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专论与综述

肠道微生物代谢物在肠易激综合征中的研究进展

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摘　要：肠易激综合征(irritable bowel syndrome, IBS)是常见的胃肠道功能障碍疾病，以腹痛、腹胀、排便习惯改变等为典型临床症状。尽管 IBS 病因复杂且发病机制并未完全阐明，但越来越多的文献报道其发病与微生物-肠-脑轴调控失常密切相关。本文以肠道微生物衍生的代谢物神经递质、短链脂肪酸和胆汁酸代谢物为切入点，对其在内脏敏感、腹痛、腹泻和精神心理障碍等 IBS 症状发展中的作用进行系统综述，为以代谢物转化细菌为靶点治疗 IBS 提供理论支撑。
关键词：肠易激综合征；微生物-肠-脑轴；5-羟色胺；短链脂肪酸；胆汁酸代谢物

Gut microbiota-derived metabolites in irritable bowel syndrome

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Abstract: Irritable bowel syndrome (IBS) is the most common functional bowel disorder with the typical clinical symptoms such as abdominal pain, abdominal distension, and changes in

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bowel habits. Although the pathogenesis of IBS is complex and has not been fully understood, it has been proven to be related to the abnormal regulation of microbiota-gut-brain axis. The effects of derivative metabolites mediated by the microbiota, such as neurotransmitter, short-chain fatty acids, and bile acids metabolites, on the development of IBS symptoms (visceral sensitivity, abdominal pain, diarrhea and mental disorders) were systematically summarized. This study is expected to provide a new insight for the treatment of IBS with metabolites transforming bacteria as targets.

Keywords: irritable bowel syndrome; microbiota-gut-brain axis; 5-hydroxytryptamine; short-chain fatty acid; bile acids metabolites

肠易激综合征(irritable bowel syndrome, IBS)是临床常见的慢性胃肠功能障碍疾病，主要表现为持续性或间歇性腹痛、排便习惯改变或伴随焦虑等症状。根据粪便性状及其排便频率,临床上将 IBS 分为腹泻型(diarrhea predominant-IBS, IBS-D)、便秘型(constipation predominant-IBS, IBS-C)、混合型(mixed IBS, IBS-M)和不定型(unclassified IBS, IBS-U) 4 个亚型，其中 IBS-D 是罗马IV标准中临床最常见亚型[1-2]。IBS 在全球大多数地区发病率高达 5%–10%左右[2]，而且多伴有焦虑抑郁等情绪障碍的特点,已成为临床上亟待解决的疾病难题[1]。现代临床主要采用口服解痉剂、止泻剂、抗抑郁等药物对 IBS 症状进行治疗，虽然短期治疗效果较好，但存在疗效有限、不良反应严重和适应范围小等问题[3-4]。

IBS 发病机制复杂，与肠道高敏感、肠黏膜屏障受损和微生物-肠-脑紊乱等密切相关[5-6]。尽管微生物-肠-脑(microbiota-gut-brain, MGB)轴的概念相对较新，但已有较多文献报道，微生物群及其代谢物通过肠神经系统(enteric nervous system, ENS)和中枢神经系统(central nervous system, CNS)之间的信号交流在 IBS 中发挥关键作用[7]。IBS 大鼠模型如 4%乙酸结合束缚应激、结直肠扩张、母婴分离等均会引起 MGB 轴的变化，包括血清中 5-羟色胺(5-hydroxytryptamine, 5-HT)、P 物质等水平升高，肠道通透性增加，肠道菌群的组成和结构发生改变[8]。此外，肠道微生物及其代谢物如胆汁酸代谢物也表现出调节肠道动力和肠道敏感性的作用，同时可以直接或间接地塑造肠道微生物[9]。本文对肠道微生物及其衍生代谢物神经递质、短链脂肪酸和胆汁酸等在 IBS 发病中的作用进行综述，以期为 IBS 的临床诊断及治疗提供指导意义。

1 微生物-肠-脑轴与 IBS 密切相关

1.1 微生物-肠-脑轴

肠-脑轴(gut-brain axis, GBA)是大脑和肠道功能整合的双向信息交流系统，该概念于 20 世纪 80 年代在蛙皮素对胆囊收缩素的调节作用中被提出[10]。肠道微生物参与 GBA 轴的功能反应，在 ENS 与 CNS 信息交流中发挥重要作用，因此，学者们提出了微生物-肠-脑轴的概念。微生物-肠-脑轴通过免疫信号通路、神经内分泌、肠神经系统和迷走神经等影响神经系统和胃肠系统相关疾病，包括帕金森、儿童孤独症和 IBS 等，同时涉及微生物代谢物如短链脂肪酸、胆汁酸等[11]。一方面，肠道微生物及其代谢物可以通过影响促炎和抗炎细胞因子等的生成，进而通过循环系统向 CNS 发出信号；另一方面，

CNS 通过应激刺激等诱导基因表达直接影响肠道微生物，也可以通过自主神经系统(autonomic nervous system, ANS)调控肠道功能，间接影响肠道微生物[11-13]。微生物-肠-脑轴信号交流途径如图 1 所示。

1.2 微生物-肠-脑轴紊乱与 IBS

IBS 诊断通用的罗马IV标准也强调了胃肠功能与中枢神经和肠神经系统的关系，进一步明确了 GBA 轴与功能性胃肠疾病的发病密切相关。Zamani 等[14]对 73 项研究进行 Meta 荟萃分析，结果显示 IBS 患者的焦虑或抑郁风险是健康志愿者的 3 倍，生活质量得分较低，同时焦虑或抑郁患者 IBS 患病率也显著升高。功能磁共振成像结果显示，IBS 患者的疼痛直肠扩

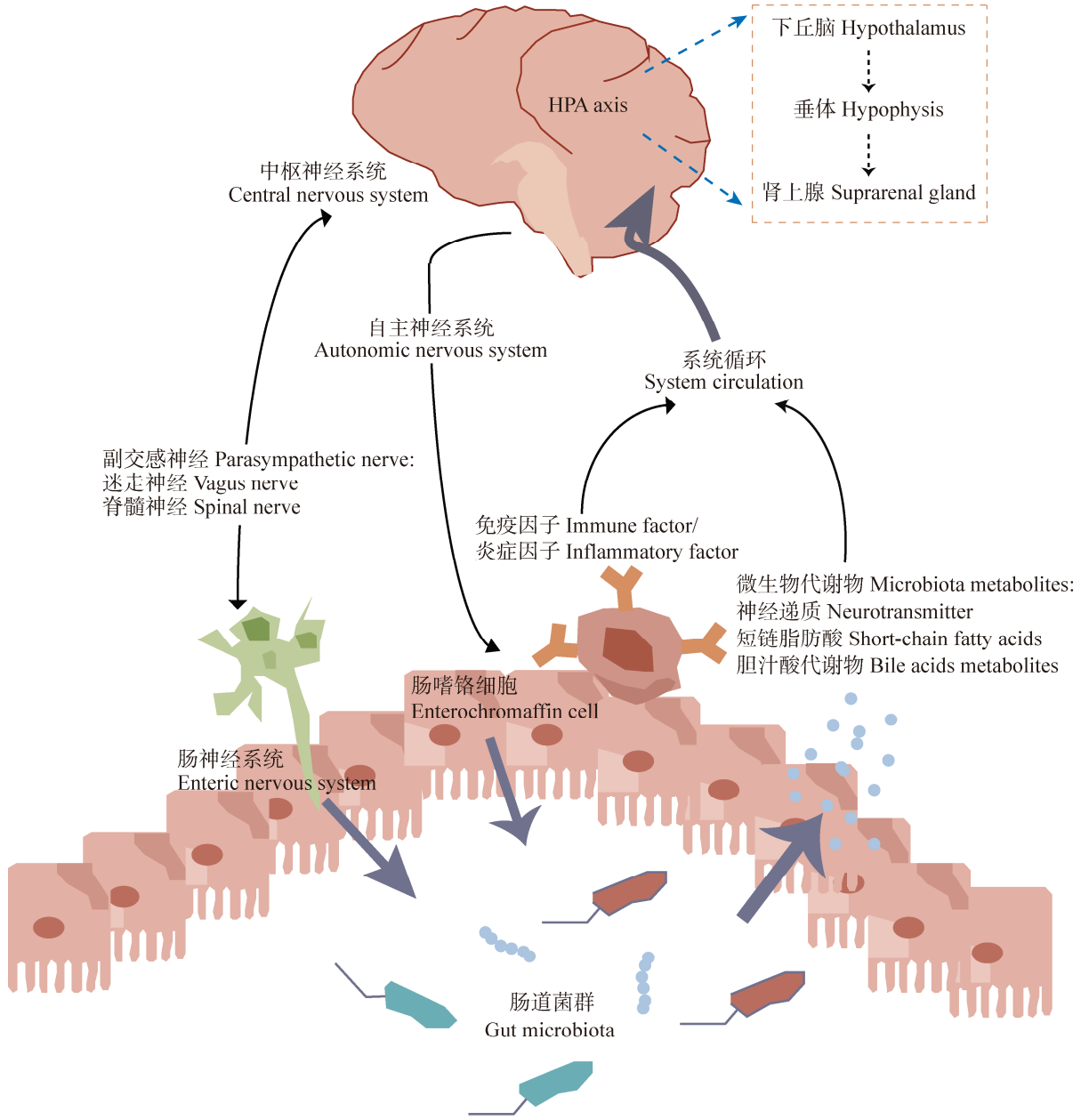

图 1 微生物-肠-脑轴信号交流

Figure 1 Microbiota-gut-brain axis communication.

张刺激能够增强扣带前回(anterior cingulate, ACC)、前额叶皮层(prefrontal cortex, PFC)和丘脑等脑区兴奋性，并且大脑皮质活动与内脏感觉呈现同步改变现象[15-16]。

IBS 患者和健康个体的肠道微生物群组成差异较大[17-19]。较多研究显示，IBS 患者粪便致病菌(大肠杆菌和肠杆菌等)和有益菌株(乳酸杆菌和双歧杆菌等)相对丰度发生改变[17]，厚壁菌门和拟杆菌门比例增加[19]。更进一步地，Wei 等[18]对 55 名 IBS-D 患者和 28 名健康志愿者的肠道微生物进行分析，发现 IBS-D 患者肠道菌群的特点是梭菌纲、梭菌目和瘤胃球菌科相对丰度降低，γ-变形菌纲、肠杆菌目和肠杆菌科相对丰度增加。肠道微生物失调引起的内分泌、神经和炎症信号可以改变大脑结构和功能[13]。

学者们进一步提出益生菌和粪菌移植等用于 IBS 治疗并取得一些进展。布拉氏酵母菌 CNCM I-745 给药后，不仅能够改善 IBS 粪菌移植引起的小鼠胃肠道快速转运，同时对其焦虑样行为也有一定缓解作用，这可能与肠道微生物群的改变和吲哚-3-乙酸水平增加有关[20]。IBS 患者接受 30 g 和 60 g 粪菌移植(来自 1 名健康志愿者，采用生理盐水与粪菌混合、过滤并通过胃镜送至十二指肠远端) 3 个月后，患者的腹部症状、疲劳和生活质量均得到明显改善，应答终点分别达到 50.0%和 70.9%，与安慰剂组相比具有明显差异[21]。以上结果均表明，肠道微生物群在 IBS 的发生中起着重要作用。

2 肠道菌群代谢物神经递质参与 IBS

神经递质是神经末梢释放的特殊化学物质，通过结合相应受体和一系列的信号转导途径产生生物学效应。肠道微生物可以通过直接或间接调控神经递质释放参与肠道功能和行为认知变化，包括 5-HT、γ-氨基丁酸(gamma-aminobutyric acid, GABA)和去甲肾上腺素(noradrenaline, NE)等[22-23]。

2.1 5-羟色胺途径紊乱

5-HT 是一种吲哚衍生物，约 95%分布于肠道内，其中 90%由肠嗜铬细胞(enterochromaffin cell, ECs)合成和分泌，是实现 MGB 轴信号交流的关键神经递质，参与胃肠运动、疼痛感、免疫反应和大脑活动等；5-HT 主要是由膳食成分衍生的 L-色氨酸(L-tryptophan, TRP)生物合成，色氨酸羟化酶(tryptophan hydroxylase, TPH)将 TRP 转化为 5-HT 的直接前体 5-羟基色氨酸(5-hydroxytryptophan, 5-HTP)，通过 5-羟基色氨酸脱羧酶(5-hydroxytryptophan decarboxylase, 5-HTPDC)催化生成 5-HT；5-HT 与受体结合后迅速解离并通过跨膜转运蛋白(serotonin transporter, SERT)重新转运至肠细胞，经单胺氧化酶(monoamine oxidase, MAO)代谢成 5-羟基吲哚乙酸(5-hydroxyindole-3-acetic acid, 5-HIAA)[23]。5-HT 合成与转运途径(图 2)失调可能会触发 IBS 发生与发展。

2.1.1 5-HT 途径介导内脏高敏感性

5-HT 信号通路主要通过转运蛋白和不同受体亚型参与肠道高敏感性调节[23-24]。肠道菌群失调可能通过上调 SERT 表达促进慢性便秘的发生[25]，而小鼠和人微生物群的土著孢子形成菌则能够促进结肠 ECs 的 5-HT 生物合成，引起腹泻发生[26]。当 SERT 表达降低时，重摄取 5-HT 减少，造成内脏感觉异常，出现腹痛、腹泻等 IBS 异常症状，因此，多数 SERT 基因敲除的大鼠会出现腹痛、腹泻症状[23]。Cui 等[24]进一步研究发现，IBS 患者和内脏高敏大鼠血浆中表皮生长因子(epidermal growth factor, EGF)水平降低，并与 SERT 蛋白表达呈相关性；

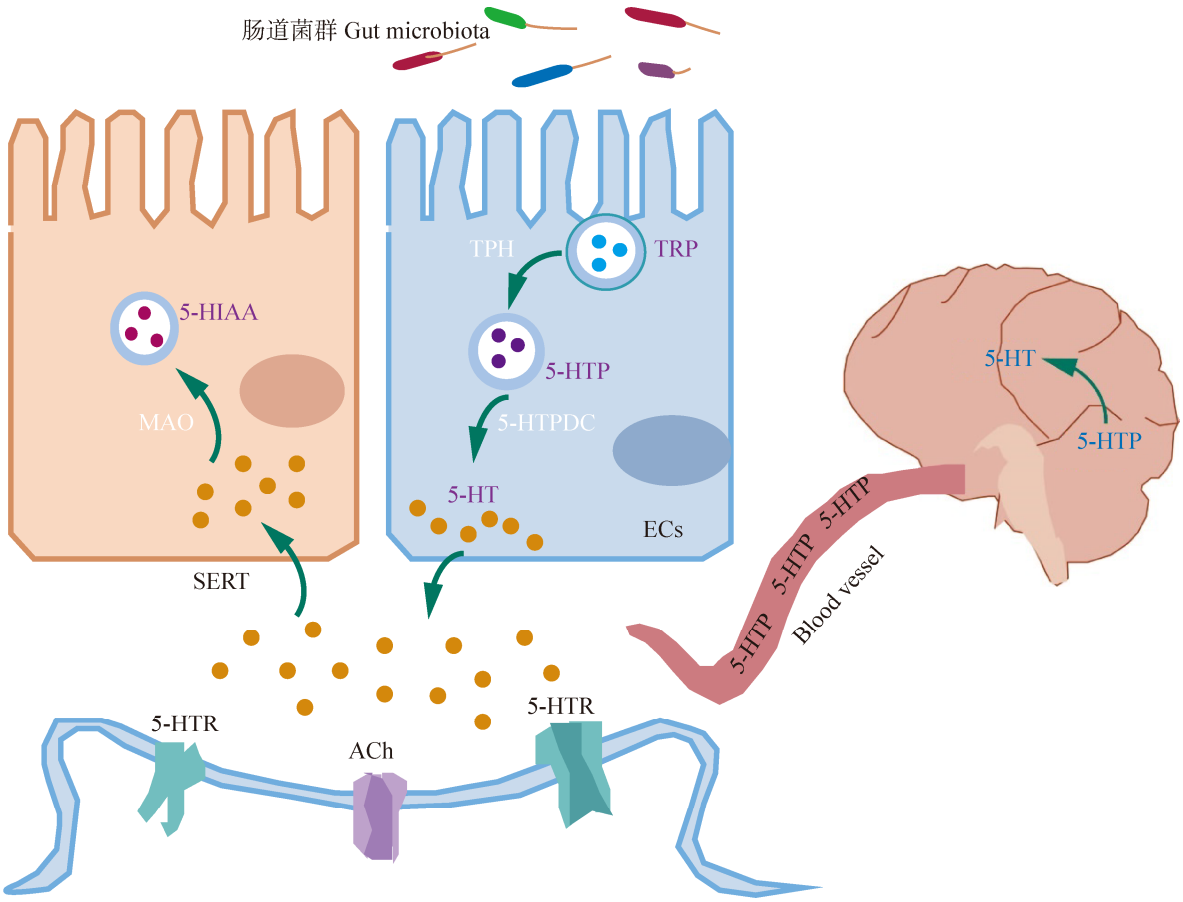

图 2　5-羟色胺合成与转运途径

Figure 2　5-HT synthesis and transport.

EGF 可能通过下调 SERT 介导肠细胞重摄取 5-HT，导致内脏高敏反应[24]。

5-HT 受体家族可分为 7 种亚型和 15 种亚亚型，其中 5-HT3R 和 5-HT4R 在胃肠道研究最多[27]。5-HT3R 拮抗剂阿洛司琼常被用于改善 IBS-D 患者的疼痛、腹泻症状。5-HT7R 在黏膜神经细胞中高度表达，不仅参与疼痛感觉的神经传递，而且在黏膜神经突起生长中起重要作用；5-HT 通过激活 5-HT7R 增强肠黏膜的神经突起生长并促进肠道痛觉过敏，口服新型 5-HT7R 拮抗剂可直接减轻痛感；此外，5-HT7R 的激活对神经生长因子(nerve growth factor, NGF) 和 (brain-derived neurotrophic factor, BDNF)基因表达产生上调作用，而神经营养素的刺激反过来增加了神经元中 5-HT7 和 5-HT 的合成，从而加快黏膜神经纤维伸长，产生内脏高敏感性[28]。

2.1.2　5-HT 途径介导胃肠动力紊乱

不同分型 IBS 患者血清中 5-HT 水平不同。较多研究显示，IBS-D 患者餐后 5-HT 水平升高，而 IBS-C 患者 5-HT 水平降低[29-30]，这种释放减少与转运显著延迟有关[30]。当胃肠道受到刺激时，ECs 释放 5-HT 并与 5-HT3R/5-HT4R 结合，增加细胞内 Ca^{2+} 水平，促进降钙素相关肽(calcitonin gene related peptide, CGRP)等神经递质的释放，引起肠胆碱能神经元释放乙酰胆碱(acetylcholine, ACh)，增强肠道平滑肌收缩，使结肠传输加快，产生腹泻症状[31-32]。一氧化氮

(nitric oxide, NO)作为非肾上腺素能非胆碱能神经的抑制性神经介质，在平滑肌松弛中起着重要作用[33]。研究表明，5-HT 与 5-HT1R 结合后触发抑制性氮能神经元产生 NO，使豚鼠升结肠平滑肌舒张，产生便秘症状[34]。此外，肠道微生物也可以通过短链脂肪酸(short-chain fatty acids, SCFAs)增加 TPH1 的转录和 5-HT 生成，从而加快结肠运动[35]。

2.1.3 5-HT 途径介导精神心理障碍

由于血脑屏障作用，血液 5-HTP 并非 5-HT 可以进入中枢神经系统，因此，5-HTP 是中枢神经系统 5-HT 合成的重要前体物质[36]。长双歧杆菌 E41 和短双歧杆菌 M2CF22M7 对小鼠抑郁有一定改善作用，与 5-HTP 表达和微生物群的调节有关[37]。临床上常应用选择性 5-HT 再摄取抑制剂(氟西汀等)对精神心理障碍的 IBS-D 患者进行治疗。结肠 SERT 蛋白表达水平越低，越容易患焦虑和抑郁[38]，可能是由于 5-HT 不能被及时转运在突触间隙积累，导致调节脑肠稳态的 5-HT 数量减少、有效浓度降低，使 IBS 患者同时出现肠道腹泻和精神障碍。动物实验研究也表明，IBS-D 大鼠结肠及下丘脑中 5-HT 含量和 5-HT3R 表达量明显升高，而 5-HT4R 和 SERT 明显降低[39-40]。

2.2 γ-氨基丁酸介导内脏敏感

GABA 是中枢神经系统的抑制性神经递质，同时也可以调节肠道功能。拟杆菌属、副拟杆菌属和埃希氏菌属等肠道微生物群参与 GABA 合成，而 GABA 又是脆弱拟杆菌 KLE1738 所需碳和能量的来源[41]。谷氨酸脱羧酶(GadB)编码基因为氨基丁酸的转化提供了遗传基础，研究表明，齿双歧杆菌共生菌通过 GadB 酶促使谷氨酸脱羧产生 GABA[41-42]。较多研究显示，肠道菌群中调节 GABA 的细菌与抑郁症相关的大脑信号有关[41,43]，如左背外侧前额叶皮层。

GABA 能信号系统在 IBS 肠道高敏感等症状中发挥重要作用，主要涉及谷氨酸脱羧酶(glutamate decarboxylase, Gad)、GABA 转氨基酶、GABA 受体($GABA_A$、$GABA_B$、$GABA_C$)、GABA 转运体(gABA transporter, GAT)[44]。Aggarwal 等[45]研究报道，IBS-D 患者血清 GABA 水平明显降低，$GABA_B$ 受体 B1 和 B2 亚型 mRNA 表达水平下降，GAT-2 表达水平升高。GABA 水平的降低和 GABA 能信号系统的改变通过下调白介素(interleukin, IL)-1β、肿瘤坏死因子-α 和 IL-8 等促炎因子诱导 IBS-D 发生[45]。在急性应激动物模型中，口服食源性乳酸菌能够显著抑制结肠应激引起的内脏超敏反应，其机制与通过 Gad 而提高胃肠道 GABA 水平从而激活 $GABA_B$ 受体有关；当动物在谷氨酸存在下接受 $GABA_B$ 受体拮抗剂 SCH-50911 时，该菌株对内脏过敏的治疗作用则完全消失[46]。直接临床证据表明，GABA 激动剂或类似物如上市药普瑞巴林(钙通道 α2δ 配体)在 IBS 患者腹痛、腹胀和腹泻等症状中表现出较好的治疗效果[47]。

3 肠道菌群代谢物短链脂肪酸参与 IBS

SCFAs 是肠道微生物群发酵膳食纤维产物，大约 95%的 SCFAs 由乙酸盐、丙酸盐和丁酸盐(摩尔比约为 3:1:1)组成；SCFAs 主要通过扩散或单羧酸转运蛋白和溶质转运蛋白进入细胞[48]。研究表明，拟杆菌门的细菌产生大量的乙酸和丙酸，而双歧杆菌产生大量的丁酸，无菌小鼠由于缺乏肠道微生物而不产生 SCFAs[49]。粪便 SCFAs 含量在不同 IBS 亚型中呈现明显差异，IBS-D 患者粪便 SCFAs 的总浓度显著升高，而 IBS-C 中 SCFAs 总浓度较低[50-51]。不同 IBS 亚型总体以乙酸的含量最高，其次是

丙酸和丁酸；IBS-C 患者乙酸盐、丙酸盐和丁酸盐均显著低于其他亚型[50]。由此，SCFAs 或可作为 IBS 亚型的潜在生物标志物。SCFAs 在 IBS 中的可能作用机制如图 3 所示。

3.1 SCFAs 介导肠道黏膜屏障保护

消化道屏障是预防有害物质和病原菌的主要防护手段，包括化学、免疫、机械等屏障，其中机械屏障占主导地位；机械屏障主要由上皮细胞和 claudins、occludin 等紧密连接蛋白(tight junction, TJ)共同构成[52]。内源性丁酸由不可消化碳水化合物和己糖低聚物的细菌发酵产生，在肠道黏膜屏障功能保护中发挥多种有益作用，其生产涉及的细菌种类有梭菌属、真杆菌属、梭杆菌属、丁酸菌属、艾氏巨球菌属、肠球菌、粪杆菌属和 *Eubacterium hallii* 真杆菌[53]。丁酸盐作为 SCFAs 的主要成员，可以通过调节 TJ 维持肠道黏膜屏障的完整性，其作用机制可能是：(1) 通过增加转录因子 SP1 与紧密连接蛋白 claudin-1 启动子之间的相互作用，在转录水平上增强 claudin-1 的表达，诱导 ZO-1 和 occludin 在细胞膜表面再分布，逆转 Ca^{2+}引起的损伤效应[54]；或与细胞内能量感受器 AMP 依赖的蛋白激酶(AMP-activated protein kinase, AMPK)相互作用，增加紧密连接蛋白 claudin-3 和 claudin-4 表达，减轻结肠通透性[55]。(2) 通过激活信号转导与转录激活因子 3 (signal tranducers and activators of transcription 3, STAT3)、抑制组蛋白去乙酰化酶(histone deacetylase, HDAC)，上调抗炎因子 IL-10 受体 α 亚基的转录激活，抑制 claudin-2 蛋白表达，从而增强人肠上皮细胞屏障形成[56]。丁酸盐对 HDAC 的抑制作用也能够上调肌动蛋白相关蛋

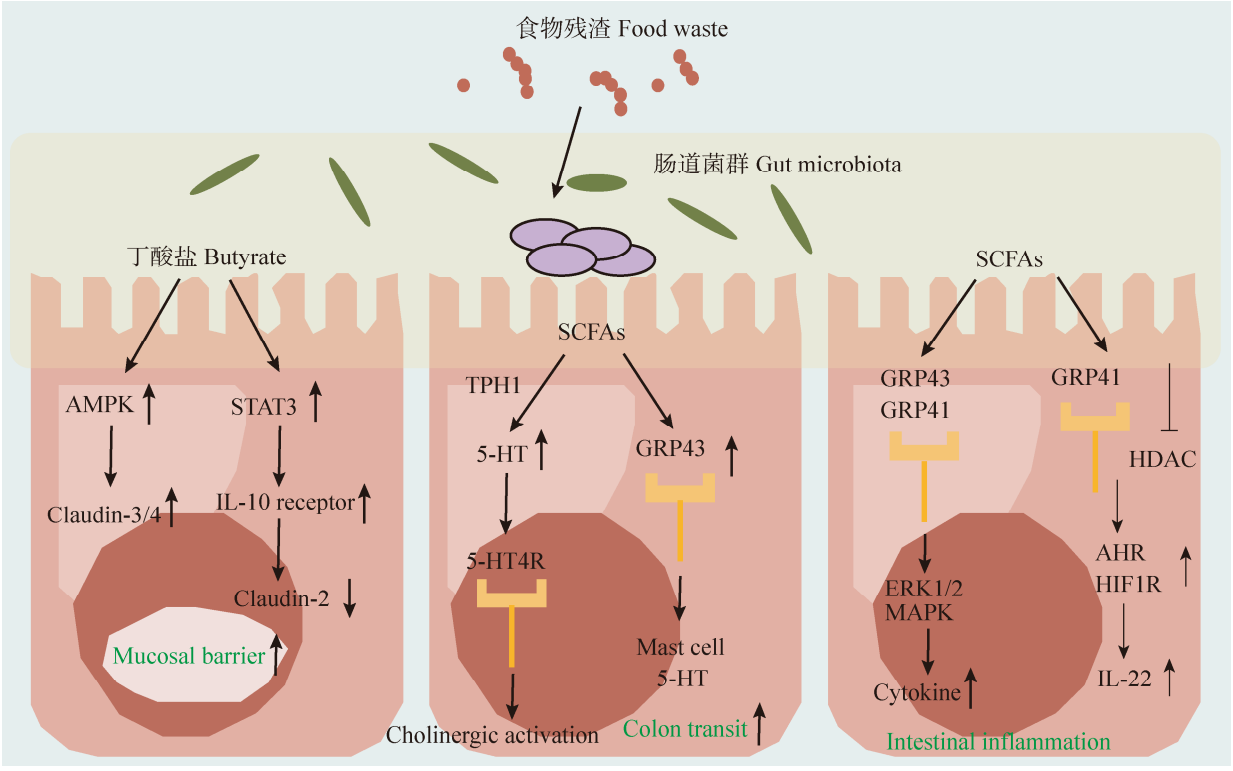

图 3 肠道菌群代谢物短链脂肪酸参与 IBS

Figure 3 Gut microbiota metabolites SCFAs in IBS.

白-突触足蛋白表达，促进损伤后肠上皮屏障的恢复[57]。

3.2 SCFAs 介导胃肠运动紊乱

不同种类 SCFAs 对结肠运动的影响有一定差异。Soret 等[58]研究表明丁酸盐而非丙酸盐或乙酸盐，能够增加肠神经系统中的胆碱乙酰转移酶(choline acetyltransferase, ChAT)免疫反应阳性的肌间神经元的比例，涉及 Src 激酶信号通路和 H3K9 的乙酰化，并通过胆碱能通路介导结肠环肌收缩[58]。SCFAs 刺激肠道中神经递质 5-HT 的释放，是 SCFAs 调节胃肠运动的关键内容。一方面，肠道微生物通过 SCFAs 刺激 ECs 增加 TPH1 mRNA 表达，促进 5-HT 的释放；5-HT 通过内源性初级传入神经元末端的 5-HT4R，激活收缩还肌的胆碱能运动神经元，从而促进结肠运动[35,59]。研究还发现，SCFAs 丁酸盐和乙酸盐主要由远端肠道微生物大量产生，以浓度依赖的方式显著影响 TPH1 的表达[35]。另一方面，SCFAs 刺激 ECs 释放 5-HT 可激活迷走神经感觉纤维上的 5-HT3R，感觉信息被传递到迷走传出神经，刺激结肠肌间神经丛释放乙酰胆碱，加快结肠收缩[60]。另有研究报道，SCFAs 可能通过激活结肠的全壁和分离黏膜的 G 蛋白偶联受体 43 (G protein-coupled receptor, GPR43)，进而激活含 5-HT 的黏膜肥大细胞，从而对结肠运动和分泌的兴奋性和抑制性生理作用产生影响；而回结肠抑制作用可能是直接刺激含肠道激素肽 YY 的肠内分泌细胞的结果[61]。以上研究表明，SCFAs 能够通过刺激结肠释放 5-HT 促进结肠运动。

3.3 SCFAs 介导肠道炎症反应

荟萃分析结果显示，超过 10%的感染性肠炎患者后期会发展为 IBS，特别是患有严重肠炎的女性[62]。无菌小鼠很少表达或不表达 SCFAs，表现出炎症反应失调现象，研究表明 SCFAs 介导肠道炎症反应的作用机制与调节肠上皮细胞 GPR41 和 GPR43 受体有关[63-64]。Kim[63]研究报道，GPR41-/-和 GPR43-/-小鼠在给予乙醇或三硝基苯磺酸(TNBS)后，中性粒细胞浸润、炎性趋化因子(CXCL1、CXCL2 和 CCL2)等炎症反应明显降低，并且对啮齿动物感染的炎症免疫反应和清除细菌的速度均较慢；更进一步地，SCFAs 通过激活肠上皮细胞 GPR41 和 GPR43 受体，调节细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK1/2)和 p38 丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路，从而诱导 ECs 在免疫应答期间产生趋化因子和细胞因子[63]。SCFAs 特别是乙酸盐和丙酸盐可以结合并激活 GPR43 受体，刺激人中性粒细胞，显著降低促炎性 C5aR 和 CXCR2 的表达[64]。此外，微生物群是肠道中诱导 CD^{4+}T 细胞产生 IL-22 的核心，补充微生物群衍生的 SCFAs 能够增加 IL-22 的产生，保护肠道免受炎症损害；SCFAs 通过 GPR41 受体和抑制 HDAC 促进 CD^{4+}T 细胞和先天性淋巴细胞(innate lymphoid cells, ILCs)上调 IL-22 的产生，其作用机制与激活哺乳动物雷帕霉素靶蛋白(mechanistic target of rapamycin, mTOR)和 STAT3，以及提高 $CD4^{+}$T 细胞中芳香烃受体(aryl hydrocarbon receptor, AhR)和缺氧诱导因子-1α (hypoxia inducible factor-1α, HIF-1α)表达有关[65]。

4 肠道菌群代谢物胆汁酸参与 IBS

越来越多证据表明，胆汁酸(bile acids, BAs)在 IBS 内脏敏感、结肠运动和肠道通透性病理生理过程中起重要作用。荟萃分析显示，16.9%–35.3%的 IBS-D 患者被诊断为 BA 吸收不

良，主要表现在粪便结合和非结合 BAs 显著增加和 BA 转化细菌的改变[66]。约 15%的 IBS-C 患者脂肪饮食 48 h 后，粪便总胆汁酸和脱氧胆酸水平降低[67]。梭菌属和 scindens 梭菌属细菌丰度的增加是 IBS 患者 BAs 含量变化的因素之一，这可能与菌群失调引起血清 7α-羟基-4-胆甾烯-3 酮(肝脏 BAs 合成标志物)变化，从而影响 IBS 患者粪便胆汁酸转化有关[67-68]。胆汁酸代谢物在 IBS 中的可能作用机制如图 4 所示。

肠道微生物可能通过胆汁酸激活 G 蛋白偶联受体(takeda G protein-coupled receptor, TGR)和法尼酯 X 受体(farnesoid x receptor, FXR)信号转导，从而调节结肠运动和大便重量[69]。IBS-D 患者粪便的初级胆汁酸占比显著高于对照组，而且与大便性状和频率相关，这可能是由于菌群失调导致 BAs 转化水平较低[70]。Wei 等[71]进一步研究发现，更频繁或更严重腹痛的 IBS-D 患者结肠黏膜中 TGR5 表达更高，并且与粪便

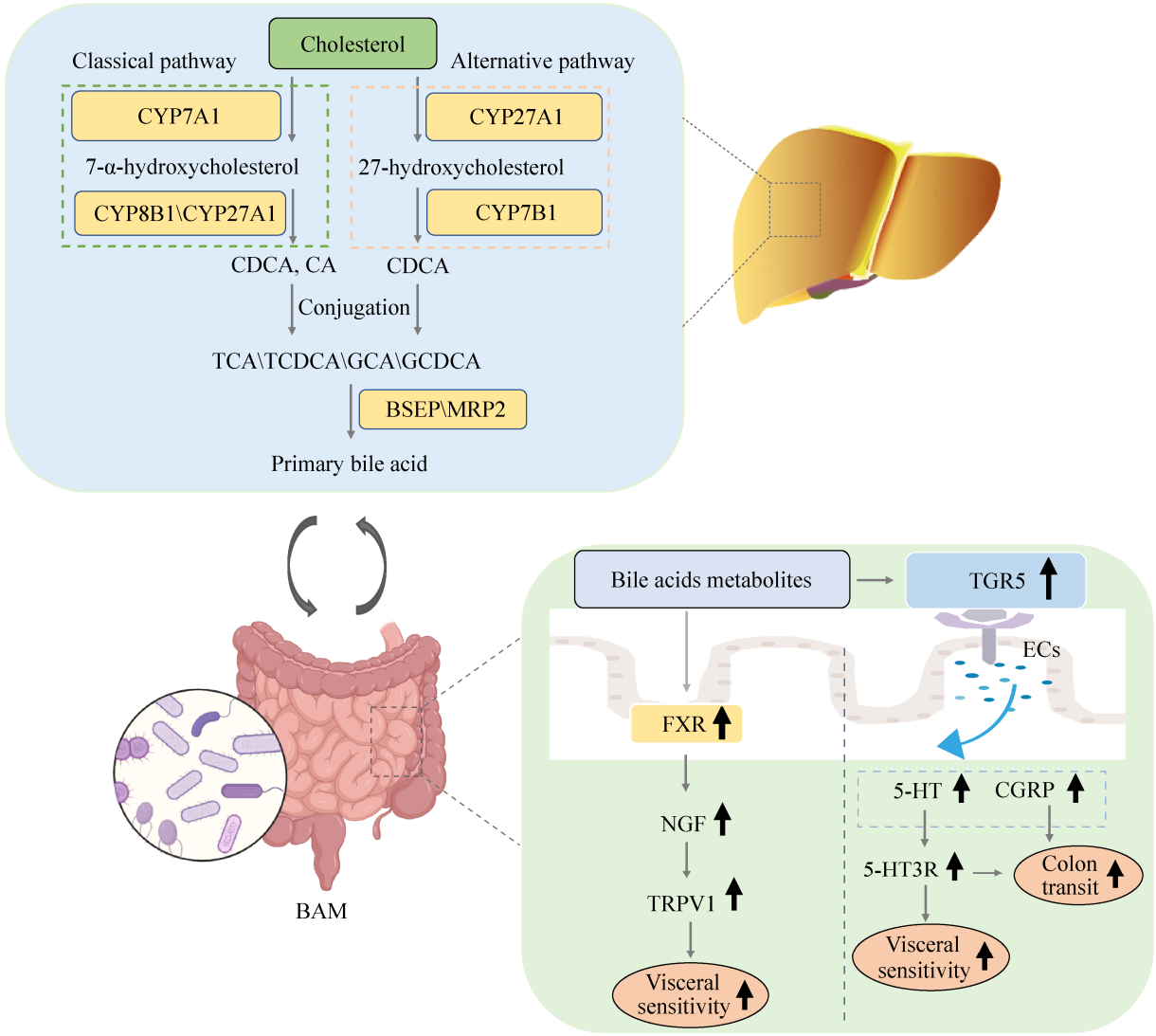

图 4　肠道菌群代谢物胆汁酸参与 IBS (BioRender)

Figure 4　Gut microbiota metabolites bile acid in IBS (BioRender).

初级 BAs 呈正相关,与粪便次级 BAs 呈负相关。尽管尚未观察到粪便 BAs 和腹痛的直接联系,但 BAs 可能通过激活 ECs 和内源性初级传入神经元表达的 TGR5 释放 5-HT 和 CGRP,这是蠕动反射传输的主要神经递质;TGR5 缺失导致胃肠转运延迟,而 TGR5 过表达则加速结肠转运,其或可作为便秘或腹泻的治疗靶点[71]。NGF 通过与肥大细胞和感觉神经纤维的相互作用,介导内脏高敏感和肠道屏障功能障碍;IBS-D 患者 NGF 基因表达、黏膜肥大细胞计数和感觉神经纤维等均显著增加,内脏敏感阈值与 NGF 表达呈负相关[72]。Li 等[73]研究发现,BAs 诱导黏膜肥大细胞依赖的 FXR 介导的内脏高敏感,该过程涉及 MKK3/6/p38 MAPK/NF-kB/NGF 信号通路和下游瞬时受体电位香草酸亚型 1 (transient receptor potential vanilloid-1, TRPV1),因而抗 NGF 治疗和 TRPV1 拮抗剂或可抑制 BAs 诱导的内脏高敏感。

5 讨论与展望

肠易激综合征的临床治疗以匹维溴铵、阿洛司琼等药物为主,但单一药物治疗难以缓解复杂症状,而且存在易复发、患者依存性低等问题。因此,亟须进一步探索 IBS 的可能发病机制,为药物开发和临床治疗提供理论依据。尽管目前尚未明确微生态失调与 IBS 的因果关系,但近年来的研究表明肠道微生物紊乱与 IBS 的发生发展密切相关。针对肠道微生物群的靶向疗法(抗生素、益生菌、粪菌移植等)可能为 IBS 提供一种有前景的治疗方式,但仍面临轻度胃肠道不适和作用机制不清楚等问题;此外,这些临床研究多为小样本试验,环境等因素对肠道微生物的影响也会对治疗造成干扰[21]。因此,基于肠道微生物的治疗策略需要从相关性研究转为更大规模的临床试验和作用机制研究。

肠道微生物群产生的代谢物神经递质、短链脂肪酸和胆汁酸代谢物可以通过调节肠道微生物-肠-脑轴在 IBS 病理生理过程中发挥作用。本文研究显示,衍生代谢物短链脂肪酸、胆汁酸代谢物等均可通过 ECs 调控 5-HT 释放,参与肠道屏障、内脏敏感和肠道运动等。5-HT 在中枢和外周均有表达,其体内合成、摄取转运及与受体(5HT-3R、5-HT4R、5-HT7R)的结合过程是一个重要环节[27-28]。5-HT 受体拮抗剂或可作为 IBS 的潜在治疗靶标,如 5-HT3 受体拮抗剂阿洛司琼可显著改善严重 IBS-D 女性患者腹痛、排便急迫等症状且具有良好的耐受性[74],但其作用机制仍不清楚,亟待开展深入研究。

经典名方痛泻药方可通过调节肠道粘膜结构、改善肠道微生态环境等改善 IBS 症状[75]。花椒是一味传统温里药,具有温中止痛功效,常用于脘腹冷痛、呕吐泄泻等症,从治疗病症来看与脾胃虚寒型 IBS 具有一致性。前期研究发现,花椒能够通过调节下丘脑-垂体-肾上腺轴和肠道菌群,减轻慢性不可预见性应激诱导的大鼠焦虑行为[76]。尽管花椒能够具有调节胃肠道和中枢神经系统作用,但其是否能够改善 IBS 症状以及在肠道环境中产生的系列变化如何在 IBS 治疗过程中发挥作用,仍需进一步结合中医理论和现代研究方法进行深入研究。

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