

专论与综述

胆汁酸代谢调节肠道菌群在遗传性球形红细胞增多症合并胆汁淤积中的作用

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摘要: 遗传性球形红细胞增多症(hereditary spherocytosis, HS)是一种遗传性溶血性疾病, 在全球范围内较为常见, 临床上常表现为贫血、黄疸、脾大等。HS 的诊断和治疗在近年来取得了显著进展, 胆石症是其最为常见的并发症, 严重影响患者身体健康。已有研究发现, HS 合并胆汁淤积的患者存在胆汁酸代谢失衡的现象, 并且胆汁酸代谢失衡又影响肠道菌群的组成和丰度。本研究就胆汁酸代谢调节肠道菌群在 HS 合并胆汁淤积中的作用机制进行综述, 为 HS 合并胆汁淤积提供了治疗新策略。

关键词: 胆汁酸代谢; 肠道菌群; 遗传性球形红细胞增多症; 胆汁淤积

Role of bile acid metabolism-gut microbiota interactions in hereditary spherocytosis associated with cholestasis

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Abstract: Hereditary spherocytosis (HS) is a hereditary hemolytic disease with a global distribution, which often presents clinically with anemia, jaundice and splenomegaly. The diagnosis and treatment of HS has progressed significantly in recent years. Cholelithiasis is the most common complication, seriously affecting the health of HS patients. It has been

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demonstrated that patients with HS associated with cholestasis have disturbed bile acid metabolism, which affects the composition and abundance of gut microbiota. This article reviewed the role and mechanism of bile acid metabolism-gut microbiota interactions in regulating HS associated with cholestasis, with the aim of providing novel treatment strategies for HS associated with cholestasis.

Keywords: bile acid metabolism; gut microbiota; hereditary spherocytosis; cholestasis

遗传性球形红细胞增多症 (hereditary spherocytosis, HS) 是一种常见的常染色体显性遗传性溶血性疾病^[1]。HS 的病理机制是编码红细胞膜或细胞骨架蛋白的基因突变, 导致红细胞膜缺陷, 促使红细胞的形态由双凹圆盘状变为球形^[2]。HS 的发病与编码红细胞膜蛋白的 5 个基因的突变相关, 即 *SPTA1*、*SPTB*、*ANK1*、*SLC4A1* 和 *EPB42*^[3]。在北欧, HS 的发病率约为 1/2 000, 中国目前尚缺乏准确的流行病学调查数据, 但国内研究表明, 溶血性疾病中 HS 占比较高^[4]。HS 患者的临床表现存在明显的异质性, 典型的临床表现为贫血、黄疸和脾肿大, 3 种临床表现既可单独出现也可以同时存在。胆石症、溶血危象和再生障碍危象是 HS 常见的并发症, 其中胆石症最为常见, 在 HS 患者中的发病率为 21%–63%^[5]。目前, HS 患者可采用定期输血、护肝降酶、补充叶酸、部分脾切除术、胆囊切除术、脾动脉栓塞术及全脾切除术等治疗手段^[6]。然而, HS 并发胆石症时所引起的胆汁淤积与患者的治疗及预后息息相关, 因此, 针对 HS 合并胆汁淤积患者探索低风险、有效的新治疗策略具有重要意义。近年来, 胆汁酸、肠道菌群与 HS 的关系日益受到关注, 三者间的相互作用可能会影响 HS 患者胆汁淤积症的发生和发展。胆汁酸是胆汁的主要成分, 进入肠道后, 肠道菌群对其进行一系列的修饰转化, 包括去结合、氧化与差向异构化、7-脱羟基化以及再结合等。而胆汁酸可作为一种信号分子, 激活下游受体, 参与调节代谢稳态、免疫反应和肠道功能等重要生理过程^[7]。胆汁酸还可通过多种途径调节肠道菌群的组成和数量^[8], 胆汁酸与肠道菌群相互作用, 共同

参与人体生命活动。研究发现, HS 患者由于高胆红素血症可并发胆结石和肝内胆汁淤积症^[9–11], 从而导致胆汁酸含量和类型, 以及肠道菌群组成和数量发生变化, 提示 HS 合并胆汁淤积患者胆汁酸代谢与肠道菌群的相互作用可能加速疾病的发展。

本研究以 HS 合并胆汁淤积的发生、发展过程, 以及治疗后胆汁酸、肠道菌群变化为切入点, 探讨 HS 与胆汁酸、肠道菌群之间的关系, 以期对 HS 合并胆汁淤积提供治疗新策略。

1 胆汁酸与肠道菌群的相关性

1.1 胆汁酸的合成与生理功能

人体每日在肝脏中合成约 0.2–0.6 g 胆汁酸^[12]。人体的总胆汁酸分为初级胆汁酸和次级胆汁酸两大类, 具有促进脂类消化和吸收、增强免疫调节、保肝护胆、维持胆固醇代谢平衡等生理功能^[13]。胆汁酸来源于胆固醇代谢^[14], 初级胆汁酸主要在肝脏中以胆固醇为原料直接合成, 包括胆酸 (cholic acid, CA) 和鹅去氧胆酸 (chenodeoxycholic acid, CDCA), 而次级胆汁酸主要在肠道菌群胆固醇 7 α -羟化酶 (cholesterol 7 α -hydroxylase, CYP7A1) 的作用下产生, 包括脱氧胆酸 (deoxycholic acid, DCA) 和石胆酸 (lithocholic acid, LCA)^[15]。完整胆汁酸的合成需要 17 种酶^[16], CYP7A1、线粒体甾醇 27 羟化酶 (mitochondrial sterol 27 hydroxylase, CYP27A1)、非特异性 7 α -羟化酶 (nonspecific 7 α -hydroxylase, CYP7B1) 和甾醇 12 α -羟化酶 (sterol 12 α -hydroxylase, CYP8B1) 是胆汁酸合成通路中的关键调节酶, 其中 CYP7A1 是肝脏中经典的胆汁酸生物合成途径的启动酶^[12]。

1.2 肠道菌群与胆汁酸代谢之间具有密切的双向调控作用

肠道连接了肝脏和肠道,肠道菌群与胆汁酸代谢之间存在双向调控作用,肠道菌群可通过生物转化来调节胆汁酸的含量和类型^[13],同时胆汁酸也对肠道菌群的组成和数量产生影响^[17]。

人体肠道具有复杂的菌群^[18],存在超过1 000种细菌^[19]。人体肠道正常菌群主要由专性厌氧菌、兼性厌氧菌和需氧菌组成,其中专性厌氧菌占比超过99%^[20]。Consortium等^[21]的研究揭示了肠道菌群的组成,肠道98%的细菌主要由拟杆菌门(*Bacteroidota*)、厚壁菌门(*Firmicutes*)、放线菌门(*Actinomycetota*)和变形菌门(*Proteobacteria*)构成,其中*Bacteroidota*和*Firmicutes*占比较高。肠道菌群具有强大且多样的转化胆汁酸的能力,如梭菌属(*Clostridium*)、双歧杆菌属(*Bifidobacterium*)、乳杆菌属(*Lactobacillus*)及拟杆菌属(*Bacteroides*)等多种细菌具有将胆汁酸去结合的功能^[22]。某些肠道细菌能够表达胆汁盐水解酶(bile salt hydrolase, BSH)和7 α -脱氢酶,促进初级胆汁酸向次级胆汁酸转化^[23]。而这种生物转化功能受到法尼醇X受体(farnesoid X receptor, FXR)和takeda G蛋白偶联受体5(takeda G protein-coupled receptor-5, TGR5)的调控,肠道菌群可通过FXR和TGR5调控胆汁酸代谢的信号传导,调节宿主胆汁酸池的含量和组成,影响宿主的胆汁酸代谢^[24]。因此,肠道菌群种类的差异决定了胆汁酸池的多样性^[25-26]。

随着组学技术的发展,研究学者提出了多种检测肠菌来源的胆汁酸的新技术,如靶向胆汁酸代谢组学分析^[27]、基于点击化学富集策略结合非靶向代谢组学方法的次级胆汁酸挖掘体系^[28]、生物传感器^[29]及超高效液相色谱-串联质谱^[30]等。这些技术不仅能够深入分析胆汁酸的组成和含量,还能够揭示胆汁酸代谢反向调控肠道菌群,在维持肠道稳态中担任重要角色^[31]。胆汁酸可通过FXR激活肠道功能调节基因的表

达^[32],加强其抑菌作用,从而防止肠道内细菌的过度定殖^[15],进而影响肠道菌群的组成^[33]。此外,胆汁酸还可通过激活小肠中的先天免疫反应相关基因,影响胆汁酸受体信号的传导^[24],或通过干扰细菌膜的完整性,直接或间接地影响肠道菌群的组成和数量^[17]。总之,肠道菌群与胆汁酸代谢之间具有密切的双向调控作用。

2 胆汁酸代谢在HS合并胆汁淤积中的变化

HS在临床上常表现为贫血、黄疸及脾大^[34]。HS合并胆石症的发生率在21%–63%左右^[5]。HS因球形红细胞的变形性和柔韧性降低,通过脾脏时容易被破坏,出现血管外溶血^[10]。此时大量的血红蛋白被代谢为间接胆红素,超出了肝脏摄取、转化和排泄的能力,引起以间接胆红素升高为主的高胆红素血症^[9],长期的高胆红素血症可并发胆结石和肝功能损害^[10],而胆红素沉积还可引起肝内胆汁淤积^[11]。Han等^[35]研究发现,HS患者并发严重肝内胆汁淤积,可能与胆结石引起的短暂性胆道梗阻和胆红素代谢异常导致的肝细胞损伤有关。周达等^[36]研究也发现,多种酶类和离子泵参与肝细胞中胆盐的处理过程;然而,缺氧和免疫炎症能抑制这些酶或离子泵的活性,使HS患者体内大量的胆红素得不到有效的代谢,可导致胆汁酸代谢平衡的异常,从而引发严重的肝内胆汁淤积。另有某病例报告指出,HS可继发脾功能亢进,大量红细胞被破坏,大量受损的红细胞诱发了肝组织免疫炎症反应,进而引起胆汁淤积^[37]。临床上,严重的肠道感染、胆道及其邻近区域的炎症,以及肝功能的代偿异常,均可能引发严重的胆汁淤积。同时,有研究发现,大量溶血的红细胞与肝血管内皮上的巨噬细胞黏附^[38],血管内溶血产生的红细胞碎片阻塞了肝内微血管床^[9],可致肝脏损伤,而高胆红素血症也能引起肝细胞功能障碍^[39],进一步加重了肝功能异常^[9]。当HS引起肝功能异常时,肝脏摄取、排

泄胆汁酸的能力降低,造成胆汁淤积。除此之外,国外曾报道过一例 HS 合并 *ABCB11* 基因突变,其中复合杂合子 *ABCB11* 基因的突变导致良性复发性肝内胆汁淤积 2 型^[40]。血清总胆汁酸(total bile acid, TBA)是反映胆汁淤积和肝细胞损伤较为灵敏的指标,HS 可并发胆汁淤积和肝细胞损伤,导致血中 TBA 水平显著增高^[41]。黄维真^[42]通过研究证实了溶血性贫血黄疸组患儿血清中 TBA 值均高于对照组。雷榆等^[43]研究也发现,当发生肝内胆汁淤积时,胆汁酸无法有效排出,导致肝脏中胆汁酸淤积并进入血液循环,从而引起血清中胆汁酸水平的增加。

胆结石能引起胆汁酸代谢障碍,更进一步加重胆汁淤积。因清除胆汁酸的能力不足,使胆汁酸浓度增高,并且胆汁酸浓度随着黄疸程度的不断增加而显著升高^[39]。张巍峨等^[44]研究发现胆结石患者存在胆囊胆汁淤积时,胆囊组织吸收 TBA 入血量增加,使得总胆汁酸池体积缩小,血液中 TBA 浓度增高。不仅如此,HS 患者胆结石的形成与胆汁酸代谢具有密切关系。当 HS 引起高胆红素血症时,高浓度的胆红素沉积在胆汁中,造成胆汁淤积,胆汁排泄不畅,易形成胆结石^[45]。患者并发胆结石时,肝肠循环中游离胆汁酸和次级胆汁酸增加^[46]。此外,胆结石在促使血液 TBA 浓度升高的同时,还降低了肝脏胆汁酸合成酶 7 α -羟化酶的活性,使胆汁酸合成减少,胆汁酸池体积缩小,胆汁酸循环率增加,导致胆汁酸丢失增多,从而降低了胆汁酸池的体积,这也更进一步地促进了胆结石的形成和发展^[47]。

目前,胆囊切除术、脾切除术及输血等是治疗 HS 的有效手段。胆囊切除术后,小肠成为调节胆汁酸肠肝循环的主要动力泵,促使肠肝循环次数增多,初级胆汁酸转化为次级胆汁酸增加,特别是石胆酸会明显增高^[48-50]。研究表明,HS 患者过量应用铁剂、长期慢性贫血、输注红细胞会造成铁过载,继发含铁血黄素沉积症^[51],引起结合型初级胆汁酸增加^[52]。因此,

HS 患者胆汁酸代谢异常与胆汁淤积密切相关,可导致胆结石发生,胆结石又促使胆汁酸代谢紊乱,加重病情,并且临床常规治疗手段也会改变胆汁酸代谢。

3 胆汁酸通过调节肠道菌群在 HS 合并胆汁淤积中发挥作用

3.1 胆汁淤积-胆汁酸-肠道菌群轴

肠道菌群与胆汁酸代谢之间存在双向调控关系,胆汁酸代谢影响肠道菌群的组成和丰度,而肠道菌群也调控胆汁酸的合成与代谢^[53]。探讨“胆汁淤积-胆汁酸-肠道菌群轴”与 HS 合并胆汁淤积之间的关系为其发病机制研究提供了一个新的视角(图 1)。HS 并发胆汁淤积时,胆汁酸代谢存在着明显的紊乱,紊乱的胆汁酸代谢又影响着肠道菌群的组成和丰度。

HS 并发胆结石的患者常出现胆汁淤积和梗阻性黄疸。Guo 等^[54]发现,继发性胆汁酸淤积通过肠道微生物组-胆汁酸-胆汁淤积轴,增加了有害菌的丰度并降低了有益菌的丰度。胆汁淤积时排入肠道的胆汁会减少或缺少,削弱了胆汁酸的抑菌作用,使肠腔 pH 调节失衡,这时宿主维持肠道菌群平衡的条件被打破,导致肠道菌群的组成发生改变^[55]、肠道细菌过度增殖,造成肠道微生态紊乱^[56]。在胆汁淤积患者中,肠道厌氧菌中 *Bifidobacterium* 的数量与血清 TBA 水平呈负相关, *Lactobacillus* 的数量与 TBA 水平无关联,而需氧菌中的大肠杆菌(*Escherichia coli*)和肠球菌属(*Enterococcus*)的数量与胆汁酸水平呈正相关,这也揭示了某些肠道细菌参与了人体胆汁酸的代谢,并且表现出菌种特异性^[56]。另一方面,当肠道菌群的平衡状态受到干扰时,肠道的通透性增加,使机会性病原体能够入侵肠道并定殖于空的生态位,从而影响肠道微生态。肠道通透性的增加还允许微生物衍生产物(如代谢物、毒力因子和其他管腔成分)进入,使肠道菌群的正常功能被破坏^[57]。同时,肠道微生态紊乱能够引发肠道炎症反应,

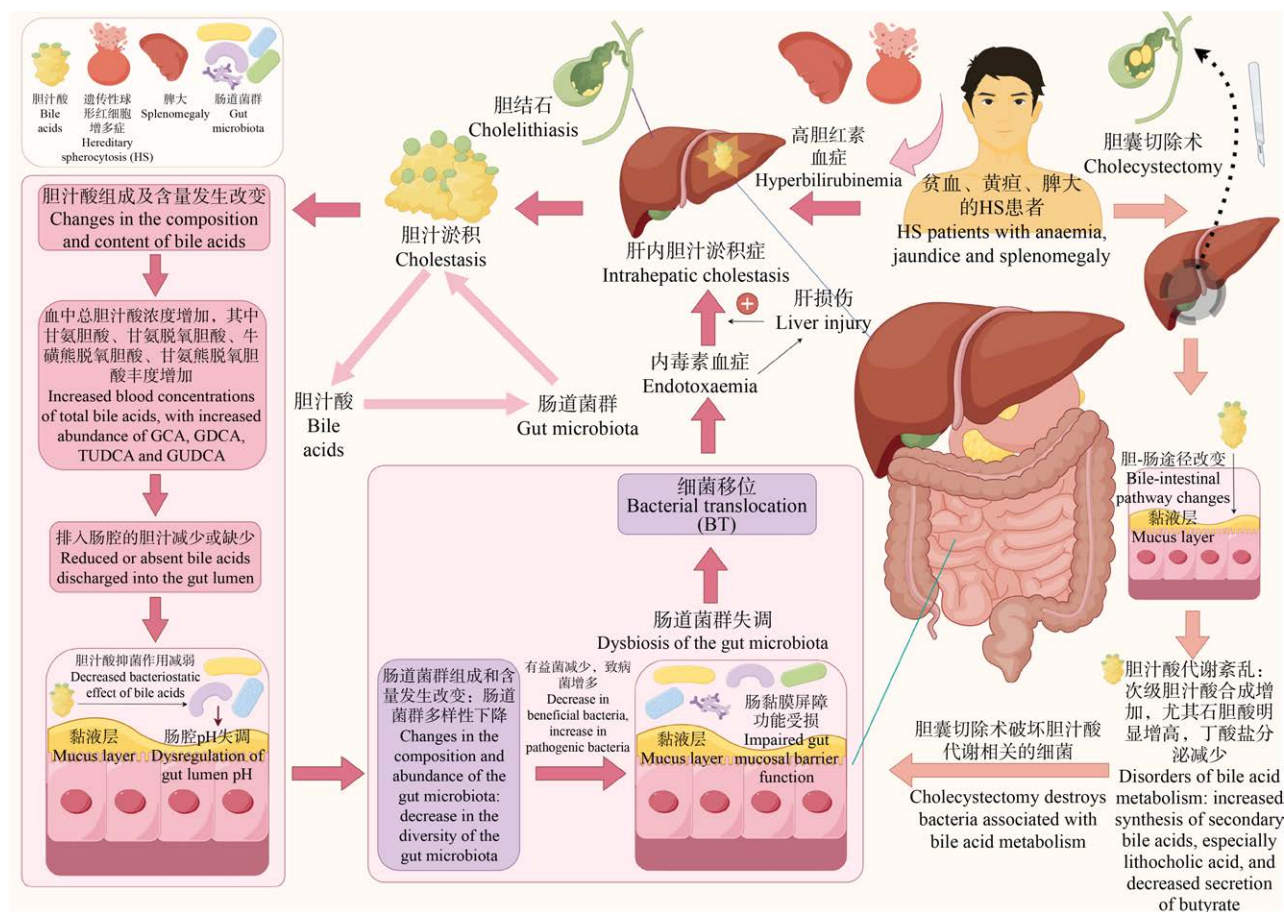


图1 胆汁淤积-胆汁酸-肠道菌群轴与遗传性球形红细胞增多症合并胆汁淤积

Figure 1 Cholestasis-bile acid-gut microbiota axis and hereditary spherocytosis (HS) associated cholestasis.

导致肠漏和肠道细菌产物的移位,进而破坏了肠上皮细胞间的紧密连接,增加了肠黏膜的通透性,从而导致肠黏膜的屏障功能受损^[58]及肠道内细菌移位(bacterial translocation, BT)。BT促使肠道细菌及其代谢产物(如内毒素)进入肝脏的门脉系统,进而诱发内毒素血症,造成肝损伤,更进一步加重了胆汁淤积^[59]。通过分析胆结石患者的胆汁,发现与肠道微生物群多样性直接相关的胆汁酸的浓度显著异常,如甘氨酸(glycocholic acid, GCA)、甘氨熊脱氧胆酸(glycoursodeoxycholic acid, GUDCA)、甘氨脱氧胆酸(glycodeoxycholic acid, GDCA)及牛磺熊去氧胆酸(tauroursodeoxycholic acid, TUDCA)等胆汁酸的丰度会增高^[60]。罗茜等^[22]的研究结果

也证实了 GUDCA、TUDCA 与肠道菌群之间存在直接关联。脆弱拟杆菌(*Bacteroides fragilis*)具有胆盐水解酶活性^[61], HS 患者在胆囊切除后,肠道菌群中的 *B. fragilis* 丰度增加^[62],使得作为 FXR 拮抗剂的特定胆汁酸——GUDCA 和 TUDCA 含量下降^[22],并且高含量的脱氧胆酸能使肠道菌群的多样性降低,其中拟杆菌属的占比增加,厚壁菌门的占比降低^[63]。

除此之外,研究发现,当 HS 患者因并发胆结石而引起梗阻性黄疸时,会出现明显的细菌移位与内毒素血症^[64-66]。梗阻性黄疸时肠道不仅缺乏胆汁酸,还缺少分泌性 IgA,使肠黏膜充血、水肿及表皮脱落,导致肠道菌群失调。另外,梗阻性黄疸能引起腹腔巨噬细胞活性降

低, 一氧化碳释放减少, 降低了人体抗感染及免疫防御的能力, 从而造成细菌移位和内毒素血症^[65]。在梗阻性黄疸的动物模型中也观察到了细菌移位现象, 表现为回肠中细菌的过度繁殖, 特别是革兰阴性需氧菌群在回肠中的大量定植, 其中大肠杆菌占绝大多数^[66]。

患者胆囊切除术后由于胆汁进入肠道的途径发生了改变, 胆汁失去节律, 直接且持续地排入十二指肠, 不受进餐时间的调节^[67-68], 使初级胆汁酸的产生增加, 胆汁酸代谢失衡, 影响肠道菌群的组成和丰度^[69]。不仅如此, 胆囊切除术还会破坏胆汁酸代谢相关的细菌^[49], 如降低了代谢丁酸盐的肠道细菌的丰度, 包括栖粪杆菌(*Faecalibacterium* sp.)和粪便罗斯拜瑞氏

菌(*Roseburia faecis*), 导致有害物质(如次级胆汁酸)代谢增加, 有益物质(如丁酸盐)分泌减少^[70]。因此, 为提高胆囊切除的 HS 患者的生活质量, 临床医生可根据其术后肠道菌群的变化, 相对应补充患者缺乏的肠道微生态制剂, 从而调节肠道微生态, 以维持胆汁酸代谢平衡。

3.2 FXR-非典型核受体小异二聚体配体 (small heterodimer partner, SHP) 轴及 FXR-成纤维细胞生长因子 15/19 (fibroblast growth factor 15/19, FGF15/FGF19) 轴

研究“FXR-SHP 轴及 FXR-FGF15/FGF19 轴”与胆汁酸-肠道菌群之间的关系对 HS 合并胆汁淤积来说至关重要(图 2)。FXR 在肠道菌群-宿主轴中起重要作用, 特别是通过控制胆汁酸的

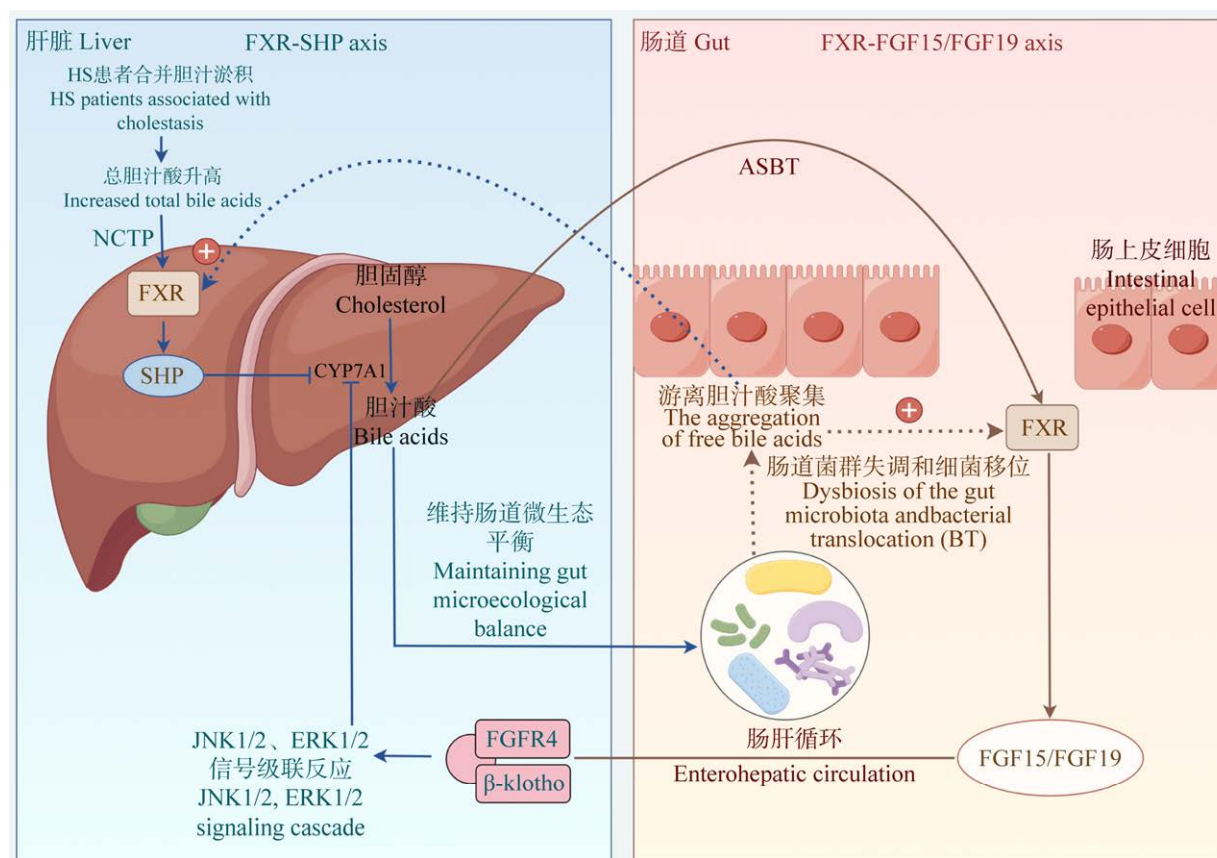


图 2 胆汁酸代谢、肠道菌群通过 FXR-SHP 轴及 FXR-FGF15/FGF19 轴影响 HS 合并胆汁淤积

Figure 2 Bile acid metabolism and gut microbiota influence HS associated with cholestasis via FXR-SHP axis and FXR-FGF15/FGF19 axis.

肝肠循环来调节肠道微生态^[71]。FXR 在肝脏和肠道中含量丰富,并且胆汁酸是 FXR 的激动剂^[72]。当 HS 并发胆汁淤积时,肝脏中 TBA 升高,升高的 TBA 在钠牛磺胆酸共转运多肽(sodium taurocholate cotransporting polypeptide, NTCP)的作用下激活 FXR^[72],进而增强了非典型核受体小异二聚体配体(small heterodimer partner, SHP)基因的转录水平,这一过程抑制了肝脏中胆汁酸合成限速酶 CYP7A1 的合成^[22]。其次,升高的 TBA 随着胆汁流进肠道,大约 95%的 TBA 在回肠远端被顶端钠依赖性胆汁酸转运蛋白(apical sodium-dependent bile acid transporter, ASBT)重吸收^[73]。在肠细胞中升高的 TBA 激活了 FXR,促进 FGF15/19 的合成和分泌增加^[22]。随后 FGF15/FGF19 经肠肝循环到达肝脏,在肝脏内 FGF15/FGF19 与 FGFR4/ β -klotho 异二聚体复合物结合,进而触发了 c-Jun 氨基末端激酶 1/2 (c-Jun N-terminal Kinase 1/2, JNK1/2)、细胞外调节蛋白激酶 1/2 (extracellular regulated protein kinases 1/2, ERK1/2)信号级联反应,该级联反应也抑制了 CYP7A1 的转录^[73]。此外,回肠内 FXR 激活比肝脏内 FXR 激活能更强地抑制 CYP7A1 介导的胆汁酸合成^[73]。综上所述,胆汁酸通过 FXR-SHP 轴及 FXR-FGF15/FGF19 轴共同抑制肝脏中 CYP7A1 的生成来负反馈调节胆汁酸的合成,使胆汁酸维持在稳定水平^[74]。

HS 患者胆汁酸肠肝循环关键调节受体 FXR 异常与胆汁淤积相关,胆汁淤积导致机体中最有效的内源性 FXR 配体——疏水性胆汁酸 CDCA 丰度增加^[11,75],疏水性胆汁酸可通过 FXR 间接重塑肠道菌群的组成^[76],影响肠道菌群的多样性^[60]。当肠道菌群失调和细菌移位时,细菌 BSH 活性增强,游离胆汁酸在肠道聚集^[77],此时,肠道菌群通过一系列过程激活 FXR-SHP 及 FXR-FGF15/FGF19 负反馈机制来调节胆汁酸代谢^[53],维持胆汁酸动态平衡。因此,HS 合并胆汁淤积患者可通过使用 FXR 激动剂,以调节

胆汁酸代谢而影响肠道菌群的组成和含量。

4 总结与展望

4.1 探讨“胆汁酸代谢-肠道菌群”为研究 HS 合并胆汁淤积提供新视角

HS 是一种遗传性溶血性疾病,因红细胞膜缺陷导致溶血,进而引起高胆红素血症,易并发胆汁淤积。而其他肝内胆汁淤积的病因包括病毒性、药物性、酒精性、遗传性、自身免疫缺陷等^[43]。不同的病因可导致不同的临床表现和疾病进展。因此,HS 合并胆汁淤积在病因上与其他胆汁淤积性肝病具有明显的差异性,但二者仍有共性。

HS 合并胆汁淤积患者的胆汁酸组分发生变化,总胆汁酸水平增加,并且紊乱的胆汁酸代谢会影响肠道菌群的组成和丰度。梁秋利等^[32]利用“胆汁酸-肠道菌群-胆汁淤积三角”解释了原发性硬化性胆管炎中胆汁酸紊乱(脱氧胆酸、石胆酸等潜在毒性胆汁酸增多)和生物多样性减少之间的关系,指出胆汁酸代谢与肠道菌群的相互影响。赵然等^[78]研究表明,原发性胆汁性胆管炎患者血清总胆汁酸升高,肠道菌群的丰度和多样性明显降低,认为胆汁酸-肠道菌群失衡是其发病的关键。向丽萍^[79]通过构建药物性肝损伤模型,研究发现胆汁酸代谢紊乱、胆汁淤积与肠道菌群失调之间的恶性循环会加重肝损伤。

综上所述,HS 合并胆汁淤积与其他胆汁淤积性肝病可能均存在胆汁酸代谢紊乱与肠道菌群失衡的现象。然而,HS 合并胆汁淤积患者的胆汁酸紊乱可能更侧重于溶血所致,肠道菌群的变化也可能由于溶血等特殊原因而表现出独特的多样性。目前,关于 HS 合并胆汁淤积的胆汁酸代谢及其与肠道菌群的变化相互作用的研究尚少,所以探讨“胆汁酸代谢-肠道菌群”将为研究 HS 合并胆汁淤积的作用机制提供一个新视角。

4.2 基于“胆汁淤积-胆汁酸-肠道菌群轴”“FXR-SHP 轴及 FXR-FGF15/FGF19 轴”探讨 HS 合并胆汁淤积的治疗新策略

HS 合并胆汁淤积的患者常通过胆囊切除术、脾切除术等外科手术或使用利胆药物进行治疗。但是,临床常规治疗方案仍有缺陷,例如全脾切除术创伤大且易形成血栓^[2];胆囊切除术由于其较深的解剖位置,以及解剖结构的多变性和复杂性,存在一定的手术危险性^[11]。因此,探讨治疗 HS 合并胆汁淤积的新策略具有重要意义。本文提出的“胆汁淤积-胆汁酸-肠道菌群轴”和“FXR-SHP 轴及 FXR-FGF15/FGF19 轴”不仅让我们更进一步认识了 HS 合并胆汁淤积中胆汁酸代谢与肠道菌群的作用机制,也为 HS 合并胆汁淤积的治疗提供了一定的理论依据、新的研究思路和新的治疗策略,如利用微生态制剂(如双歧杆菌、双歧三联活菌)、补充低聚糖等益生元、粪便微生物移植、微生物细胞重编程技术来重塑肠道菌群的组成和功能,调控肠道微生物群稳态,进而影响胆汁酸池,或利用 FXR 激动剂调节胆汁酸水平而影响肠道微生态。严海燕等^[80]研究发现,益生菌辅助治疗能够提高婴儿肝内胆汁淤积性肝病的临床治疗效果,调节肠道微生态,在一定程度上缓解了胆汁淤积。此外,张灵雁等^[81]研究表明,茵栀黄颗粒可通过上调 FXR mRNA 水平、下调 CYP7A1 mRNA 水平,从而调节胆汁酸成分和肠道菌群组成,改善小鼠胆汁淤积症。这些已有的研究均证实了上述提出的 HS 合并胆汁淤积的治疗新思路和治疗新策略的可行性。因此,这些方法有望作为未来 HS 合并胆汁淤积治疗的重要辅助手段。

4.3 局限和展望

然而,HS 合并胆汁淤积患者具体的肠道菌群、胆汁酸代谢的具体变化及其两者的相互作用还需要进一步研究证实。益生元、益生菌、粪菌移植、FXR 激动剂能够改善胆汁淤积^[23],但仍需大量样本随机对照临床研究验证。HS 合

并胆汁淤积与胆汁酸代谢、肠道菌群之间的关系密不可分,希望未来的研究能从中找到治疗的新突破口,能够在体内代谢层面改善胆汁淤积。

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