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肠道菌群－胆汁酸通路与2型糖尿病的关系

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摘　要

肠道菌群通过多种途径参与2型糖尿病(T2DM)的发生发展过程，导致胰岛素抵抗(IR)、胰岛β细胞功能损伤和糖原合成及代谢紊乱，不断推动糖脂代谢并发症的发展。胆汁酸(BAs)作为肠道菌群代谢产物，与其内源性受体结合，包括法尼醇X核受体(FXR)和G蛋白偶联胆汁酸受体1 (TGR5)，对T2DM产生影响。本文对肠道菌群－胆汁酸轴与T2DM关系的内在机制及相互影响进行综述。

关键词

2型糖尿病，肠道菌群，胆汁酸，法尼醇X核受体，G蛋白偶联胆汁酸受体1

Correlation between Intestinal Flora-Bile Acid Related Pathway and Type 2 Diabetes

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Abstract

Intestinal flora participates in the occurrence and development of type 2 diabetes (T2DM) through various ways, leading to insulin resistance (IR) and pancreatic islets β damage to cellular function and disruption of glycogen synthesis and metabolism, continuing to drive the development of complications in glycolipid metabolism. Bile acids (BAs), as metabolites of Intestinal flora, bind to their endogenous receptors, including farnesol X Nuclear receptor (FXR) and G protein coupled Bile acid receptor 1 (TGR5), which affect T2DM. This article reviews the internal mechanism and interaction between Intestinal flora-Bile acid axis and T2DM.

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Keywords

Type 2 Diabetes Mellitus, Intestinal Flora, Bile Acid, Farnesoid X Receptor, G Protein Coupled Bile Acid Receptor 5

1. 肠道菌群与 T2DM

肠道菌群与肥胖、慢性炎症和胰岛素抵抗有关，而这些均与 T2DM 的发展有关[1]。肠道菌群失衡可通过肠－脑轴影响中枢神经系统，减少乳酸杆菌和双歧杆菌产生，缩短饭后的饱腹感，导致肥胖[2]。厚壁菌/拟杆菌比率随着体重指数(BMI)的增加而增加，是肥胖 T2DM 患者肠道微生物群的一个重要特征[3]。肥胖促进内毒素脂多糖的分泌，从而导致糖耐量紊乱、慢性低水平炎症和肠内抗炎细菌(粪便杆菌)丰度降低[4]。Li 等人认为[5]，由于 T2DM 患者在饮食上出现机体营养不良及随年龄增长引起组织结构变化，导致肠道菌群统动态平衡紊乱，机体吸收大量毒素，导致胃肠道甚至全身产生炎症反应，释放炎症介质。血糖升高会导致肠上皮细胞的葡萄糖转运蛋白 2 (GLUT-2)的非特异性糖基化[6]，改变肠道通透性使内毒素进入体循环[7]，导致菌群失调，诱发胰岛素抵抗，影响糖耐量机制和促进代谢疾病的发展[8] [9]。双歧杆菌、脆弱拟杆菌、大肠杆菌都被证明能改善葡萄糖代谢和胰岛素敏感性，抑制促炎细胞因子，保持肠道屏障的完整性，降低糖尿病发生的风险[10] [11]。因此肠道微生物代谢物可通过调节葡萄糖代谢异常、β 细胞功能障碍和低度炎症等生理过程影响 T2DM 的发展。

2. 胆汁酸与 T2DM

BAs 是胆汁的主要脂质成分，作为一种对脂质和葡萄糖代谢具有调节作用的信号分子[12]，BA 代谢受损与 T2DM 的发展和进展有关。研究表明，口服葡萄糖耐量试验(OGTT) 30 分钟后结合胆汁酸升高，提示 T2DM 患者餐后总胆汁酸曲线下面积均高于对照组[13]。OGTT 期间甘氨鹅脱氧胆酸减少，并与空腹胰岛素呈负相关相反。类内(即原发性和继发性)和类间(即非共轭和共轭) BAs 协同调控在糖尿病患病之前就已存在，证明 BAs 可以独立于 OGTT 预测糖尿病的发生率。WANG 等人研究结果表明[14]，T2DM 患者中的石胆酸(LCA)和牛磺胆酸(TCA)升高，而熊去氧胆酸(UDCA)降低。认为 UDCA 浓度和 UDCA/LCA 比值与胰岛素分泌呈正相关，并建议在治疗后进行纠正[15]。相反地，有研究发现，BAs 水平降低时患者更易引起血糖上升，重症肠胆汁酸缺乏患者血糖异常升高的比例约为 30% [16]。胆固醇 7α 羟化酶(CYP7A1)染色质组蛋白乙酰化可以被葡萄糖和胰岛素促进，激活经典 BA 合成途径，使 CA (胆酸)、DCA (脱氧胆酸)与 CDCA (鹅去氧胆酸)的比例升高，通过刺激胆固醇吸收而导致血脂异常、糖尿病[17]，且与胰岛素抵抗呈正相关[18]。总 HCA (猪胆酸)/总 CDCA 比值与体重指数、胰岛素抵抗指数和糖化血红蛋白呈负相关[19]。6α-羟基化(6α-OH) BAs 与 T2DM 的代谢改变呈负相关，12α-羟基化(12α-OH) BAs 和 12α-OH 与非 12α-OH BAs 的比例与胰岛素抵抗有关[20]。总之，BAs 参与机体代谢、胰岛素抵抗和能量代谢，表明胆汁酸可以代表 T2DM 的潜在治疗靶标。

3. 肠道菌群－胆汁酸轴与 T2DM

肠道菌群酶(包括胆汁酸水解酶(BSH)和胆汁酸诱导酶(BAI))通过解共轭和去羟化反应生成未共轭胆

汁酸和次生胆汁酸，胆汁酸是宿主细胞受体(包括 FXR、TGR5 受体)的配体，通过两条信号通路的改变调节胃肠道内激素的分泌，包括胰高血糖素样肽-1 (GLP-1)和肽 YY (PYY)，肝脏糖异生，糖原合成，能量消耗和肠道菌群的组成。

3.1. 肠道菌群－胆汁酸-FXR 通路

FXR 由核受体亚家族 1H 组成员-4 基因编码，主要分布于细胞核，作为胆汁酸的主要传感器，在肝脏和肠道中的不同部位启动不同的下游靶基因转录。鹅去氧胆酸(CDCA)是激活 FXR 最有效的内源性胆汁酸[21]，可抑制膜钾通道，从而增加钙内流，导致更多葡萄糖刺激的胰岛素分泌[12]。α-和 β-胆酸(MCA)作为啮齿动物中的胆汁酸，已经被确定为 FXR 拮抗剂[22] [23]，负反馈抑制胆汁酸合成，维持肝内胆汁酸的低水平，以防止胆汁淤积性肝损伤，维持肠道通透性、形态变化和肠道微生物群的组成。肠道细菌和内毒素进入血液后，黏膜屏障受损，肠道中 BAs 水平降低导致肠上皮细胞凋亡和肠黏液萎缩，分别导致菌血症和内毒素血症[24]，从而改变细胞的代谢和功能[21]。

FXR 通过肠肝循环后，有 2 条主要途径影响肠道菌群调控 Bas：小异源二聚体(SHP)途径和人成纤维细胞生长因子 19 (FGF19)途径。(1) BAs-FXR-SHP 途径：FXR 的下游靶点之一是非典型核受体-SHP [25]，激活 FXR-SHP 信号通路，减少胆汁酸通过门静脉进入肝脏的量，加快 BAs 通过小管膜和基底外侧膜的外排。肠道中的细菌过度增殖后，BAs 可以通过 FXR 产生的直接抗菌作用的抗菌肽，稳定肠道通透性和肠道微生物群的菌群平衡。此外，BsA 作为一种辅抑制因子，肝脏 FXR 的激活增加了目的基因 SHP 表达[26]。肠道微生物群及肠道屏障的组成和结构的破坏触发肝细胞上的 FGF 受体 4 (FGFR4)/β-Klotho (βKL)异二聚体复合物，进一步激活下游 JNK/ERK 信号，SHP 通过抑制肝受体同源物-1 和肝核因子-4α 转录活性，从而下调 CYP7A1 和羟化胆固醇 7-羟化酶(CYP7B1)基因表达，抑制 BAs 合成及能量消耗增加[27]。(2) BAs-FXR-FGF19 通路：FGF19 被认为是胆汁酸、碳水化合物和能量稳态以及肝脏再生的关键调节因子[28]。作用于肝细胞内的细胞表面成纤维细胞生长因子受体-4 (FGFR4)上，由于肠道微生物群可以改变胆汁酸结构和池组成，它间接通过依赖于 c-Jun n 末端激酶(JNK)的途径负反馈抑制肝细胞中的 CYP7A1 的活性[29]，防止微生物群生长过度和黏膜破坏的基因表达。体循环允许微生物代谢的胆汁酸充当内分泌分子，激活胆汁酸介导的途径，从而调节宿主代谢过程，包括增加能量消耗、降低体重和改善葡萄糖耐受性[30]。肠道微生物群中胆盐水解酶活性的增加降低了肠道 β-MCA 的拮抗作用[31]，而肠道乳酸杆菌和拟杆菌属也相应增多[32]，刺激 FGF19 的产生，以抑制 BAs 合成。通过肠肝循环，激活肝脏 FGFR4 和 β KL 形成二元受体复合物，抑制两种羟化酶的表达，并调节涉及胆固醇、BA 和糖脂代谢的表达。非依赖性胰岛素肠道 FGF19 的降糖作用对糖尿病治疗提供新思路[33]。

3.2. 肠道菌群－胆汁酸-TGR5 通路

TGR5 作为一种经典的膜受体，广泛表达于多个组织，在肝、胃、小肠、脂肪、肾等部位均有表达，TGR5 已被证明参与调节肠道环境的稳定性和调节葡萄糖代谢[34]。次级胆汁酸 LCA 和 DCA 是激活 TGR5 最有效的内源性胆汁酸。肠道菌群组成成分变化受到肠道内激素调节，通过激活位于肠内分泌 L 细胞基底外侧膜的 TGR5 和刺激 GLP-1 的释放，调节餐后胰岛素释放和血糖水平[35]，抑制胃排空和食欲，并通过 GLP-1 作用分泌胰高血糖素[36]。研究发现，通 GLP-1 与胰岛 β 细胞膜上的 GLP-1 受体结合激活细胞膜上的腺苷酸环化酶(AC)，将三磷酸腺苷(ATP)转化为环磷腺苷(cAMP)，激活 cAMP/蛋白激酶 A(PKA)效应元件结合蛋白途径，调节鸟嘌呤核苷酸交换因子 II 促进 GLP-1 释放后影响胰岛素分泌，改善胰岛 β 细胞功能[37]，同时 TGR5 会使 α 细胞分泌表型从胰高血糖素转变为 GLP-1，从而促进 β 细胞的旁分泌作用，刺激胰岛素分泌[38]，从而调控机体的糖脂代谢[39]；并诱导细胞表面的钠离子依赖性胆汁酸转运体

(ASBT)转运，从而增加胆汁酸的重吸收，在胆汁淤积中，菌群总体多样性相对减少，厚壁菌门细菌水平降低[40]，因此发挥利胆的作用[41]。PKA 和交换蛋白(EPAC)/磷脂酶 C(PLC)被激活，通过电压依赖性Ca^{2+}通道诱导细胞内 Ca^{2+}的增加，Ca^{2+}内流刺激 β 细胞分泌胰岛素。肠道菌群失调后，BAs 抑制 GLP-1 的 G 蛋白耦联受体，增加食物摄入，胰岛素敏感性降低，脂肪积累，导致全身炎症。在脂肪组织中，TGR5 的激活诱导甲状腺激素脱碘酶 2 型(Dio2)，它将甲状腺激素甲状腺素(T4)转化为三碘甲状腺原氨酸(T3)，以刺激能量代谢和白色脂肪组织褐变。细胞 cAMP 水平升高，BAs 通过碘甲状腺原氨酸脱碘酶(D2)增加骨骼肌和棕色脂肪组织的能量消耗，从而预防肥胖[42]，提高甲状腺激素的水平，增加氧气的消耗和能量的产生，避免了肥胖和胰岛素抵抗的发生[43]。可见，BAs-TGR5-cAMP-Dio2 信号通路，是调节能量平衡的重要机制。

研究表明，BAs 与肠道菌群相互作用，TGR5 改善糖脂代谢的作用主要包括[44]：促进肝糖原合成和胰岛素敏感性；胰腺胰岛素分泌增加；促进能量消耗，特别是棕色脂肪组织和肌肉；促进产热，导致体重减轻；调节大脑中的饱腹感[45]。这些作用是由 TGR5 介导的，这就是为什么基于胆汁酸的 TGR5 激动剂可能是糖尿病的治疗靶点。

4. 小结

综上所诉，T2DM 患者体内肠道菌群与胆汁酸代谢产物关系密切，通过 FXR、TGR5 信号通路及控制胆汁酸池组成和相关免疫和代谢功能，最终影响糖脂代谢变化。因此，调节和维持肠道菌群及胆汁酸的正常代谢对 T2DM 的治疗和预防具有重要意义。糖尿病及其并发症严重影响人类生命健康，发病机制复杂，需要从多角度研究和治疗。通过多学科共同探索，完善总结相关作用机制，为今后 T2DM 的治疗提供更多安全有效的参考。

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