肠道菌群调控代谢性疾病发生和发展

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摘要 人体肠道是一个巨大的复杂生态系统, 肠道菌群、营养物质和宿主细胞的相互作用及其稳态对宿主健康以及疾病的发生发展至关重要。肠道菌群的各种菌落具有众多功能, 如参与营养物质的合成与分解代谢、形成肠道天然屏障等。肠道菌群紊乱会对健康造成负面影响, 许多代谢性疾病的发生和发展均与肠道菌群紊乱存在密切关系。肠道菌群与健康及疾病之间的紧密关系已引起人们对益生菌的关注。益生菌可调节肠道菌群稳态并预防代谢性疾病的发生和发展。本文回顾了肠道菌群尤其是益生菌在肥胖和糖尿病等代谢性疾病发生发展中的作用及其作用机理, 并且评估了益生菌在治疗代谢性疾病中的转化应用价值。

关键词 肠道菌群, 益生菌, 肥胖, 糖尿病

超重/肥胖(overweight/obesity)和2型糖尿病(type 2 diabetes mellitus, T2DM)等代谢性疾病的防治是全球性公共卫生问题。超重/肥胖和T2DM的患病率在世界范围内呈现逐年上升的趋势, 其增速逐年加快。糖尿病的发病率在世界公共卫生的非传染性疾病类别中排第4位, 肥胖和超重人群的患病人数从1980年的8.57亿增加到2013年的21亿^[1]。糖尿病的全球管理成本日益增加, 预计到2030年可能达到2.1万亿美元^[2], 给社会和家庭带来沉重的医疗和经济负担, 其相关的治疗和管理也充满挑战。

目前低成本和高热量摄入的饮食结构, 伴随缩减的体育运动时间和长时间久坐不动的生活及工作模式,

极大地减少了机体能量消耗, 加速超重/肥胖的发生和发展^[3]。肥胖是与T2DM发病相关的重要危险因素之一^[4]。然而, 环境和遗传因素的结合并不能完全解释超重/肥胖和T2DM的发病机理。研究发现, 基因和免疫系统等其他因素可以部分解释肥胖症和T2DM及其代谢并发症的发生和发展^[5]。近期研究表明, 宿主微生物在T2DM的发生发展过程中扮演了重要的角色^[6]。肠道菌群的不一致性(也称为营养不良型)与T2DM密切相关。据报道, T2DM患者的肠道菌群主要由机会性病原体组成, 伴随有益微生物数量的减少, 尤其是产丁酸盐的肠道细菌^[7]。

广义的益生菌是活的非致病性微生物, 可用于改

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善宿主体内微生物的平衡^[8],而狭义的益生菌是指食品级的益生菌。世界卫生组织和联合国粮食及农业组织专家工作组还定义了被视为益生菌的细菌菌株的特性^[9],其中包括:(1)该菌株必须到达其作用部位(通常是肠道);(2)在摄取过程中能够承受生理压力,如胃肠道酸碱环境;(3)菌株必须被证明对宿主有益;(4)菌株的摄入不会对宿主造成任何风险;(5)菌株在制造过程中必须保持其特性,并能维持稳定性且可保存在其所混入的基质中。

益生菌的作用方式与宿主微生物群的调节有关。最早提出的一种作用方式^[10]是机体对病原菌的“屏障”效应,也称为机体对定植的抗性,即限制或防止其定植。此作用方式可能是由产生广谱抗菌肽或代谢产物(如短链脂肪酸)导致pH降低而对细菌生长不利,或者是由具有抗菌活性的生物表面活性剂所产生。这种屏障作用可通过多种机制起作用,如竞争结合位点、抑制黏附等。第二种作用方式^[10]涉及肠黏膜屏障功能的改善。这种屏障功能与肠上皮细胞之间紧密连接的质量有关。潘氏细胞和黏液细胞所产生的抗菌肽以黏液的形式充当保护层,防止机体与肠腔细菌的直接接触。而益生菌可以在信号传导途径水平上起作用,从而导致黏液层增加或防御素生成,并通过作用于紧密连接蛋白从而改善生理屏障。第三种作用方式^[10]是免疫系统的调节。免疫反应的激活需要识别先天免疫细胞的特定受体,即模式识别受体(pattern recognition receptor, PRR),具体包括Toll样(toll-like receptor, TLR)和核苷酸结合寡聚域剂(nucleotide-binding oligomerization domain, NOD)。特定受体可被微生物相关分子模式即微生物表面重出现的结构性成分所识别,从而与肠道上皮相互作用,并刺激固有层水平的肠道免疫系统细胞^[11]。越来越多的研究证据表明,肠道菌群与宿主的遗传学、饮食以及其他环境因素相互作用,肠道菌群功能的改善有助于防治超重/肥胖和糖尿病及其并发症的发生和发展。本文回顾了肠道菌群在肥胖症、T2DM等代谢性疾病发生和发展过程中所扮演的角色,并且重点阐述了益生微生物在代谢性疾病防治过程中转化应用的最新研究进展。

1 肠道菌群与肥胖

1.1 肠道菌群紊乱参与肥胖的发生和发展

体重与肠道菌群组之间的关联已成为当前代谢性

疾病研究的热点之一。众多研究指出,改变啮齿动物中的肠道菌群组成和功能可降低体脂含量并改善胰岛素敏感性^[5]。Turnbaugh等人^[12]首次证明,利用粪菌移植的方法将遗传性肥胖小鼠(*ob/ob*小鼠)的肠道微生物组转移至无菌小鼠可导致后者体脂和体重增加,这种关联已被饮食诱导肥胖的啮齿动物肠道微生物组和肥胖人类肠道微生物组所证实^[13,14]。此外,将具有不同表型的肥胖症双胞胎的粪便移植至无菌小鼠,可诱导出人类供体的各自表型^[12]。这些细菌与乳酸、乙酸盐和丁酸盐水平的升高存在密切关系,它们是脂肪酸合成的底物。肠道菌群低多样性还与肥胖的相对风险升高存在密切关系。然而该研究并未阐明肠道菌群与肥胖发生的因果关系。本课题组前期已自主分离5株益生菌,并利用益生菌发酵代谢产物干预正常和高脂饮食饲养的小鼠。实验结果显示,益生菌发酵代谢产物显著抑制高脂饲料诱导的体重的增加速率。糖耐量实验结果显示,此益生菌发酵产物显著改善胰岛素敏感性(insulin resistance, IR)。此外,我们还研究发现,益生菌发酵产物可促进肥胖小鼠白色脂肪组织米色样变,增加产热相关基因及蛋白表达,减少棕色脂肪组织、肝脏组织的脂质异位堆积。此外,细菌低丰富度与肥胖及其代谢并发症有关^[5,14-16]。可以根据肠道中所携带的细菌基因的数量来对个体进行分类^[17]。Le Chatelier等人^[17]根据其微生物组中存在的基因数量(低基因计数或高基因计数)对169名肥胖和123名非肥胖丹麦受试者进行了分类,结果显示超重或肥胖患者是低基因计数组的主要人群。Kasai等人^[18]的研究指出,与23名非肥胖受试者相比,33名日本肥胖受试者的细菌多样性显著降低。研究结果显示,丰富的肠道菌群结构有助于机体吸收食物中的营养物质、增强免疫力和控制体重等。肠道菌群多样性的降低则会导致肠道内硫化氢、氨、酚、靛基质等有毒物质增加,进一步对心、脑、肝和肾等重要脏器造成损伤,增加多种疾病的发病风险。微量元素的过多摄入或者不足会不同程度地引起人体生理异常甚至引发疾病。铁元素是个体生长、细胞代谢和免疫反应所必需的微量元素。铁稳态的失调与各种疾病的发生和发展有关。Zhao等人^[19]通过分析表明,与非超重人群相比,超重和肥胖人群中低铁蛋白血症的患病率更高。并对血液铁标志物的荟萃分析显示,血清铁浓度和转铁蛋白饱和度(transferrin saturation, TS)存在显著差异,这两种标志物用于测量循环铁水平的重要标志物。肥胖与机体缺铁的风险呈正相关。多项研究表明,

铁的失衡会导致肠道菌群的变化,从而导致微生物多样性的破坏、病原体丰度的增加以及肠道炎症的发生.本团队^[20]利用C57BL/6J小鼠构建了铁紊乱动物模型,结合机器学习算法可以利用肠道菌群精确地预测肠上皮细胞和肝脏的铁水平,并可能作为一种无创方式用于铁代谢异常相关疾病的早期辅助诊断.扩增子测序和生物信息学分析结果表明,来自同一个地区的肥胖和非肥胖受试者的肠道菌群组成存在显著差异.研究还发现,超重/肥胖患者的厚壁菌门/拟杆菌门比率(F/B)更高,并且随着身体质量指数(body mass index, BMI)的增加,女性的这一比例存在更高的趋势^[21].减肥手术和减轻体重后,该比率随着厚壁菌门的减少和拟杆菌门的增加而降低^[22-24].然而,有学者认为,厚壁菌门比拟杆菌门更能有效地作为一种指标,从而促进热量有效存储和体重增加^[12].Turnbaugh等人^[12]比较肥胖和健康的双胞胎肠道菌群发现,厚壁菌门在肥胖受试者的微生物区系中占主导地位,并且富集与营养素转运蛋白相关的基因.在瘦双胞胎的微生物群落中发现了较高的拟杆菌门相对丰度和与碳水化合物代谢有关的基因的富集.然而,在Schwartz等人^[25]的研究中,超重和肥胖受试者中厚壁菌门与拟杆菌门的比例与体重变化不一致.有学者认为,这种现象与肠道厌氧细菌的相对比例和血糖水平之间的关系有关,即较高的血糖水平与老年人肠道中拟杆菌的相对比例呈负相关^[26].但是,荟萃分析发现,该比率与BMI或肥胖之间存在弱关联,强调该比率或特定的微生物特征无法区分正常人与肥胖人^[27,28].值得注意的是,这种统计学差异可能是由于人种差异、样本量不足和研究方法不同所造成的.针对肠道菌群组成的研究表明,肥胖与菌群多样性降低,尤其与颤藻菌属、双歧杆菌属及阿克曼菌属的数量减少有关^[29].

总体而言,截至目前的大多数研究显示,肥胖受试者的肠道菌群具有低多样性的特点,但针对健康或肥胖的肠道菌群组的精准微生物组成仍然存在很多争议,相关结论需要更多可重复的实验数据支撑^[18].因此,仍有必要在生物门的水平(即 F/B)或更深的属、种水平进一步探索.就当前研究方法而言,本团队开发了基于机器学习算法,使用包括随机森林和LASSO回归模型在内的两个机器学习模型构建预测的模型,有助于识别肠道菌群中关键分类单元,将模型中的关键分类单元合并以用作关键分类单元来预测组织中微量元素的含量^[20].此外,标本取样及DNA提取方案的标准化、生

物信息学分析的应用以及进行大规模的前瞻性研究是探索肠道菌群在代谢性疾病研究中获得足够可重复性的重要手段.

1.2 肠道菌群及其代谢产物与肥胖和代谢紊乱之间的生物学联系

1.2.1 短链脂肪酸与肥胖和代谢紊乱之间的生物学联系

肠道菌群参与食物中营养元素的分解和合成代谢.人体中约有10%循环代谢物来自细菌,并参与人类的系统代谢调控^[30].在近端结肠,碳水化合物经肠道细菌发酵后可产生短链脂肪酸(short-chain fatty acids, SCFAs).大量体内外研究显示,SCFAs是预防和治疗肥胖症及相关代谢紊乱的有益微生物代谢物^[31].相反,在远端结肠中,蛋白质水解发酵可产生如支链脂肪酸(branched chain fatty acid, BCAAs)、酚和氨等多种有害的代谢产物. SCFAs是具有2~6个碳原子的有机脂肪酸,如丁酸盐、乙酸盐和丙酸盐. SCFAs除在调节结肠功能方面发挥重要作用外,还可被吸收并调节多个代谢性器官(肌肉、脂肪、肝等功能)^[5].与体型偏瘦的个体相比,肥胖和IR的受试者肠道SCFAs存在显著差异^[32].一方面,Fernandes等人^[33]的研究表明,由于肥胖人群结肠发酵的差异,其粪便样本中的SCFAs含量低于正常人群.另一方面,SCFAs可减少机体脂肪积累并控制体重^[32,34,35]. SCFAs发挥减脂作用的机制可能与促进饱腹感、激活脂肪组织产热有关.研究发现,丁酸酯作用于肠细胞从而增加胰高血糖素样肽1(glucagon-like peptide-1, GLP-1)的产生,丙酸酯影响肠道糖异生从而改善葡萄糖稳态和饱腹感^[29,34,35]. SCFA还可以刺激厌食性肽YY(peptide YY, PYY)和脂肪组织饱腹激素瘦素的分泌^[29].此外,丁酸酯可通过增加线粒体功能、促进产热并进一步通过肠道-大脑神经回路激活棕色脂肪组织来增加能量消耗,并呈现抗炎特性^[36,37].

1.2.2 支链脂肪酸与肥胖和代谢紊乱之间的生物学联系

在肥胖、IR、T2DM动物模型以及患者体内发现了较高的循环支链氨基酸(BCAAs)和芳香族氨基酸. BCAAs水平的降低与胰岛素敏感性的提高密切相关,而不仅仅是体重的减轻^[38].肠道菌群尤其是拟杆菌,可以提高BCAAs降解的效率^[39].在多组学研究发现,IR患者肠道菌群具有丰富的BCAA生物合成潜力,而普雷沃氏菌和普通拟杆菌是导致BCAAs生物合成与IR之

间联系的主要物种^[40]。

1.2.3 胆汁酸与肥胖和代谢紊乱之间的生物学联系

肠道菌群也参与胆汁酸(bile acid, BA)代谢。BA可调节胆固醇和甘油三酸酯的代谢,并维持葡萄糖和能量的稳态^[41,42]。肠道菌群与BA代谢密切相关,这种关系由FXR-FGF15-FGFR4介导的肠肝信号转导轴直接调节。最新的研究发现^[43],饮用普洱茶的人群及小鼠肠道中产胆汁酸水解酶(bile acid hydrolase, BSH)的乳杆菌、芽孢杆菌、链球菌和乳球菌的相对丰度降低,且普洱茶中茶黄素可直接抑制肠道BSH酶的活性,抑制小肠中胆汁酸的结合,进而影响肝和血清胆固醇水平。该团队进一步证明了肠道中抑制FXR信号通路以及激活肝脏中FXR信号通路和替代胆汁酸的合成途径,可能是普洱茶改善饮食诱发的肥胖症和高胆固醇血症的重要机制。姜长涛研究团队^[44]报道了初诊T2DM患者口服二甲双胍后,肠道菌群发生重塑,脆弱拟杆菌的丰度下降和结合型胆汁酸甘氨酸熊去氧胆酸(conjugated bile acid glycyursodeoxycholic acid, GUDCA)的含量升高。二甲双胍通过抑制脆弱拟杆菌合成的胆汁酸水解酶活性,使GUDCA的水平增加,提示GUDCA是人法尼醇X受体FXR的内源性拮抗剂,具有潜在的治疗T2DM的作用。二甲双胍通过肠道脆弱拟杆菌-胆汁酸GUDCA-肠FXR代谢轴发挥降糖作用。对肠道菌群和胆汁酸以及代谢性疾病之间的关系已有一定的理解,但仍需更深入的研究阐明肠道菌群在调节胆汁酸池中的作用。

2 肠道菌群与糖尿病

2.1 肠道菌群对T2DM的影响

研究表明,宿主微生物组在糖尿病的发生和管理中起着至关重要的作用,尤其是T2DM。对T2DM患者和健康人群的人体研究^[45-47]报道了乳酸杆菌属的丰度与T2DM之间的正相关关系。值得注意的是,乳酸杆菌属下的若干菌种与T2DM的关联是物种特异性的。如T2DM患者中嗜酸乳杆菌^[48]和加氏乳杆菌^[49]减少,而木糖乳杆菌^[50]增加。这些结果表明,该属细菌对宿主代谢的功能影响呈现高度多样性。多项研究提示,乳酸杆菌属参与调控宿主糖代谢的功能可能与双歧杆菌属协同作用有关。具体而言,一项随机双盲的临床试验发现,患有冠心病的糖尿病患者服用益生菌胶囊(内含嗜酸乳杆菌、双歧杆菌)12周后可显著降低空腹血浆葡

萄糖(fasting plasma glucose, FPG)、血清胰岛素、HOMA- β 和QUICKI的水平^[51]。虽然既往已有多项研究报道鲁米诺球菌属、梭菌属和蓝藻属与T2DM发病呈正相关^[45,52-58],但在菌种水平的研究却发现相互矛盾的结果^[48,58]。肠道菌群对宿主代谢功能影响的不一致性可能是由不同类型的治疗、地域分布等差异造成。

2.2 肠道菌群是影响T2DM患者糖脂代谢的潜在机制

代谢性疾病患者中肠道菌群调控糖脂代谢的分子机制主要有炎症反应、菌群-营养成分互作、肠道通透性、葡萄糖和脂质代谢、胰岛素敏感性和系统能量稳态。

2.2.1 缓解系统炎症症状

T2DM与促炎细胞因子、趋化因子和炎性蛋白水平升高有关,一些肠道菌群和微生物代谢产物会刺激抗炎细胞因子和趋化因子的分泌。例如,肠道中的玫瑰菌、脆弱拟杆菌、嗜黏蛋白-艾克曼菌、植物乳杆菌和干酪乳杆菌诱导白介素-10(interleukin-10, IL-10)可能有助于改善葡萄糖代谢^[59-61]。有研究表明,在肌肉中过表达IL-10可防止与骨骼肌衰老相关的IR的发生^[62]。罗氏弧菌可以增加抗炎细胞因子白介素-22(interleukin-22, IL-22)的产生^[63,64]。已有研究表明,IL-22可以恢复胰岛素敏感性并减轻糖尿病的症状^[65],同时可以促进T调节细胞分化,诱导转化生长因子- β (transforming growth factor- β , TGF- β)并抑制肠道炎症^[60,63,64]。抑制促炎性细胞因子和趋化因子是有益微生物预防炎症的另一种途径。各种乳酸杆菌(植物乳杆菌、副干酪乳杆菌、干酪乳杆菌)可以降低白介素-1 β (interleukin-1 β , IL-1 β)、单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)、细胞间黏附分子-1(cell adhesion molecule-1, CAM-1)、白介素-8(interleukin-8, IL-8)和C反应蛋白(C-reactive protein, CRP)水平^[66,67]。副干酪乳杆菌和脆弱类芽孢杆菌可抑制IL-6的表达。同样,已发现,乳酸杆菌、拟杆菌和艾克曼菌也可以抑制肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)的表达^[68-71]。

2.2.2 降低肠道通透性缓解T2DM症状

人类T2DM伴随肠道通透性的增加,其会导致代谢性内毒素血症^[72]。已经发现两种潜在细菌(拟杆菌和*B. dorei*)的数量增多有益于T2DM患者结肠中紧密连接蛋白的表达,从而导致肠道通透性降低、脂多糖(lipopolysaccharide, LPS)生成的减少以及内毒素血症的减轻^[73]。另一种益生菌——嗜黏蛋白-艾克曼菌,利用细

胞外小泡降低肠道通透性, 这些小泡通过上皮中的AMP依赖的蛋白激酶活化改善了肠道紧密连接^[74]. 该细菌的外膜蛋白增强封闭蛋白(occludin)和紧密连接蛋白1(tight junction protein-1, Tjp-1)的表达, 进而改善肠道完整性. 外膜蛋白还抑制肠道中的1类大麻素受体(cannabinoid receptor 1, CB1), 进而降低肠道通透性和LPS水平. 虽然尚未确定普氏杆菌的特定细菌成分, 但已证明, 培养细菌的发酵液可增强紧密连接蛋白的表达, 改善结肠炎模型中的肠屏障功能^[75]. 此外, 由粪杆菌属生成的丁酸盐也具有通过5-羟色胺转运蛋白和PPAR- γ 途径降低肠道通透性的潜力^[76].

2.2.3 改善代谢器官葡萄糖和脂质代谢

肠道菌群改善T2DM症状的方式有: 改善主要代谢器官(例如肝脏、肌肉和脂肪)的葡萄糖稳态、IR和影响葡萄糖的消化, 调控消化过程中肠道激素的产生. 乳酸双歧杆菌可增加糖原合成, 降低与肝糖异生相关基因的表达^[77]. 乳酸双歧杆菌还可改善葡萄糖转运蛋白4(glucose transporter 4, GLUT4)的转运和胰岛素刺激的葡萄糖摄取. 格氏乳杆菌BNR17还可增加肌肉中GLUT4的表达, 具有潜在地改善糖尿病症状的作用^[78]. 嗜黏蛋白-艾克曼菌和植物乳杆菌可降低肝黄素单加氧酶3(flavin-containing monooxygenase 3, Fmo3)的表达^[66], 已发现将Fmo3基因敲除可防止IR小鼠中高血糖和高脂血症的发生和发展^[79]. 干酪乳杆菌可通过增加肝脏中磷脂酰肌醇-3-激酶(phosphatidylinositol-3-kinase, PI3K)、胰岛素受体底物2(insulin receptor substrate 2, IRS2)、AMP依赖的蛋白激酶、Akt2和糖原合成相关基因表达水平来改善IR^[70,80]. 干酪乳杆菌还通过胆汁酸-氯化物交换机制降低高血糖症, 它还降低白色脂肪组织中的胰岛素降解酶(insulin-degrading enzyme, IDE)和胰岛素样生长因子结合蛋白3(insulin like growth factor binding protein 3, IGFBP-3)来降低T2DM患者血糖^[81]. 某些乳酸杆菌和嗜黏蛋白-艾克曼菌具有强大的 α -葡萄糖苷酶活性抑制功能, 可防止复杂碳水化合物的分解并控制餐后高血糖. 微生物群及其代谢产物可以调节肠道激素和酶, 并改善IR和葡萄糖耐量. 丁酸盐可作为肠道中G蛋白偶联受体的配体, 并促进肠内分泌L细胞释放肠激素GLP-1和PYY.

2.2.4 促进脂肪酸的氧化和能量消耗

增加脂肪酸的氧化和能量消耗并减少脂肪酸的合成可减轻肥胖症, 从而改善T2DM^[82]. 据报道, 嗜黏蛋白-艾克曼菌、产酸拟杆菌、加氏乳杆菌和短链脂肪酸会

增加脂肪组织中的脂肪酸氧化. 嗜黏蛋白-艾克曼菌被发现可增加2-棕榈酰甘油和2-酰基甘油的水平^[83]. 脂肪组织中的2-油酰甘油、2-棕榈酰甘油和2-酰基甘油可增加脂肪酸氧化和促进脂肪分解. 此外, 拟杆菌还可以通过TGR5-PPAR- α 途径改善脂肪组织中的脂肪酸氧化^[84]. 丁酸盐可通过抑制肌肉中的组蛋白脱乙酰基过程, 从而促进脂肪酸利用, 加速线粒体产能, 增加能量消耗^[85]. 在肝脏和脂肪组织中, 丁酸酯和其他两种SCFAs(丙酸酯和乙酸酯)则可降低PPAR- γ 的表达^[32], 从而增加脂肪酸的氧化. 此外, 加氏乳杆菌可通过上调脂肪酸氧化和降低脂肪酸合成相关基因表达来减轻肥胖症^[78]. 而糖尿病啮齿类动物的A嗜黏蛋白-艾克曼菌还可以降低脂质氧化损伤的标志性代谢物丙二醛的水平^[80].

2.3 益生菌调控葡萄糖代谢过程

肠道菌群参与T2DM的临床前动物模型葡萄糖代谢的调控. 国内外研究发现, 双歧杆菌属、拟杆菌属、费氏细菌属、艾克曼属和玫瑰菌属与T2DM呈负相关, 而鲁米诺球菌、梭菌属和蓝藻属与T2DM呈正相关. 拟杆菌和双歧杆菌被认为是辅助治疗T2DM的有益菌属. 几乎所有研究都报道了双歧杆菌属与T2DM之间存在负相关^[45,56,57]. 而双歧杆菌还没有被单独用作T2DM辅助治疗的益生菌, 但双歧杆菌属中多个菌种(长双歧杆菌、婴儿双歧杆菌、动物双歧杆菌、短双歧杆菌)的动物研究均提示该菌属具有改善葡萄糖耐量的作用^[86-90]. 除双歧杆菌属外, 拟杆菌属亦可作为益生菌引入防治T2DM. 在He等人^[91,92]的研究中检测到的23个OTU(OTU: operational taxonomic units, 每一个OTU通常被视为一个微生物物种)中, 有21个与T2DM呈负相关. 在这些研究中, 服用产酸拟杆菌^[84]和单形拟杆菌^[93]可显著改善糖尿病小鼠的葡萄糖耐量和IR. 此外, 有研究发现, 玫瑰双孢菌、粪杆菌和艾克曼菌等菌属也能发挥与产酸拟杆菌(68)和单形拟杆菌相同的作用^[94]. 还有研究发现, 益生菌制剂干预8周, 包括不同浓度的嗜酸乳杆菌、干酪乳杆菌、鼠李糖乳杆菌、保加利亚乳杆菌、短小芽孢杆菌、长双歧杆菌和嗜热链球菌菌株, 以及低聚果糖, 与安慰剂对照相比, T2DM患者的FPG水平显著降低^[95]. 与基线相比, IR指数(HOMA-IR)得分有所提高, 但与安慰剂对照组相比, 益生菌组的HOMA-IR得分相对较低. 此外, 补充益生菌可显著改善T2DM患者的谷胱甘肽水平, 表明补充益生菌可能提高患者的抗氧化状态进而控制糖尿病. 多菌株益生菌

混合物(每天 10^{10} CFU; 嗜酸乳杆菌、干酪乳杆菌、乳酸乳杆菌、双歧杆菌、长双歧杆菌和婴儿双歧杆菌)持续干预12周显示, 除空腹胰岛素和糖化血红蛋白(HbA1c)水平有一定程度的改善外, HOMA-IR、QUICKI(定量胰岛素敏感性检查指数)、超敏C-反应蛋白(hs-CRP)和脂质谱没有明显改善。

众多研究表明, 在遗传性肥胖、糖尿病以及饮食诱发肥胖的小鼠中嗜黏蛋白-艾克曼菌的丰度与体重、脂肪量、炎症、IR和葡萄糖耐量的程度呈负相关^[83,96-99]。嗜黏蛋白-艾克曼菌是一种黏液定殖细菌, 在肠道屏障功能中起着重要作用。Depommier等人^[100]研究发现, 口服嗜黏蛋白-艾克曼菌能够显著降低血浆LPS水平。LPS可能通过与先天免疫细胞表面的CD14-TLR4复合物结合而引发炎症^[83,101,102]。若LPS在局部和全身器官中释放, 将导致代谢性内毒素血症和IR^[72,103]。

据报道, 单益生菌的菌种(孢子乳杆菌^[104,105]、干酪乳杆菌^[106]、罗伊氏乳杆菌^[107])的使用可改善人类T2DM的IR。如植物乳杆菌(*L. plantarum*)是发酵食品中发现的细菌, 研究表明, 该菌可改善饮食诱导和遗传模型的T2DM糖代谢^[108,109]。然而, 该物种在4个临床试验中对葡萄糖代谢没有显著影响^[110-112]。乳酸杆菌混合制剂而非单独服用才出现乳酸杆菌具有抗糖尿病作用^[51,113]。总体而言, 乳杆菌属是高度多样化且在人体肠道的丰度相对较高。乳杆菌属对辅助改善T2DM糖代谢紊乱的功效可能是物种特异性的, 甚至是菌株特异性的, 这或许是细菌属水平分析缺乏一致性的原因。

肠道菌群通过影响宿主体内的各种代谢途径而具有动态的代谢潜力, 部分地解释了肥胖症和糖尿病代谢紊乱的发展。许多研究已证实了益生菌对代谢性疾病存在影响, 例如: 益生菌可缓解慢性肠道炎症, 规律性地服用益生菌可降低罹患结肠癌的风险、腹泻发生率和胆固醇水平, 改善免疫系统。益生菌可通过不同的机制缓解代谢性疾病相关症状, 如减轻炎症、改善肠道通透性和代谢器官糖脂代谢并降低血脂。这些发现提示, 使用益生菌可能有助于降低代谢性疾病的发生发展。然而仍需要更多的研究来阐明其中的机制、替代性治疗的安全性及稳定性。

3 肠道菌群与其他代谢性疾病

3.1 肠道菌群与代谢综合征

肠道菌群与代谢综合征(metabolic syndrome, MS)

是一种复杂的代谢紊乱症候群, 具体表现为肥胖、高血压、高血糖和血脂异常等。在MS模型鼠(tsumura-Suzuki-obese-diabetes mice, TSOD)相关研究发现, 该鼠存在明显肠道失调, 表现为SCFAs分布紊乱^[114]。使TSOD小鼠每日摄入咖啡因和绿原酸16周后, 部分改善了血浆中SCFA水平^[115]。Loomba和Sanyal等人^[116]发现, 遗传缺陷的Toll样受体5(TLR-5)的啮齿类动物会出现嗜食症和肥胖、IR、高脂血症和高血压的增加, 将TLR-5缺陷小鼠的肠道微生物群转移到GF小鼠中将会导致MS特征的出现。

3.2 肠道菌群与非酒精性脂肪肝

肠道菌群与非酒精性脂肪肝(nonalcoholic fatty liver, NAFLD)是全球慢性肝病的主要病因之一, 也是肝细胞癌(hepatocellular carcinoma, HCC)的第三大病因^[117]。NAFLD主要表现为肝脏中脂肪的积累, 定义为肝细胞中脂肪变性>5%。人类粪便宏基因组分析已证明NAFLD患者肠道微生物组的改变, 即NAFLD中存在肠道失调^[118]。NAFLD在儿童和成人患者(尤其是脂肪性肝炎患者)均表现出类杆菌数量增加、硬壁菌数量减少、肠道菌群组成中大肠杆菌属和普氏菌属所占比例更高^[119], 这表明肠道微生物群在NAFLD发病机制中可能发挥作用。相关研究进一步揭示, 肠道微生物组可能参与NAFLD极其严重程度的潜在机制包括: (1) 肠道炎症和通透性功能障碍; (2) 胆汁酸代谢; (3) 厌氧发酵; (4) 通过细菌LPS激活TLR4和丝氨酸激酶, 以及胰岛素受体底物-1的丝氨酸磷酸化^[118]。

4 小结与展望

肠道菌群通过影响宿主体内的各种代谢途径而具有动态的代谢调控潜力。本文部分地剖析了肥胖、T2DM等代谢性疾病发生和发展的机理, 有条理地论述了肠道菌群与肥胖和T2DM的关系, 能够为后续相关研究提供理论基础。近年来, 有关肠道菌群与肥胖和T2DM等代谢性疾病的研究数量呈指数增长。虽然我们对不同肥胖和糖尿病人群有关的微生物特征, 以及它们与饮食、年龄和宿主遗传学的相互作用方面有一定的理解, 但是进行大规模多组学研究不可避免, 以进一步阐明, 肠道菌群与宿主在代谢性疾病的发生和发展中的相互作用。针对肠道菌群及其代谢物与代谢紊乱之间的关系, 开发包括宏基因组学、宏转录组学和高分辨代谢组学在内的新一代多组学技术, 通过揭示和

理解肠道菌群与宿主之间的代谢相互作用, 进而为筛选功能性益生菌、开发益生菌制剂以及优化基于益生

菌制剂的个性化治疗策略提供理论基础, 为防治肥胖和糖尿病及其相关的并发症提供理论和实践依据。

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Summary for “肠道菌群调控代谢性疾病发生和发展”

Intestinal flora regulating the occurrence and development of metabolic diseases

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The human gastrointestinal (GI) tract is a huge and complex micro-ecosystem, hosting trillions of microorganisms including but not limited to bacteria, fungi and viruses. The interactions and homeostasis among gut microorganisms, nutrient metabolism and epithelium of the GI tract are critical to host health. Disrupting the composition of GI microbiota may result in the development and progression of diseases.

Gut bacteria, accounting for more than 90% of GI microorganisms, have shown diverse functions, such as affecting nutrient biosynthesis and bio-degradation, regulating drug metabolism and therapeutic efficacy, as well as maintaining intestinal mucosa structure and function. Numerous studies have demonstrated that the dysbiosis of gut bacteria may interrupt the intestinal and systemic immune homeostasis, leading to the development of various kinds of diseases. Furthermore, pathogenic metabolites released from gut bacteria may also interact with the host. Most metabolic diseases are closely associated with the alteration of gut bacterial structure and function. In recent years, researchers have established the link between metabolic diseases and dysbiosis of gut bacteria, such as type 2 diabetes and obesity. By performing the fecal microbiota transplantation, the obese feature could be reversed in mice, pigs and humans. The above discoveries suggested that fecal microbiota transplantation from healthy individuals could be a potential therapeutic strategy for several metabolic diseases. Diet intervention and exercise are still two important alternative and auxiliary therapeutic approaches for metabolic diseases together with other gut microbiota-related therapy. As food-derived nutrients could directly interact with gut microbiota and alter the composition, diversity and function of gut bacteria, we have found that both the level of dietary iron and host iron storage are closely associated with the composition of gut microbiota.

Other than fecal transplantation-mediated therapy, probiotics have attracted attention as a supplement to improve the gut microenvironment for health-relevant applications, e.g., metabolic disease prevention and auxiliary therapy. Plenty of clinical investigations worldwide have provided first-hand data to support the therapeutic value of probiotics as a potential supplement for metabolic diseases. However, the therapeutic effect varies, which may due to the inconsistent probiotic strains and various dietary habits. In contrast to probiotics, probiotic fermentation metabolites (also named postbiotics) have shown its superior and beneficial effects beyond probiotics. Postbiotics generated by probiotics fermentation could be directly absorbed by the host and improve host systemic metabolic homeostasis. Our unpublished data suggest that postbiotics are able to effectively alleviate HFD-induced body weight gain, improve insulin sensitivity, decrease systemic inflammation and induce white adipocyte beigeing. In *in vitro* adipocyte culture system, purified postbiotics could suppress adipogenesis, and decrease lipid droplet formation.

Overall, in this review, we summarized recent findings of the role of gut microbiota, especially the probiotics, in the development and progression of metabolic diseases such as obesity and type 2 diabetes.

intestinal flora, probiotics, obesity, diabetes

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