过改善肠道微生物组成也能进一步影响宿主脂质代谢以及肥胖进程. 本团队[39]利用粪便微生物移植技术重塑肠道微生物组成, 显著改善了高脂日粮饲喂小鼠的脂质代谢状态. 同时, 大量研究证实, 许多益生菌也具有脂质代谢调节作用, 并可缓解高脂食物或饲料诱导的肥胖, 比如*Lactobacillus*和*Bifidobacterium*菌属等[5], 这些研究为临床上预防和治疗肥胖提供了微生物策略.

综上所述, 肠道微生物与宿主脂质代谢密切关联. 宿主脂质代谢紊乱能够影响肠道微生物组成, 而肠道微生物也能进一步影响宿主脂质代谢反应. 因此, 研究肥胖微生物机制有助于寻找改善宿主脂质代谢的微生物靶标以及筛选抗肥胖益生菌.

2 肠道微生物对脂质代谢的调控机制

大量的代谢疾病研究已经建立了肠道微生物与宿主代谢之间的初步联系, 然而肠道微生物影响宿主脂质代谢机制复杂, 呈现出多维度、多层次以及时空延续性等特点. 本文将从微生物本身及其代谢产物影响宿主代谢的角度出发, 探讨微生物介导宿主脂质代谢的潜在机制.

2.1 肠道微生物-短链脂肪酸-脂质代谢

肠道微生物能将结肠道中不易被消化的碳水化合物或者膳食纤维通过生物转化生成短链脂肪酸(包括乙酸、丙酸、异丁酸、丁酸、异戊酸和戊酸)[40], 其中对宿主代谢最为重要的是乙酸、丙酸和丁酸. 短链脂肪酸被肠道吸收后在肝脏中转化为乙酰辅酶A和丙酰辅酶A, 再作为原料参与糖原合成、糖异生、胆固醇合成等代谢过程, 最终对宿主脂质代谢产生影响[41]. 同时, 短链脂肪酸还可以作为信号分子通过激活细胞膜上的G蛋白偶联受体(G protein-coupled receptor, GPR)参与多种细胞生理代谢反应, 包括调控胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)、肽YY(peptide YY, PYY)以及瘦素的分泌等[42]. 例如, 可溶性膳食纤维果胶在通过肠道微生物发酵后, 产生的丁酸可降低小鼠的血清总胆固醇和低密度脂蛋白胆固醇[43]. 同时, 有研究报道, 食乳酸菌和双歧杆菌能够促进肠道丁酸盐的产生, 并进一步通过Gpr109a抑制高脂饲料诱导的肥胖与炎症反应[44]. Araújo等人[45]通过体内外实验发现, 大肠杆菌RB01产生的乙酸能影响肠上皮细胞的脂质代谢, 抑制乳糜微粒的分泌, 而乙酸被肠细胞吸收代谢为乙酰辅酶A和AMP后, 还能上调AMPK/PGC-1α/PPAR-α信号通路, 最终促进肠细胞中脂肪酸β氧化. 但也有研究指出, 高脂饮食大鼠的肠道菌群发生了改变, 乙酸的产生激活了副交感神经系统, 结果导致胃饥饿素与胰岛素的分泌, 最终引起高脂血症和肝脏与肌肉中的异位脂质沉积[46]. 因此, 肠道微生物与短链脂肪酸在脂质代谢中的作用和机制仍需进一步研究, 以期为靶向调控肠道微生物-短链脂肪酸轴改善宿主脂质代谢、脂肪沉积以及肥胖进程提供理论参考.

2.2 肠道微生物-胆汁酸-脂质代谢

胆汁酸是一种具有24个碳原子的两性分子, 含有亲水性与亲脂性的双重特征, 90%的胆汁酸由肝脏中的经典生物合成途径产生[47]. 95%的初级胆汁酸在回肠末端被重新吸收, 再通过门静脉返回肝脏. 肠道中剩余的初级胆汁酸会被肠道微生物中的胆酸盐水解酶(bile salt hydrolase, BSH)水解, 再经过脱氢、去羟基化和去甲基化, 分解为次级胆汁酸和三级胆汁酸, 如胆酸盐、脱氧胆酸盐、鹅去氧胆酸、牛磺酸和甘氨酸脱氧胆酸盐、乌索脱氧胆酸盐、石胆酸盐以及去氧胆酸盐等[48]. BSH通常存在于*Bacteroides thetaiotaomicron*, *Bifidobacterium longum*, *Enteroccocus faecalis*, *Lactobacillus salivarius*以及*Clostridium perfringens*等菌

表 1　肠道微生物与人肥胖密切相关[8]

Table 1　Close correlation between gut microbes and human beings[8]

资料来源	研究对象	比较对象	研究数量	菌群变化
Ley等人[12]	成人	肥胖与体重正常者	肥胖12例, 体重正常2例	Bacteroidetes↓
Collado等人[13]	孕妇	肥胖与体重正常孕妇	超重孕妇18例, 正常孕妇36例	*Bacteroides*↑ *Staphylococcus aureus*↑
Zhang等人[14]	成人	肥胖者、体重正常者与胃旁路手术后病人	体重正常3例, 肥胖3例, 胃旁路术后3例	Bacteroidetes↑ Proteobacteria↑ *Coriobacteriacee*↑ *Methanobacteriales*↑
Kalliomäki等人[15]	儿童	超重、肥胖与体重正常者	超重者25例, 肥胖7例, 正常体重24例	*Bifidobacteria*↓ *Staphylococcus aureus*↑
Duncan等人[16]	男性	肥胖与体重正常者	肥胖15例, 体重正常14例	*E.rectale/C. coccoides*↓
Turnbaugh等人[17]	双胞胎	肥胖双胞胎和正常双胞胎及其母亲	154例: 31对同卵双胞胎, 23对异卵双胞胎, 46位母亲	Bacteroidetes↓ Actinobacteria↑
Armougom等人[18]	成人	厌食症患者、肥胖与体重正常者	正常体重20例, 肥胖20例, 厌食症9例	*Lactobacillus*↑ *M. smithii*↑ Bacteroidetes↓
Nadal等人[19]	青少年	限制热量饮食10周的前后	39例超重青少年	Bacteroidetes/*Prevotella*↑ *Eubacterium rectale*↓ *Clostridium coccoides*↓ *C. histolyticum*↓
Santacruz等人[20]	青少年	饮食和运动10周的前后	肥胖青少年36例	*Bacteroides fragilis*↑ *Lactobacillus*↑ *C. coccoides*↓
Schwiertz等人[21]	成人	超重、肥胖与体重正常者	正常体重33例, 超重者35例, 肥胖33例	Firmicutes↓ Bacteroidetes↑ *Bifidobacteria*↓ *Methanobrevibacter* spp.↓
Balamurugan等人[22]	儿童	肥胖与非肥胖	肥胖15例, 正常体重13例	*Fecalibacterium prausntzi*↑
Santacruz等人[23]	孕妇	超重或肥胖的孕妇和正常体重的孕妇	超重孕妇16例, 正常体重 孕妇34例	*Bifidobacterium*↓ *Bacteroides*↓ *Escherichia coli*↑ *Staphilococcus*↑
Abdallah Ismail等人[24]	儿童与成人	肥胖与体重正常者	肥胖51例, 正常体重28例	Bacteroidetes↑ Firmicutes↑
Furet等人[25]	胃旁路手术后的肥胖患者	胃旁路手术前后	手术后肥胖患者36例, 正常体重13例	*Bacteroides/Prevotella*↑ *F. Prausnitzii*↓
Zuo等人[26]	成人	肥胖与体重正常者	肥胖52例, 正常体重52例	*Bacteroides*↓ *Clostridium perfringens*↓
Vael等人[27]	儿童	3周、26周和52周的儿童	共138例	*Bacteroides fragilis*↑ *Staphylococcus*↑
Patil等人[28]	成人	瘦、正常、肥胖和手术治疗的肥胖患者	共20例: 瘦人5例、正常5例、 肥胖5例、手术治疗5例	Bacteroidetes↑
Xu等人[29]	儿童	超重、肥胖与体重正常者	共175名儿童: 正常91例, 超重62例, 肥胖22例	Bacteroidetes↓
Munukka等人[30]	绝经前妇女	有或没有代谢紊乱的超重或肥胖女性	绝经前妇女85例	*E. rectale/C. coccoides*↑
Million等人[31]	成人	肥胖与体重正常者	肥胖68例, 正常体重47例	*Lactobacillus. paracasei*↑ *Lactobacillus. reuteri*↑ *Lactobacillus. gasseri*↑ Bacteroidetes↓

(续表1)

资料来源	研究对象	比较对象	研究数量	菌群变化
Simões等人[32]	双胞胎	肥胖、超重和体重正常者	20对双胞胎	*Bacteroides* spp.↑ *Bifidobacteria*↑
Ferrer等人[33]	青少年	肥胖与体重正常者	肥胖1例, 正常体重1例	Bacteroidetes↓ Firmicutes↑
Bervoets等人[34]	儿童	肥胖、超重、病态肥胖(O/O组)和正常、苗条(C组)	超重或肥胖26例, 正常体重27例	*Lactobacillus* spp.↑ Firmicutes↑ Bacteroidetes↓
Tims等人[35]	双胞胎	双胞胎中BMI一致与不一致	BMI不一致的双胞胎20例, BMI一致的双胞胎20例	*Clostridium* cluster IV↓ *Eubacterium ventriosum/Roseburia intestinalis*↑
Zeng等人[36]	成人	健康、无代谢异常的肥胖和临床指标异常的肥胖	共1914例	*Blautia*↑ *Clostridium* sensu stricto↑ *Romboutsia*↑ *Clostridium* sensu stricto↑ *Ruminococcus*↑
Ozato等人[37]	成人	健康、超重与肥胖男性; 健康、超重与肥胖女性	共1001例日本居民: 男性391例, 女性610例	Firmicutes↓ Bacteroidetes↑
Ottosson等人[38]	成人	不同BMI指数	共920例瑞典居民, 并对其中674例进行了肠道菌群测序	*Proteobateria*↑ Actinobacteria↑ *Spirochaetes*↑

中[49]. 将野生型和BSH基因敲除的*Bacteroides thetaiotaomicron*菌株分别定植无菌小鼠, 结果发现, 缺乏BSH的小鼠体重增加、代谢紊乱和呼吸交换率降低, 并伴随着昼夜节律和免疫相关因子的转录变化[50]. 由此提示, 肠道微生物中胆汁酸水解酶活性的高低能显著影响宿主脂质代谢过程和脂肪沉积[51].

同时, 胆汁酸及代谢物还能作为信号分子, 激活细胞核上的法尼醇X受体(farnesoid X receptor, FXR)和细胞膜上的G蛋白偶联胆汁酸受体5(G protein-coupled bile acid receptor, TGR5)[52,53]. FXR在肝、肠和肾等组织都呈现出高表达, 并通过调节肠肝循环中胆汁酸的合成、运输、偶联反应调控机体脂质代谢[54]. 同时, 研究显示FXR对次级胆汁酸和三级胆汁酸更加敏感[52], 提示肠道微生物通过水解胆汁酸间接参与宿主脂质代谢. 此外, TGR5能被初级和次级胆汁酸激活, 并参与调节机体脂质代谢[55], 而GTR5基因敲除小鼠呈现出明显的肥胖表型(血脂升高、脂肪沉积增加以及炎症反应等)[56]. 不仅如此, Zheng等人[57]比较了不同物种血液胆汁酸差异谱, 并发现猪胆酸(hyocholic acid, HCA)可通过HCA-TGR5/FXR-GLP-1信号通路促进肠L细胞分泌GLP-1, 进一步介导代谢反应. 总之, 肠道微生物可以通过BSH酶活性参与肠道胆汁酸代谢, 并通过激活FXR和TGR5进一步影响宿主脂质代谢.

2.3 肠道微生物-氨基酸-脂质代谢

绝大多数氨基酸都会在小肠中被吸收, 剩下的氨基酸进入结肠参与微生物代谢, 并产生大量代谢产物(包括氨、胺、短链脂肪酸、支链脂肪酸、硫化氢、有机酸和酚类等)[58,59]. 研究表明, 支链氨基酸(包括缬氨酸、亮氨酸和异亮氨酸)和芳香族氨基酸(包括苯丙氨酸、酪氨酸和色氨酸)是肥胖、胰岛素抵抗、糖尿病和脂肪肝等疾病脂质代谢紊乱的关键因素[60]. 日粮补充支链氨基酸可促进肠道*Ruminococcus flavefaciens*等产乙酸菌群增殖, 从而通过乙酸信号调节宿主脂质代谢[61]. 肠道中色氨酸除了被吸收合成蛋白质外, 还能被微生物代谢为吲哚、硫酸吲哚酚、色胺、粪臭素和吲哚衍生物[62]. Beaumont等人[63]发现, 色氨酸代谢产物吲哚能通过核因子-κB(nuclear factor-κB, NF-κB)信号通路缓解肥胖小鼠肝脏中内毒素诱导的炎症, 且提高肝内4β-羟胆固醇水平调控胆固醇代谢. 同时, 吲哚-3-乙酸(indole-3-acetic acid, IAA)和吲哚-3-丙酸(indole-3-propionic acid, IPA)等其他吲哚衍生物都表现出调控脂质代谢的作用[64,65]. 不仅如此, Ottosson等人[38]发现, *Blautia*, *Dorea*, *Ruminococcus*和*SHA-98*等肠道菌群与谷氨酸和支链氨基酸等BMI(body mass index)预测血浆代谢物之间具有密切联系, 表明这些代谢物也可能是连接肠道菌群与肥胖的重要因子. 以上研究提

示，微生物介导的肠道氨基酸代谢可能参与宿主脂质代谢，但是其代谢途径以及如何靶向调控宿主脂质代谢仍需要进一步研究.

2.4　肠道微生物-内毒素-脂质代谢

内毒素(endotoxin)是革兰氏阴性菌中存在的毒性物质的总称, 通常指的是外膜成分中的脂多糖(lipopolysaccharide, LPS)[66]. LPS可以通过肠道细胞旁途径直接扩散进入宿主循环系统，此外，肠道上皮细胞能将LPS转运至高尔基复合体中，并竞争性地与乳糜微粒结合进入循环系统[67]. 因此，LPS的吸收量与食物中脂肪含量成正比[67]. 同时，高脂饮食还能增加肠道中的产LPS菌，诱导小鼠回肠肿瘤坏死因子α(tumor necrosis factor α, TNF-α)的表达和NF-κB信号通路的激活[68]. LPS以及TNF-α是细胞凋亡信号-调节激酶1(apoptosis signal-regulating kinase 1, ASK1)的激活剂，其对脂肪组织褐变起抑制作用，引起能量消耗减少, 间接导致肥胖及相关代谢疾病[69]. 研究显示, LPS能促进白色脂肪组织促炎性细胞因子的产生，并进一步通过改变胰岛素受体底物蛋白的磷酸化来减弱胰岛素信号，最终导致胰岛素抵抗和脂质代谢紊乱[70]. 不仅如此，Liu等人[71]研究发现，LPS能作用于巨噬细胞使其分泌细胞因子(如TNF-α)诱导半胱天冬酶-3(caspase-3)的激活，从而抑制肠道对脂肪酸的吸收摄取.

2.5　肠道微生物节律与脂质代谢

绝大多数哺乳动物都存在24小时左右的昼夜节律，而引起昼夜节律变化的核心机制是存在于大多数细胞中的细胞自主转录-翻译反馈环，表现为宿主各种生理代谢的昼夜节律变化[72]. 最近研究显示, 肠道微生物组成和代谢产物也存在24小时的昼夜节律[73]. 本团队[11]研究发现, 肠道菌群中与节律基因表达相关的有29个菌属, 而不同时间点(8: 00和16: 00)的粪菌移植对小鼠脂质代谢指标影响存在差异，进一步证实肠道微生物节律性. 同时, 肠道微生物节律曲线在小鼠饲喂高脂日粮模型中存在明显差异，提示肠道微生物节律可能参与宿主脂质代谢. Wang等人[74]也发现，高脂日粮破坏了小鼠肠道微生物的节律，而蛋氨酸限饲对肠道微生物节律紊乱具有缓解作用，并时间特异性地增加了产短链脂肪酸菌属丰度，从而影响脂质代谢反应. 此外，Kuang等人[75]研究表明，微生物菌群可以通过组蛋白脱乙酰酶3(histone deacetylase 3)调控上皮细胞组蛋白乙酰化的昼夜节律，最终影响宿主脂肪的吸收和β氧化. 尽管过去几年在昼夜节律和脂质代谢方面取得了一些研究进展，但是肠道微生物节律驱动机制及其如何调控宿主脂质代谢的详细机制目前尚不明确，仍需进一步研究.

3　总结

宿主体内脂质代谢水平可以反应宿主的健康程度，而研究表明，体内的肠道微生物与脂质代谢疾病有关(表1). 肠道微生物与脂质代谢的关系主要表现在脂质代谢紊乱能改变肠道微生物组成, 而重塑肠道微生物组成也能改善宿主脂质代谢. 因此，筛选影响脂质代谢的益生菌对改善和预防肥胖的发生具有重要的意义. 此外，关于肠道微生物与宿主脂质代谢的互作机制作为热点话题获得了国内外广泛关注, 目前研究提示，肠道微生物可能通过其代谢产物(如短链脂肪酸、次级胆汁酸、三级胆汁酸、氨基酸以及LPS等)直接或间接调控宿主脂质代谢(图1)，但是其不同代谢产物产生菌属以及介导脂质代谢作用途径仍需进一步研究; 此外, 本团队和其他研究者均发现, 肠道微生物昼夜节律会影响宿主自身代谢的昼夜节律，微生物节律的紊乱可对宿主脂质代谢产生影响, 而脂质代谢也存在昼夜节律，二者如何连接仍不清楚; 近年来也有研究发现, 微生物鞭毛、微生物DNA以及miRNA等也参与微生物与宿主脂质代谢[76]，但是其不同作用机制仍需深入研究；肠道脂肪吸收是机体脂肪沉积的重要前提, 肠道脂肪转运和代谢广泛参与机体脂质代谢, 目前关于微生物与宿主脂质代谢的研究主要集中于脂肪沉积, 而微生物如何调控肠道脂肪吸收机制仍报道较少; 不同物种、品系拥有不同的肠道微生物菌群，且对脂肪吸收代谢响应各不相同, 本团队正在开展地方特色猪种资源肠道微生物筛选研究，以期解析地方猪种脂肪沉积的微生物机制; 同时，肠道微生物受摄入营养水平和组成影响，通过精准营养理论调控宿主脂质代谢也需要进一步研究[77]. 总之, 肠道微生物参与宿主脂质代谢机制复杂, 通过多层次全面探索肠道微生物介导肠道脂肪吸收

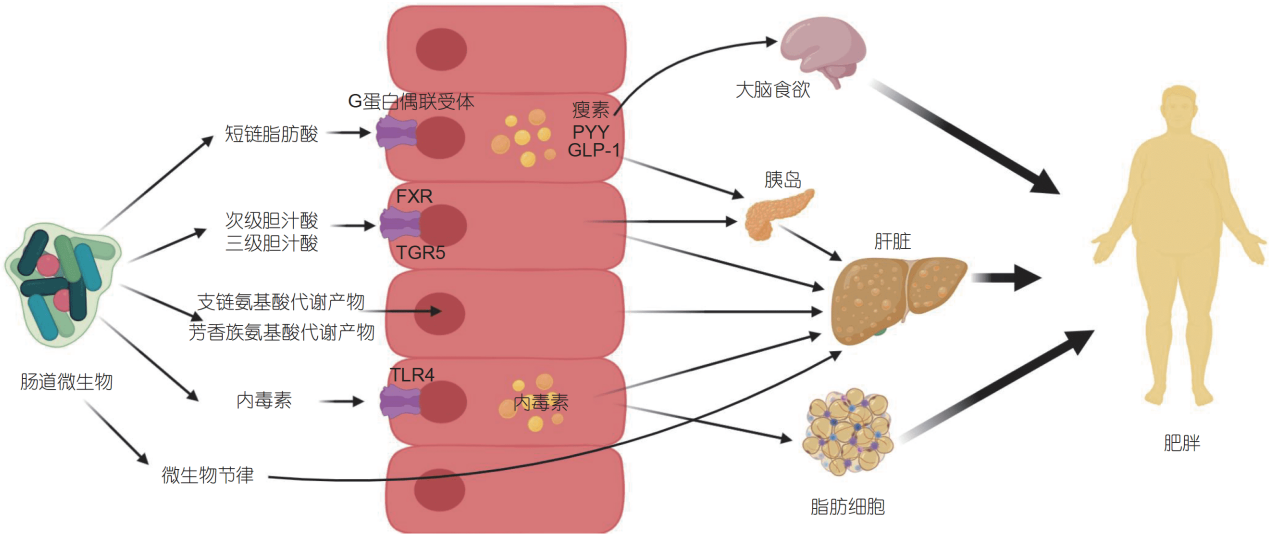

图 1 肠道微生物调控宿主脂质代谢机制

Figure 1 The mechanisms of gut microbiota-mediated host lipid metabolism

和宿主脂肪沉积机制, 有助于提高人们对微生物和宿主脂质代谢互作的认识, 并通过靶向调控肠道微生物组成和代谢改善宿主脂质代谢, 为预防和治疗肥胖提供理论依据.

致谢 感谢湖南农业大学动物科学技术学院动物营养基因组与种质创新研究中心提供帮助.

参考文献

1 Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell, 2016, 164: 337–340
2 Wang T W, Cao Y H, Yang G, et al. Effects of lactic acid bacteria on the quality of silage and health of ruminants (in Chinese). Sci Sin Vitae, 2020, 50: 927–938 [王天威, 曹艳红, 杨果, 等. 乳酸菌对青贮品质及草食家畜健康的影响. 中国科学: 生命科学, 2020, 50: 927–938]
3 Clarke G, Stilling R M, Kennedy P J, et al. Minireview: Gut microbiota: the neglected endocrine organ. Mol Endocrinol, 2014, 28: 1221–1238
4 Lee C J, Sears C L, Maruthur N. Gut microbiome and its role in obesity and insulin resistance. Ann N Y Acad Sci, 2020, 1461: 37–52
5 Kobyliak N, Conte C, Cammarota G, et al. Probiotics in prevention and treatment of obesity: a critical view. Nutr Metab (Lond), 2016, 13: 14
6 Lee P, Yacyshyn B R, Yacyshyn M B. Gut microbiota and obesity: An opportunity to alter obesity through faecal microbiota transplant (FMT). Diabetes Obes Metab, 2019, 21: 479–490
7 Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol, 2021, 19: 55–71
8 Abenavoli L, Scarpellini E, Colica C, et al. Gut microbiota and obesity: a role for probiotics. Nutrients, 2019, 11: 2690
9 Turnbaugh P J, Bäckhed F, Fulton L, et al. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe, 2008, 3: 213–223
10 Velagapudi V R, Hezaveh R, Reigstad C S, et al. The gut microbiota modulates host energy and lipid metabolism in mice. J Lipid Res, 2010, 51: 1101–1112
11 Yin J, Li Y, Han H, et al. Administration of exogenous melatonin improves the diurnal rhythms of the gut microbiota in mice fed a high-fat diet. mSystems, 2020, 5
12 Ley R E, Bäckhed F, Turnbaugh P, et al. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA, 2005, 102: 11070–11075
13 Collado M C, Isolauri E, Laitinen K, et al. Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women.

Am J Clin Nutr, 2008, 88: 894–899
14 Zhang H, DiBaise J K, Zuccolo A, et al. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci USA, 2009, 106: 2365–2370
15 Kalliomäki M, Carmen Collado M, Salminen S, et al. Early differences in fecal microbiota composition in children may predict overweight. Am J Clin Nutr, 2008, 87: 534–538
16 Duncan S H, Lobley G E, Holtrop G, et al. Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes, 2008, 32: 1720–1724
17 Turnbaugh P J, Ley R E, Mahowald M A, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature, 2006, 444: 1027–1031
18 Armougom F, Henry M, Vialettes B, et al. Monitoring bacterial community of human gut microbiota reveals an increase in *Lactobacillus* in obese patients and *Methanogens* in anorexic patients. PLoS ONE, 2009, 4: e7125
19 Nadal I, Santacruz A, Marcos A, et al. Shifts in clostridia, *Bacteroides* and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. Int J Obes, 2009, 33: 758–767
20 Santacruz A, Marcos A, Wärnberg J, et al. Interplay between weight loss and gut microbiota composition in overweight adolescents. Obesity, 2009, 17: 1906–1915
21 Schwiertz A, Taras D, Schäfer K, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity, 2010, 18: 190–195
22 Balamurugan R, George G, Kabeerdoss J, et al. Quantitative differences in intestinal *Faecalibacterium prausnitzii* in obese Indian children. Br J Nutr, 2010, 103: 335–338
23 Santacruz A, Collado M C, García-Valdés L, et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr, 2010, 104: 83–92
24 Abdallah Ismail N, Ragab S H, Abd Elbaky A, et al. Frequency of Firmicutes and Bacteroidetes in gut microbiota in obese and normal weight Egyptian children and adults. Arch Med Sci, 2011, 3: 501–507
25 Furet J P, Kong L C, Tap J, et al. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: Links with metabolic and low-grade inflammation markers. Diabetes, 2010, 59: 3049–3057
26 Zuo H J, Xie Z M, Zhang W W, et al. Gut bacteria alteration in obese people and its relationship with gene polymorphism. World J Gastroenterol, 2011, 17: 1076–1081
27 Vael C, Verhulst S L, Nelen V, et al. Intestinal microflora and body mass index during the first three years of life: an observational study. Gut Pathog, 2011, 3: 8
28 Patil D P, Dhotre D P, Chavan S G, et al. Molecular analysis of gut microbiota in obesity among Indian individuals. J Biosci, 2012, 37: 647–657
29 Xu P, Li M, Zhang J, et al. Correlation of intestinal microbiota with overweight and obesity in Kazakh school children. BMC Microbiol, 2012, 12: 283
30 Munukka E, Wiklund P, Pekkala S, et al. Women with and without metabolic disorder differ in their gut microbiota composition. Obesity, 2012, 20: 1082–1087
31 Million M, Maraninchi M, Henry M, et al. Obesity-associated gut microbiota is enriched in *Lactobacillus reuteri* and depleted in *Bifidobacterium animalis* and *Methanobrevibacter smithii*. Int J Obes, 2012, 36: 817–825
32 Simões C D, Maukonen J, Kaprio J, et al. Habitual dietary intake is associated with stool microbiota composition in monozygotic twins. J Nutr, 2013, 143: 417–423
33 Ferrer M, Ruiz A, Lanza F, et al. Microbiota from the distal guts of lean and obese adolescents exhibit partial functional redundancy besides clear differences in community structure. Environ Microbiol, 2013, 15: 211–226
34 Bervoets L, Van Hoorenbeeck K, Kortleven I, et al. Differences in gut microbiota composition between obese and lean children: A cross-sectional study. Gut Pathog, 2013, 5: 10
35 Tims S, Derom C, Jonkers D M, et al. Microbiota conservation and BMI signatures in adult monozygotic twins. ISME J, 2013, 7: 707–717
36 Zeng Q, Li D, He Y, et al. Discrepant gut microbiota markers for the classification of obesity-related metabolic abnormalities. Sci Rep, 2019, 9: 13424
37 Ozato N, Saito S, Yamaguchi T, et al. Blautia genus associated with visceral fat accumulation in adults 20–76 years of age. NPJ Biofilms Microbiomes, 2019, 5: 28

38 Ottosson F, Brunkwall L, Ericson U, et al. Connection between BMI-related plasma metabolite profile and gut microbiota. J Clin Endocrinol Metab, 2018, 103: 1491–1501
39 Yin J, Li Y, Han H, et al. Melatonin reprogramming of gut microbiota improves lipid dysmetabolism in high-fat diet-fed mice. J Pineal Res, 2018, 65: e12524
40 Alexander C, Swanson K S, Fahey Jr G C, et al. Perspective: physiologic importance of short-chain fatty acids from nondigestible carbohydrate fermentation. Adv Nutr, 2019, 10: 576–589
41 den Besten G, Lange K, Havinga R, et al. Gut-derived short-chain fatty acids are vividly assimilated into host carbohydrates and lipids. Am J Physiol Gastrointest Liver Physiol, 2013, 305: G900–G910
42 Schoeler M, Caesar R. Dietary lipids, gut microbiota and lipid metabolism. Rev Endocr Metab Disord, 2019, 20: 461–472
43 Chen Y, Xu C, Huang R, et al. Butyrate from pectin fermentation inhibits intestinal cholesterol absorption and attenuates atherosclerosis in apolipoprotein E-deficient mice. J Nutr Biochem, 2018, 56: 175–182
44 Liang Y, Lin C, Zhang Y, et al. Probiotic mixture of *Lactobacillus* and *Bifidobacterium* alleviates systemic adiposity and inflammation in non-alcoholic fatty liver disease rats through Gpr109a and the commensal metabolite butyrate. Inflammopharmacology, 2018, 26: 1051–1055
45 Araújo J R, Tazi A, Burlen-Defranoux O, et al. Fermentation products of commensal bacteria alter enterocyte lipid metabolism. Cell Host Microbe, 2020, 27: 358–375.e7
46 Perry R J, Peng L, Barry N A, et al. Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome. Nature, 2016, 534: 213–217
47 Šarenac T M, Mikov M. Bile acid synthesis: from nature to the chemical modification and synthesis and their applications as drugs and nutrients. Front Pharmacol, 2018, 9: 939
48 Behr C, Slopianka M, Haake V, et al. Analysis of metabolome changes in the bile acid pool in feces and plasma of antibiotic-treated rats. Toxicol Appl Pharmacol, 2019, 363: 79–87
49 Foley M H, O'Flaherty S, Barrangou R, et al. Bile salt hydrolases: Gatekeepers of bile acid metabolism and host-microbiome crosstalk in the gastrointestinal tract. PLoS Pathog, 2019, 15: e1007581
50 Yao L, Seaton S C, Ndousse-Fetter S, et al. A selective gut bacterial bile salt hydrolase alters host metabolism. eLife, 2018, 7: e37182
51 Joyce S A, MacSharry J, Casey P G, et al. Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. Proc Natl Acad Sci USA, 2014, 111: 7421–7426
52 Chiang J Y L, Ferrell J M. Bile acid metabolism in liver pathobiology. Gene Expr, 2018, 18: 71–87
53 Ramírez-Pérez O, Cruz-Ramón V, Chinchilla-López P, et al. The role of the gut microbiota in bile acid metabolism. Ann Hepatol, 2017, 16: S21–S26
54 Chen X, Lou G, Meng Z, et al. TGR5: a novel target for weight maintenance and glucose metabolism. Exp Diabetes Res, 2011, 2011: 1–5
55 Keitel V, Häussinger D. Role of TGR5 (GPBAR1) in liver disease. Semin Liver Dis, 2018, 38: 333–339
56 Bensalem A, Murtaza B, Hichami A, et al. Bile acid receptor TGR5 is critically involved in preference for dietary lipids and obesity. J Nutr Biochem, 2020, 76: 108298
57 Zheng X, Chen T, Jiang R, et al. Hyocholic acid species improve glucose homeostasis through a distinct TGR5 and FXR signaling mechanism. Cell Metab, 2020, doi: 10.1016/j.cmet.2020.11.017
58 Abdallah A, Elemba E, Zhong Q, et al. Gastrointestinal interaction between dietary amino acids and gut microbiota: with special emphasis on host nutrition. Curr Protein Pept Sci, 2020, 21: 785–798
59 Ma N, Ma X. Dietary amino acids and the gut-microbiome-immune axis: physiological metabolism and therapeutic prospects. Comprehens Rev Food Sci Food Saf, 2019, 18: 221–242
60 Ejtahed H S, Angoorani P, Soroush A R, et al. Gut microbiota-derived metabolites in obesity: a systematic review. Biosci Microbiota Food Health, 2020, 39: 65–76
61 Iwao M, Gotoh K, Arakawa M, et al. Supplementation of branched-chain amino acids decreases fat accumulation in the liver through intestinal microbiota-mediated production of acetic acid. Sci Rep, 2020, 10: 18768
62 Gao J, Xu K, Liu H, et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. Front Cell Infect Microbiol, 2018, 8: 13
63 Beaumont M, Neyrinck A M, Olivares M, et al. The gut microbiota metabolite indole alleviates liver inflammation in mice. FASEB J, 2018, 32:

6681–6693
64 Ji Y, Gao Y, Chen H, et al. Indole-3-acetic acid alleviates nonalcoholic fatty liver disease in mice via attenuation of hepatic lipogenesis, and oxidative and inflammatory stress. Nutrients, 2019, 11: 2062
65 Zhao Z H, Xin F Z, Xue Y, et al. Indole-3-propionic acid inhibits gut dysbiosis and endotoxin leakage to attenuate steatohepatitis in rats. Exp Mol Med, 2019, 51: 1–14
66 Rietschel E T, Kirikae T, Schade F U, et al. Bacterial endotoxin: molecular relationships of structure to activity and function. FASEB J, 1994, 8: 217–225
67 Ghoshal S, Witta J, Zhong J, et al. Chylomicrons promote intestinal absorption of lipopolysaccharides. J Lipid Res, 2009, 50: 90–97
68 Konrad D, Wueest S. The gut-adipose-liver axis in the metabolic syndrome. Physiology, 2014, 29: 304–313
69 Lucchini F C, Wueest S, Challa T D, et al. ASK1 inhibits browning of white adipose tissue in obesity. Nat Commun, 2020, 11: 1642
70 Moreira A P B, Texeira T F S, Ferreira A B, et al. Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. Br J Nutr, 2012, 108: 801–809
71 Liu H, Kai L, Du H, et al. LPS inhibits fatty acid absorption in enterocytes through TNF-α secreted by macrophages. Cells, 2019, 8: 1626
72 Liang X, FitzGerald G A. Timing the microbes: the circadian rhythm of the gut microbiome. J Biol Rhythms, 2017, 32: 505–515
73 Li Y, Ma J, Yao K, et al. Circadian rhythms and obesity: Timekeeping governs lipid metabolism. J Pineal Res, 2020, 69
74 Wang L, Ren B, Hui Y, et al. Methionine restriction regulates cognitive function in high-fat diet-fed mice: roles of diurnal rhythms of SCFAs producing- and inflammation-related microbes. Mol Nutr Food Res, 2020, 64: 2000190
75 Kuang Z, Wang Y, Li Y, et al. The intestinal microbiota programs diurnal rhythms in host metabolism through histone deacetylase 3. Science, 2019, 365: 1428–1434
76 Li Y M, Li N S, Zhao W G. Advancements in microRNA research in dyslipidemia (in Chinese). Sci Sin Vitae, 2020, 50: 954–965 [李圆梦, 李乃适, 赵维纲. 微RNA在血脂异常研究中的进展. 中国科学: 生命科学, 2020, 50: 954–965]
77 Yin Y L. Animal nutrition: precise nutrition and intestinal barrier wall in the era of no antibiotic (in Chinese). Sci Sin Vitae, 2020, 50: 895–896 [印遇龙. 动物营养学: 无抗时代下的精准营养与肠道城墙. 中国科学: 生命科学, 2020, 50: 895–896]

Recent advances in the interaction between gut microbiota/metabolites and host lipid metabolism

GONG SaiMing[1], MA Jie[1], LI FengNa[2], LI TieJun[2], LIU Gang[3], TAN BiE[1], HUANG XingGuo[1], YIN Jie[1] & YIN YuLong[1,2]

1 College of Animal Science and Technology, Hunan Agricultural University, Changsha 410128, China;
2 Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha 410125, China;
3 College of Bioscience and Biotechnology, Hunan Agricultural University, Changsha 410128, China

In recent years, the study of gut microbiota and host lipid metabolism has received widespread attention. Firstly, the diversity and compositions of gut microbiota are significantly altered in animal models of lipodystrophia or human clinical trials, and the host lipid metabolism can also be regulated by reshaping the gut microbiota compositions using fecal bacteria transplantation, probiotics, and nutritional interventions. In this paper, we discuss the link between gut microbes and host metabolism, and summarize the studies focusing on the mechanisms of lipid metabolism regulated by gut microbes: short-chain fatty acids, bile acids, amino acids, endotoxin and microbial rhythms, in order to provide targets for nutritional intervention in lipid dysmetabolism-caused diseases.

gut microbes, lipid metabolism, obesity

doi: 10.1360/SSV-2020-0396