胆汁酸-肠道菌群与腹泻型肠易激综合征的研究进展

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[摘要] 肠易激综合征(IBS)是最常见的功能性肠病，其中腹泻型肠易激综合征(IBS-D)为我国最常见的IBS分型。IBS致病原因众多，其中胆汁酸代谢异常及肠道菌群紊乱为主要的致病因素。IBS-D患者存在胆汁酸代谢异常及肠道菌群紊乱。肠道菌群在胆汁酸合成调控中十分关键，肠道菌群紊乱可能会导致胆汁酸代谢异常。胆汁酸通路(FXR)激动剂可通过调控受体胆汁酸代谢及肠道菌群而缓解IBS-D症状。该文就胆汁酸-肠道菌群与IBS-D的相互作用及其作用机制进行综述。

[关键词] 肠易激综合征；胆汁酸；肠道菌群

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Research progress of bile acid-intestinal flora and diarrhea-predominant irritable bowel syndrome

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[**Abstract**] Irritable bowel syndrome (IBS) is the most common functional bowel disease, and diarrhea-predominant IBS (IBS-D) is the most common type of IBS in our country. There are many causes of IBS, among which abnormal bile acid metabolism and intestinal flora disorder are the main pathogenic factors. Abnormal bile acid metabolism and intestinal flora disorders are found in patients with IBS-D. Intestinal flora is critical in the regulation of bile acid synthesis. Disorders of intestinal flora may lead to abnormal bile acid metabolism. Studies have pointed out that bile acid pathway (farnesoid X receptor, FXR) agonists can improve IBS-D symptoms by regulating receptor bile acid metabolism and intestinal flora. The interaction and corresponding mechanism of bile acid-intestinal flora and IBS-D were summarized in present paper.

[**Key words**] irritable bowel syndrome; bile acid; intestinal flora

近年来，肠易激综合征(irritable bowel syndrome，IBS)的发病率逐年上升，其全球发病率为10%~15%[1-2]，我国的发病率为1.40%~11.5%[3]。IBS是最常见的功能性肠病[4]，主要表现为伴随排便习惯或性状改变的腹痛，可分为腹泻型肠易激综合征(diarrhea-predominant IBS，IBS-D)、便秘型肠易激综合征(constipation-predominant IBS，IBS-C)、混合型肠易激综合征(mixed diarrhea and constipation IBS，IBS-M)及未定型肠易激综合征(unspecified IBS，IBS-U)，其中，IBS-D为我国最常见的IBS分型[5-8]。

IBS的致病原因众多，大致可分为两类，即外周因素(饮食、肠道菌群、宿主与肠道微生物间的相互作用、胆汁酸代谢异常、低度慢性肠道炎症、胃肠道内分泌细胞异常、胃肠道运动及内脏器官超敏性改变等)和中枢因素(心理压力、认知功能障碍、情绪唤醒系统反应异常及睡眠功能障碍等)[9-15]。遗传因素被认为可能是外周与中枢因素病理生理机制的基础[16]。IBS-D患者体内胆汁酸代谢及肠道菌群存在异常，而胆汁酸与宿主肠道菌群关系密切，既相互作用，又互相调节。本文主要对胆汁酸-肠道菌群与IBS-D的关系进行综述。

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1 胆汁酸及其通路

1.1 胆汁酸 胆汁酸是一种具有广泛生物学功能的信号分子，在葡萄糖及脂质代谢、能量稳态以及免疫应答的调节中起重要作用[17-18]。在肝脏中，胆汁酸是胆固醇分解代谢的最终产物[19]，成年人的肝脏每天合成0.5 g胆汁酸[20]。胆汁酸的合成主要有经典途径及替代途径两种方式[21]。经典途径为其主要途径，胆固醇经胆固醇7α羟化酶(cholesterol 7α hydroxylase，CYP7A1)及胆固醇12α羟化酶(cholesterol 12α hydroxylase，CYP8B1)依次氧化后生成胆酸(cholic acid，CA)，其中CYP7A1为胆汁酸合成过程的限速酶[22]。替代途径主要由胆固醇27α羟化酶(cholesterol 27α hydroxylase，CYP27A1)及胆固醇25α7羟化酶(cholesterol 25α 7 hydroxylase，

CYP7B1)参与，胆固醇被转化为鹅脱氧胆酸(chenodeoxycholic acid，CDCA)，为胆汁酸合成的补充途径[23]。胆汁酸合成后通过主动转运方式分泌到小管中形成胆汁。胆汁酸储存在胆囊中，进餐后通过胆总管将其释放到肠道中[24]。在回肠中，大多数胆汁酸经肠肝循环途径被重新吸收，通过门静脉途径进入肝脏。胆汁酸的肠肝循环平均每天发生6~8次，以维持约3 g的恒定胆汁酸池大小，对于机体胆汁酸稳态起到重要作用[25]。除此之外，还有少量胆汁酸(5%)随粪便一起排入体外，流失的粪便胆汁酸可通过肝脏中的从头合成得到补充[26]。

1.2 胆汁酸合成及转运通路 法尼醇受体(farnesoid X receptor，FXR)为胆汁酸的天然受体[27]，在肝脏、肠道、肾上腺、脂肪组织及心脏等组织中表达，且在肝脏、肠道内表达量较高，被视为全身能量稳态的关键代谢调节剂[28-29]。FXR在调节胆汁酸合成、分泌及转运中起着至关重要的作用，主要通过肝脏及肠道的FXR通路进行[30]。肝脏中FXR的下游靶点为小分子异源二聚体(short heterodimer partner，SHP)及CYP7A1。在肝脏中，胆汁酸合成主要受FXR-SHP通路调节：肝脏内胆汁酸过多时激活FXR，下游SHP表达增加，进而抑制CYP7A1的表达，减少胆汁酸的合成[31]。胆汁酸合成后，FXR能及时激活肝细胞顶端的胆盐输出泵，促进其排至胆囊，加速其转运。门静脉的存在是经典胆汁酸肠肝循环的生理基础。肠道内多余的胆汁酸可激活肠道FXR，上调FXR及其下游成纤维细胞生长因子15/19(fibroblast growth factor 15，FGF15/19)的表达[31]。FGF15/19作为信号分子，经门静脉进入肝脏，进一步激活FGFR4，下调CYP7A1的表达，从而减少胆汁酸合成。机体通过肝脏及肠道FXR通路调控胆汁酸合成，维持胆汁酸稳态。此外，其他胆汁酸受体如G蛋白偶联受体5(the g-protein coupled receptor 5，TGR5)在胆汁酸的合成和转运中也发挥着重要作用。

2 胆汁酸通路与IBS-D的关系

有研究发现，68%的IBS-D患者存在粪便胆汁酸排泄增加或胆汁酸吸收不良[32]。另有研究表明，12%~43%的IBS-D患者存在粪便胆汁酸过度排泄[33]，此类患者被称为特发性胆汁酸相关性腹泻[34]。胆汁酸能够直接诱发结肠运动加速及内脏超敏反应[35-36]，也有研究表明，粪便胆汁酸的增加与患者的腹痛及结肠加速转运密切相关[37]，这些因素都与IBS-D的发病密切相关。一项临床研究分析了IBS-D患者(n=16)与健康者(n=5)的血液及粪便标本，发现IBS-D患者血清及粪便中初级胆汁酸明显升高，而次级胆汁酸明显降低[37]。一项双盲、安慰剂对照试验采用胆汁酸螯合剂鹅脱氧胆酸钠治疗IBS-D，结果显示患者的粪便胆汁酸排泄减少，部分IBS-D症状缓解[38]。综上所述，胆汁酸代谢紊乱在IBS-D发病机制中起着重要作用，干预胆汁酸代谢有望成为治疗IBS-D的靶点。FXR通路在调节机体胆汁酸合成方面起重要作用，其信号传导异常加剧了IBS-D的疾病进展，而FXR下游信号分子FGFR4异常加速了IBS-D患者结肠的转运速率[39]。

3 IBS-D患者肠道菌群的变化

关于IBS-D患者肠道菌群变化的研究较多，但结果不尽相同。较早的一项临床研究获取IBS-D患者(n=41)与健康者(n=26)的粪便及十二指肠黏膜刷样本，使用荧光原位杂交(FISH)技术分析粪便标本中菌群的组成，随后利用PCR分析粪便及十二指肠黏膜刷样本中双歧杆菌的组成，结果发现，IBS-D患者粪便中的双歧杆菌水平降低了50%，且链状双歧杆菌水平也出现降低[40]。还有研究分别获取IBS-D患者(n=10)与健康者(n=10)的粪便及结肠黏膜活检标本，提取DNA后通过实时定量PCR分析特定菌群，结果发现IBS-D患者粪便中需氧细菌的浓度明显降低，但乳酸杆菌浓度增加了3.6倍[41]。另一项研究分析了IBS-D患者(n=16)与健康者(n=21)粪便及结肠黏膜标本的微生物群落组成，发现IBS-D患者粪便中微生物的生物多样性比健康者低20%，但在结肠黏膜标本中未发现生物多样性存在差异[42]。有研究采用16S rRNA基因技术对IBS-D患者(n=23)与健康者(n=23)的粪便进行分析，发现IBS-D患者16S rRNA序列的丰度明显降低，而肠杆菌科的丰度显著增加[43]。随着菌群分析技术的不断进步，从判定粪便中某一特定菌群的水平变化到对全菌群进行系统分析，关于IBS-D患者肠道菌群的研究也取得了长足的进步。尽管大多数临床研究结果不尽相同，但在IBS-D患者肠道微生物多样性降低这一观点上却基本一致。

4 肠道菌群-胆汁酸与IBS-D的关系

4.1 IBS-D患者体内肠道菌群稳态及胆汁酸代谢存在差异 肠道菌群在初级胆汁酸到次级胆汁酸的转化中起着重要作用，肠道菌群紊乱可能会导致胆汁酸代谢异常。Zhao等[44]采用代谢及宏基因组学方法对290例IBS-D患者与89例健康者的胆汁酸及肠道菌群进行分析，结果发现，24.5%的IBS-D患者粪便胆汁酸过量排泄，且其肠道中与胆汁酸代谢相关菌群的丰度发生改变。另一项临床研究表明，与健康人群相比，伴有胆汁酸排泄及合成增加的

IBS-D患者表现出更明显的病理生理变化，如体重指数、粪便脂肪、CDCA百分比及结肠通透性均明显增加[32]。一项Meta分析纳入了13篇有关肠道菌群与IBS关系的研究，涉及360例IBS患者与268名健康者，结果发现IBS患者尤其是IBS-D患者的乳酸杆菌(*Lactobacillus*)、双歧杆菌(*Bifidobacterium*)及普拉梭菌(*F. prausnitzii*)丰度均下降[45]。

4.2 胆汁酸-肠道菌群紊乱促进IBS-D的疾病进展 胆汁酸通过经典与替代途径合成得到的CA及CDCA均为初级胆汁酸，其在肠道内某些特定菌群的作用下，通过去结合、7α-去羟基化、氧化、脱硫及酯化反应等，被转化为脱氧胆酸(deoxycholic acid，DCA)及石胆酸(lithocholic acid，LCA)[46]，其中7α-去羟基化为最关键的一环。研究表明，梭菌属及优杆菌属在7α-去羟基化过程中发挥重要作用，但具体机制尚未明确[47]。此外，特定的肠道菌群能影响牛磺酸和(或)甘氨酸与游离胆汁酸的结合，从而调控结合胆汁酸。肠道菌群能影响胆汁酸的转化与结合，反之，胆汁酸对肠道菌群也有直接的抗菌作用，DCA是最有效的抗菌胆汁之一，其杀菌活性是CA的10倍，并且可显著抑制乳酸杆菌、产气荚膜梭菌、双歧杆菌及脆弱拟杆菌等肠道微生物的生长[48-49]。胆汁酸作为代谢调节剂及营养传感器，其浓度较高时会产生细胞毒性作用，导致细胞膜稳定性下降，引起细胞凋亡，诱导促炎作用及细胞DNA损伤，进而导致某些胃肠道疾病[32,50]。FXR通路在机体内主导胆汁酸代谢，IBS-D患者胆汁酸代谢紊乱与其通路信号异常密不可分。有临床研究发现，与健康者相比，IBS-D患者肠道FGF19表达降低，肠道胆汁酸合成增加[51]，进一步证实了胆汁酸代谢异常及其通路受损在IBS-D发病机制中的重要地位。在动物实验中，与野生型($FXR^{+/+}$)小鼠相比，FXR基因敲除型($FXR^{-/-}$)小鼠表现出明显的肠道炎症、肠道菌群紊乱及肠黏膜屏障功能受损[52]。有研究发现，在IBS-D患者中，胆汁酸通过黏膜肥大细胞到痛觉感受器的信号传导诱导内脏超敏反应，该信号传导涉及FXR-神经生长因子-瞬时受体电位香草酸亚型1轴[53]。可见，除调节胆汁酸代谢外，FXR在调控肠道炎症、维护肠道黏膜屏障功能及调节内脏超敏反应等方面也起着重要作用[54-55]。FXR通路除了在胆汁酸合成及运输的调节中发挥作用外，还是胆汁酸调节的转录因子及保护性传感器，可在胃肠道组织中诱导保护性细胞反应，并调节炎症水平[56]。综上可知，胆汁酸与肠道菌群之间存在特殊的关系，既相互作用，又互相调节。当两者其一或均出现异常时，宿主罹患IBS尤其是IBS-D的概率将会相应增加。

5 总结与展望

目前对肠道菌群的研究多集中在益生菌方面。益生菌被联合国粮食及农业组织定义为一种活微生物，适量应用可给宿主带来健康益处[57]。益生菌在治疗IBS-D中的作用是多样的。研究表明，益生菌对IBS-D患者有较好的治疗效果[58-59]。笔者前期研究也表明，益生菌可能具有类似FXR激动剂的作用，能激活小鼠FXR通路，调控机体胆汁酸代谢[60]。此外，益生菌在调控宿主肠道菌群、降低内脏超敏反应性等方面也起着重要作用[61-62]。鉴于FXR在IBS-D发病机制中所起的作用，调控FXR通路水平也是IBS-D治疗的一种选择。考来烯胺散为胆汁酸螯合剂的一种，动物实验证实其能够调控小鼠FXR下游SHP的表达水平，现已用于IBS-D的治疗[63-64]。总之，胆汁酸-肠道菌群有望成为治疗IBS-D的新靶点。然而，并非每位IBS-D患者都存在胆汁酸代谢异常，仍需实施个性化的治疗方案。

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