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本刊编委凌江红, 教授, 上海中医药大学附属曙光医院消化内科, 专长为中医药治疗功能性胃肠病的创新研究, 揭示疏肝理气法能经内质网应激、线粒体自噬相关通路调节中枢和外周部分脑肠肽及其受体发挥促胃动力作用, 为疏肝治疗功能性胃肠病提供科学依据. 主持国家自然基金课题4项, 省(部)级课题4项. 作为全国组长, 牵头GCP项目1项. 发表论文150余篇, 其中SCI论文10篇; 主编专著1部, 获得专利2项, 获得省级科技进步奖二等奖1项, 其他各类奖项6项. 第一批广西医学高层次骨干人才、第十二届广西青年科技奖获得者.

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述评 EDITORIAL

肠菌移植治疗肠易激综合征的研究进展及展望

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Fecal microbiota transplantation for treatment of irritable bowel syndrome: Current advances and future perspectives

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Abstract

Irritable bowel syndrome (IBS) is a kind of functional gastrointestinal disorder, characterized by recurrent abdominal pain and altered bowel habits. IBS adversely affects the quality of life of patients for the lack of effective treatment. The etiology of IBS remains poorly known. Previous studies suggested a possible role of gut dysbiosis in IBS pathogenesis. Fecal microbiota transplantation (FMT), which aims to reverse the gut dysbiosis, is a promising strategy in IBS management. In this review, we summarize the role of the gut microbiota in IBS pathogenesis from different aspects. We also review recent studies on efficacy evaluation of FMT in IBS. Besides, we discuss factors affecting the efficacy of FMT, hoping to provide a reference for future IBS treatment strategies targeting the gut microbiota.

Key Words: Irritable bowel syndrome; Gastrointestinal microbiome; Fecal microbiota transplantation; Brain-gut axis

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摘要

肠易激综合征(irritable bowel syndrome, IBS)是以反复发作的腹痛伴排便习惯改变为特点的功能性胃肠病, 目前尚无有效治疗方法, 严重影响患者生活质量. IBS的病理生理机制未明, 既往研究提示肠道菌群失调可能参与IBS发病, 而以调节肠道菌群为靶点的肠菌移植(fecal microbiota transplantation, FMT)有望成为IBS重要的治疗策略. 本文从多方面总结了肠道菌群参与IBS发病的可能机制, 并对FMT治疗IBS的研究进展进行综述, 对影响FMT疗效的因素进行了讨论, 以期为今后以肠道菌群为靶点的IBS治疗策略提供参考.

关键词: 肠易激综合征; 肠道菌群; 肠菌移植; 脑-肠轴

核心提要: 肠道菌群通过代谢产物, 以及病原相关分子模式-模式识别受体之间的相互作用参与肠易激综合征(irritable bowel syndrome, IBS)的发生发展. 粪菌移植有望用于IBS的治疗, 但不同研究间异质性大, 其疗效与安全性有待更多研究进一步验证.

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0 引言

人体肠道内定植着数以亿计的微生物, 包括细菌、真菌、古菌、病毒等, 统称为肠道菌群[1]. 正常情况下, 这些微生物和宿主互利共生, 参与合成人体所需的维生素、抑制致病微生物定植, 维护肠粘膜屏障的完整性, 并在消化吸收、物质代谢、免疫应答等多个生理环节中发挥关键作用. 受饮食、疾病、用药等因素影响, 肠道菌群的组成和功能发生改变, 即肠道菌群失调, 则会引起消化道内外多种疾病的发生, 如艰难梭菌感染[2]、炎症性肠病[3-6]、代谢性疾病[7-9]、恶性肿瘤[10]等.

肠易激综合征(irritable bowel syndrome, IBS)是一种常见的功能性胃肠病, 以反复发作的腹痛伴排便频率或大便性状改变为特点[11]. 依据主导的大便形态, IBS可以分为腹泻型(diarrhea-dominant IBS, IBS-D)、便秘型(constipation-dominant IBS, IBS-C)、混合型(IBS with mixed stool pattern, IBS-M)、未定型(IBS unclassified, IBS-U). 在世界范围内, IBS的患病率可达5%-10%[11]. 在我国, IBS的患病率为1.4%-11.5%, 是消化科门诊的常见病之一, 病程慢性, 反复发作, 严重影响患者的社会功能和生活质量[12]. 目前IBS的治疗以对症为主, 包含止泻药、解痉剂、泻药、胃肠动力调节剂、神经递质调节剂、中医药等, 疗效短暂且具有较大个体差异性[12]. 由于常规医学检查难以发现器质性病变, 而患者主观不适明显, 通常需要长期服药控制症状, 因此患者往往四处求医问诊, 造成大量医疗资源的消耗. 据统计, 我国每年与IBS直接或间接相关的支出可达1230亿[13]. IBS的治疗成为临床实践中的一大难题.

目前IBS的病理生理机制尚未阐明, 既往研究认为可能与脑-肠轴互动异常、内脏高敏感、消化道动力异常、肠道菌群失调、肠屏障受损、肠道免疫激活等多种因素有关[12,14]. 近几年许多研究提示, 肠道菌群失调可能是IBS发病的重要环节. 动物实验表明, 口服抗生素或大肠杆菌灌胃可以诱导小鼠内脏敏感性增高, 反之, 预先口服干酪乳杆菌、酪酸梭菌等益生菌则有助于减轻内脏高敏感性[15-17], 而内脏高敏感性被认为是IBS患者腹痛、腹胀等症状的重要机制. Meta分析显示[18], 胃肠道感染是IBS的重要危险因素, 过去12 mo曾患急性胃肠炎者随后罹患IBS的风险, 是对照组的4.2倍, 提示肠道菌群失调可能是IBS发病的驱动因素. 因此, 临床实践和研究开始探索以调节肠道菌群为靶点的治疗策略, 如益生菌、抗生素, 发现菌群调节类药物虽然能改善部分患者的症状, 但疗效难以维持且具有较大个体差异[19]. 肠菌移植(fecal microbiota transplantation, FMT)作为重建肠道微生态的最佳方法, 其在IBS领域的应用价值备受关注. 本文总结了肠道菌群在IBS发病中的作用机制, 对FMT治疗IBS的研究进展进行综述, 并对现有研究存在的问题进行讨论, 以期为今后相关领域的研究和临床实践提供参考.

1 IBS患者肠道菌群的变化

大量研究表明, IBS患者肠道菌群的多样性及组成明显不同于健康人. 相比健康对照组, IBS患者肠道菌群的多样性减少[20,21], 双歧杆菌、粪杆菌属、普拉梭菌丰度降低, 乳杆菌科、肠杆菌科和拟杆菌属丰度增加[22], 且IBS症状严重程度和肠杆菌科细菌丰度呈正相关, 和普拉梭菌丰度呈负相关[23]. Pozuelo等[24]进一步对不同IBS亚型进行分析, 发现相比健康对照组, IBS-D和IBS-M患者肠道内产丁酸菌和产甲烷菌的丰度降低. 前者产生的丁酸是重要的短链脂肪酸(short-chain fatty acid, SCFA)之一, 能为结肠上皮细胞提供能量, 并维护肠屏障功能[25]. 丁酸减少导致肠屏障通透性增加, 是IBS重要的发病机制之一. 而产甲烷菌是肠道内处理氢气的重要微生物[26], 其丰度减少可能与IBS患者的胃肠胀气有关. 与之相反, IBS-C患者肠道内产甲烷菌的丰度高于对照组[24,27]. 动物实验表明甲烷能减慢小肠运输, 与慢传输型便秘密切相关[26]. 此外, IBS患者乳果糖氢气结合甲烷呼气试验的阳性率显著高于健康人, 提示存在小肠细菌过度生长[28].

上述研究提示, IBS患者存在肠道菌群紊乱, 并和临床症状密切相关, 但肠道菌群失调和IBS之间的因果关系仍未明确. 既往一些研究支持肠道菌群紊乱是IBS的始动因素. 首先, 胃肠道感染是IBS发病的重要危险因素之一[18], 感染后IBS(post-infection IBS, PI-IBS)在发病前即有肠道菌群紊乱. 其次, 精神心理应激是IBS发病中的重要诱因, 多被用于诱导IBS动物模型. 研究表明, 应激会引起乳酸杆菌和双歧杆菌的脱落, 并促进大肠杆菌的繁殖, 进而影响肠道微生态的稳定性[16]. 最后, 移植了IBS-D患者肠道菌群的无菌小鼠表现出肠屏障受损、固有免疫激活、胃肠道传输加快和焦虑样行为等IBS特征性的临床表型[29]. 尽管如此, 考虑到部分IBS患者症状的

出现常与摄入特定食物有关, 患者往往规避这类加重症状的食物, 长此以往可能导致肠道菌群的结构发生改变, 对于肠道菌群失调和IBS发病的先后关系有待更多研究进一步验证.

2 肠道菌群参与IBS发病的可能机制

肠道菌群的改变可引起功能及下游代谢产物的变化, 或者通过表达多种病原相关分子模式(pathogen-associated molecular pattern, PAMP), 激活相应的模式识别受体(pattern recognition receptor, PRR), 调节炎症因子的转录, 影响IBS的发生发展, 现分述如下.

2.1 神经递质 肠-脑轴(gut-brain axis, GBA)是中枢神经系统(central nerve system, CNS)与肠神经系统(enteric nerve system, ENS)之间的神经体液双向交互网络, 参与调控摄食、睡眠、情绪、免疫等多个生理过程[30]. 肠道菌群通过GBA影响神经系统发育与功能, 同时CNS参与调控胃肠动力、内脏痛觉感受等消化道生理过程[31]. CNS疾病如帕金森病、孤独症患者常伴有便秘、腹泻等消化系统症状[32], 且肠道菌群失调已被证实参与许多神经精神系统疾病如抑郁症[33-36]、孤独症[37,38]、帕金森病[39,40]的发生发展, 提示CNS与胃肠道之间的密切联系. 大量研究证实IBS是脑肠轴调节失常所致. 动物实验表明[41], 急慢性应激可以诱导小鼠出现内脏敏感性增高等IBS表型. 前瞻性队列研究显示焦虑抑郁是IBS发病的重要危险因素[42], 且随着胃肠道症状的发生频率和严重程度增加, IBS患者共患焦虑抑郁的比例也逐步增加[43]. 此外, 许多神经递质如5-羟色胺(5-hydroxytryptamine, 5-HT)、γ-氨基丁酸(γ-aminobutyric acid, GABA)同时调控CNS和胃肠道功能[44]. 大量研究证实肠道菌群可以通过调控上述神经递质参与IBS发病.

2.1.1 5-HT: 5-HT是是重要的神经递质之一, 在中枢参与情绪调节, 在外周参与调控胃肠动力、腺体分泌、内脏感受[45]. 机体超过90%的5-HT来源于消化道, 其中大部分由肠嗜铬细胞(enterochromaffin cell, EC)合成并储存. 色氨酸羟化酶1(tryptophan hydroxylase 1, TPH1)是5-HT合成的限速酶[46]. 生理状态下, 5-HT的释放主要受肠腔内容物的机械和化学刺激调控[47,48], 发挥作用后再经5-HT再摄取转运体(serotonin reuptake transporter, SERT)回收, 避免5-HT能信号过度激活. 既往研究证实, IBS患者存在5-HT能信号通路异常. 相比健康对照, IBS患者肠粘膜SERT表达减少, 5-HT含量增加[49-51]. 异常激活的5-HT信号促进胃肠分泌, 缩短结肠传输时间, 增加内脏敏感性, 进而引起腹泻、腹痛等IBS典型症状. 研究表明, 肠道菌群参与调控5-HT合成. 无菌小鼠肠道内5-HT水平明显低于正常, 而菌群移植能快速恢复5-HT含量[52]. Yano等[53]发现, 产芽孢菌通过调节肠腔代谢物的变化诱导EC上调TPH1的表达, 促进5-HT合成, 引起胃肠动力增加. 高5-HT的肠腔环境又促进产芽孢菌的定植, 形成5-HT信号异常激活的正反馈环[54]. 此外, 多种肠道菌群的代谢产物已被证实可以促进5-HT合成. SCFA可以诱导EC细胞上调TPH1表达, 刺激5-HT的生物合成[55]. Sugiyama等[56]发现活泼瘤胃球菌等共生微生物可以表达芳香族氨基酸脱羧酶, 产生大量芳香胺, 后者激活EC细胞的痕量胺相关受体1(trace amine-associated receptor 1, TAAR1)诱导5-HT合成[57]. 不仅细菌, 肠道真菌同样参与5-HT信号的调控. Gu等[58]发现布拉氏酵母菌可以通过激活表皮生长因子受体上调SERT的表达, 进而降低5-HT的含量, 抑制胃肠动力.

2.1.2 GABA: GABA是重要的抑制性神经递质, 由谷氨酸脱羧酶(glutamic acid decarboxylase, GAD)以谷氨酸为底物催化合成. GABA主要来源于CNS, 其信号异常与焦虑障碍、癫痫、失眠、疼痛等疾病相关. 同时GABA也是ENS重要的信号分子, 参与调控胃肠动力、分泌以及伤害感受[59,60]. 研究表明[44], IBS-D患者血清中GAD、$GABA_B$受体含量减少, 而负责重摄取GABA的转运体(GABA transporter, GAT)明显增加, 提示IBS-D患者体内GABA能信号受到抑制. 部分肠道微生物如双歧杆菌、乳酸杆菌能直接合成GABA. 而IBS患者肠道内双歧杆菌丰度显著降低[22], 可能导致GABA合成减少. 动物实验显示, 口服表达GAD的乳酸乳球菌或齿双歧杆菌能缓解大鼠的内脏高敏感性, 而这种效应能被$GABA_B$受体拮抗剂废除[61,62]. 此外, GABA还具有抗炎活性. 经GABA预处理的结肠上皮细胞经脂多糖刺激后, 炎症因子表达减少[63]. GABA能信号下调可能与IBS的肠黏膜慢性低度炎症有关.

2.2 胆汁酸 Meta分析显示, 16.9%-35.3%的IBS-D患者粪便胆汁酸含量升高, 表现出胆汁酸吸收不良[64]. 正常情况下肝脏合成的初级胆汁酸排入肠道后, 大部分在回肠经肠肝循环重吸收, 只有约5%进入结肠, 在肠道细菌的作用下转变为次级胆汁酸, 并随粪便排出体外. 到达回肠的胆汁酸, 激活回肠上皮细胞的核法尼醇X受体(farnesoid X Receptor, FXR), 引起成纤维细胞生长因子19(fibroblast growth factor 19, FGF19)的释放, 后者随胆汁酸经肠肝循环回到肝脏, 结合成纤维细胞生长因子受体4(fibroblast growth factor receptor 4, FGFR4),抑制胆汁酸合成的限速酶CYP7A1, 由此负向调控胆汁酸合成. 胆汁酸通过减少钠离子吸收、增加氯离子分泌从而刺激肠上皮细胞分泌[44], 并参与调节胃肠动力. 研究表明, IBS-D患者肠道菌群紊乱继发胆汁酸代谢异常, 导致肠腔内

胆汁酸含量过高, 使粪便含水量增加、结肠传输加快, 引进腹泻. Zhao等[65]发现肠道梭菌属尤其是*Clostridium scindens*丰度增加与IBS-D患者粪便胆汁酸排泄过多相关. 梭菌属产生的胆汁酸能抑制回肠FGF19的表达, 阻断胆汁酸合成的负反馈调节[65]. 与之相反, IBS-C患者粪便胆汁酸含量低于健康人[44]. 移植了慢传输型便秘患者肠道菌群的无菌小鼠肠道内次级胆汁酸的含量减少, 而补充脱氧胆酸能恢复小鼠结肠平滑肌的收缩力[66]. 此外, 胆汁酸代谢异常还可能引起肠屏障受损、内脏敏感性增加[67]. Hollister等[68]发现, 粪便胆汁酸含量和儿童IBS患者的腹痛频率及严重程度呈正相关. 研究表明, 结合胆红素经肠道细菌的β葡萄糖醛酸酶作用转变为非结合胆红素, 后者能抑制肠道蛋白酶的活性, 对于调节肠屏障功能及神经元敏化至关重要[69]. Edwinson等[69]发现部分IBS患者粪便中另枝菌属尤其是*Alistipes putredinis*丰度明显降低, 伴随β葡萄糖醛酸酶活性减弱, 导致非结合胆红素生成减少, 蛋白酶活性增加, 引起肠屏障受损、内脏高敏感性.

2.3 短链脂肪酸 SCFA是食物中的可发酵纤维经肠道细菌发酵产生的. 乙酸、丙酸、丁酸约占SCFA总量的95%[70]. SCFA为结肠上皮细胞提供能量, 促进其更新和修复, 参与维护肠屏障功能, 并具有抗炎作用[25]. 应激诱导的IBS小鼠模型中可以观察到毛螺菌科等产丁酸菌丰度降低, 丁酸代谢通路表达下调, 紧密连接蛋白表达减少, 而补充人源罗氏菌可以提高结肠丁酸的含量, 上调紧密连接蛋白的表达, 改善内脏高敏感性[71]. 临床研究同样发现IBS-D患者肠道内普拉梭菌等SCFA产生菌丰度降低[20], 而口服产丁酸梭菌能减少排便次数, 改善IBS-D症状严重程度[72]. 近期一项多中心RCT显示, 口服双歧杆菌四联活菌片能显著缓解IBS-D的腹痛和腹泻, 并能提高多种SCFA产生菌的丰度及粪便SCFA含量, 提示SCFA对IBS-D的保护作用[19]. 但也有研究提示SCFA促进IBS的发生发展. Ringel-Kulka等[73]发现, 粪便SCFA含量和结肠传输时间负相关, 和排便频率正相关. 动物实验显示, 乙酸、丁酸灌肠均能诱导持续的结肠高敏状态[74,75]. 其机制可能与SCFA促进5-HT合成有关[55]. 5-HT受体拮抗剂被证实可以阻断丁酸诱导的内脏高敏反应[74]. 此外, 丁酸也可以通过激活背根神经元的MAPK-ERK1/2信号通路, 诱导内脏敏感性增高. 值得注意的是, Meta分析显示IBS患者粪便中的SCFA含量与健康人相比并无显著差异[76], 可能与不同研究纳入的IBS亚型差异有关, 研究发现IBS-C患者粪便中多种SCFA含量低于IBS-D患者[77]. 因此, 不同SCFA在不同IBS亚型中的作用可能截然不同, 有待更多研究进一步探索.

2.4 组胺 组胺由组氨酸脱羧酶催化组氨酸转化而成, 主要存在于肥大细胞和嗜碱性粒细胞, 是过敏反应的重要介质[59]. 组胺受体包含H_1、H_2、H_3、H_4四种亚型, 其中H_1、H_4是调节胃肠功能的主要受体, H_2与胃酸分泌有关[78]. 研究发现[79], 相比健康人, IBS-D患者结肠黏膜有更多的肥大细胞浸润, 且肥大细胞介质如组胺、色氨酸酶、前列腺素E_2(prostaglandin E_2, PGE_2)、环氧化酶-2(cyclooxygenase-2, COX-2)表达增多[80,81]. 尿组胺水平和IBS腹痛严重程度相关, 移植了高尿组胺IBS患者粪便菌群的无菌小鼠会表现出内脏敏感性增高, 肥大细胞激活, 提示肠道菌群可能通过调节组胺水平参与IBS发病. 既往研究表明, 肠道微生物能直接合成组胺或间接调控肥大细胞激活, 使后者脱颗粒释放组胺. 尿组胺含量高的IBS患者, 其粪便菌群中富集产气克雷伯菌, 能编码组氨酸脱羧酶产生大量组胺, 进而激活H_4受体, 驱动肥大细胞募集, 诱导内脏高敏感性[82]. Botschuijver等[41]发现应激引起肠道真菌失调, 通过真菌细胞壁成分β-葡聚糖激活Dectin-1/Syk信号通路, 触发肥大细胞脱颗粒, 释放组胺. 后者进一步激活感觉神经元的H_1受体, 引起内脏敏感性增加[83]. 组胺受体拮抗剂被证实可以改善应激诱导的大鼠内脏敏感性增高[83]. 临床研究也显示H_1受体拮抗剂依巴斯汀能有效缓解IBS患者的腹痛症状[84].

2.5 PAMP-PRR互作 慢性低度炎症是IBS重要的病理生理机制之一. 相比健康人, IBS患者肠黏膜浸润的淋巴细胞数目增多[85], 促炎的白介素6(interleukin 6, IL-6)、C-X-C基序趋化因子11(C-X-C motif chemokine ligand 11, CXCL-11)、C-X-C基序趋化因子受体3(C-X-C motif chemokine receptor 3, CXCR-3)表达上调, 而抗炎的IL-10表达减少[86], 提示IBS患者存在促炎-抗炎失衡. 研究显示, 肠道微生物通过表达多种病原相关分子模式(pathogen-associated molecular pattern, PAMP), 激活模式识别受体(pattern recognition receptor, PRR), 产生的免疫应答与IBS的肠粘膜慢性低度炎症有关. Shukla等[86]发现, IBS患者肠道Toll样受体4/5(toll-like receptor 4/5, TLR4/5)表达上调, 并和排便频率正相关. TLR4或其下游转录因子NF-κB的抑制剂能显著下调肿瘤坏死因子α(tumor necrosis factor α, TNF-α)、IL-8的表达, 增加IL-10的水平, 改善G^-菌细胞壁组分脂多糖(lipopolysaccharide, LPS)诱导的内脏痛觉过敏[87,88]. Mallaret等[89]发现应激诱导的IBS小鼠表现出肠道菌群失调尤其是带鞭毛的细菌丰度增高, 并有TLR5表达上调. 直肠内滴注TL5激动剂鞭毛蛋白可引起内脏高敏反应[89]. 此外, PAMP-TLR相互作用还能影响胃肠动力和肠神经系统. 用LPS孵育肠神经元细胞, 引起NF-κB激活, 有助于神经元存活, 而用广谱抗生素清除肠道菌群或敲除TLR4会引起胃肠动力减弱, 氮能神经元数目减少[90]. Gao等[91]发现LPS协同胰蛋白酶可

以激活粘膜肥大细胞, 引起PGE_2的释放, 进而下调SERT, 提高肠粘膜5-HT水平. 顾湘等[92]发现具核梭杆菌可能通过外膜蛋白FomA作用于EC细胞的TLR2受体, 从而介导5-HT的分泌. 接受FomA阳性的大肠杆菌灌胃可以增加IBS小鼠结肠EC细胞的数量, 上调肠粘膜TLR2和TPH1表达[92].

3 FMT治疗IBS的研究进展

鉴于大量研究支持肠道菌群失调参与了IBS的发生发展, 以调节肠道菌群为靶点的治疗策略如益生菌、抗生素在临床实践中取得了广泛应用, 但疗效难以持久且具有较大个体差异性, 亟需探索更有效的方法纠正患者的肠道菌群失衡. FMT是指将健康人粪便中的功能菌群, 整体移植到患者肠道内, 重建新的肠道微生态, 已被逐渐用于治疗许多菌群紊乱相关的疾病. 考虑到肠道菌群数目庞大, 相互之间的作用错综复杂, 目前尚不能明确在IBS中发挥作用的关键物种, 因此, 将健康人的肠道菌群整体移植到患者体内, 可能是修复IBS患者肠道微生态失衡的最佳策略. 近几年已有许多高质量临床研究证实了FMT应用于IBS的可行性. 2018年一项单中心随机对照研究(randomized controlled trial, RCT)纳入83名中重度IBS-D及IBS-M患者, 治疗组经肠镜注入来自健康人的新鲜/冷冻菌液, 对照组接受自体粪菌移植. 随访3 mo, 干预组的治疗应答率明显高于对照组, 且新鲜菌液和冷冻菌液同样有效[93]. 但在治疗后12 mo, 治疗组和安慰剂组的应答率无显著差异[93], 提示疗效随着停药时间的延长而减弱. 同样是经结肠镜给药, Lahtinen等[94]的研究发现FMT仅能引起短暂的症状缓解, 治疗后12 wk组间有效率无显著差异. 值得注意的是, 研究者对受试者治疗前后的粪便样本进行16S rRNA测序分析, 发现FMT使IBS患者的肠道菌群趋近于健康供体, 且这种改变较为持久, 提示菌群变化和临床疗效间并不平行[94]. 研究表明[95], 部分接受异体FMT治疗的患者粪便和结肠黏膜菌群并未发生显著变化, 反之, 自体FMT也可能引起肠菌组成的改变. 然而也有研究显示增加的α多样性、菌群结构趋向供体的转变和FMT疗效相关[96]. 因此, 菌群变化和疗效的相关性有待更多高质量研究进一步探讨.

除了经结肠镜给药, 经上消化道途径的FMT同样有效. El-Salhy等[97]纳入165名中重度IBS患者, 等比例分配至低剂量FMT、高剂量FMT、安慰剂三组, 菌液经胃镜送达十二指肠远端. 随访3 mo, 相比对照组, 治疗组的腹部症状、疲劳程度和生活质量均明显改善, 且疗效呈现剂量相关性[97]. 研究者进一步对这些患者进行了长达3年的随访, 发现FMT能引起显著而持久的改善, 低剂量和高剂量组的3年有效率分别为64.9%和71.8%[23], 高于经肠镜给药的两项研究. FMT不仅能改善疾病总体严重程度, 对单一的IBS症状同样有效. Holvoet等[98]招募了62名伴有严重腹胀的难治性IBS-D和IBS-M患者, 治疗组经鼻肠管注射粪菌混悬液, 治疗后患者的排便急迫感、腹痛、腹胀均有明显缓解, 排便次数减少. 随访一年, 24名应答者中有19人失效, 中位失效时间为4 mo[98], 提示FMT治疗IBS的远期疗效不佳, 与大多数研究一致. Yau等[99]探索了间隔4 wk的重复FMT治疗对中国IBS-D患者的有效性, 结果显示治疗组和安慰剂组的应答率无统计学差异.

也有研究显示FMT治疗IBS效果不佳. Halkjær等[100]纳入52名中重度IBS患者, 治疗组连续口服FMT胶囊12 d, 对照组口服食用色素和甘油制成的安慰剂胶囊. 研究发现FMT胶囊虽然能显著提高IBS患者的肠道菌群多样性, 并使患者的肠道菌群趋近于健康供体, 但治疗组的有效率及生活质量改善情况均明显劣于对照组, 提示肠菌变化不能完全反映临床疗效[100]. 另一项以口服胶囊作为FMT给药途径的RCT同样得出了FMT不优于安慰剂的阴性结果[101]. Meta分析显示, 相比对照组, 经中、下消化道行FMT可明显缓解IBS症状, 而口服胶囊则无显著疗效[102].

4 影响FMT疗效的因素探讨

4.1 供体的选择 选择合适的供体是FMT成功的关键. 尽管国内外已有许多指南对FMT供体选择列出了具体标准[103-105], 但通过一系列客观的实验室检查仅能确保治疗的安全性而非有效性. 部分研究提示供体的菌群特征与FMT治疗溃疡性结肠炎的疗效密切相关[106,107]. 因此有研究将多个供体的粪便混合作为移植物来源[93,100], 在一定程度上可能可以发挥“取长补短”的作用, 使物种组成更加多样均衡, 避免单个供体引起疗效不佳的情况. 而El-Salhy等[23]的研究中使用了超级供体. “超级供体”假说认为存在万能供体, 其来源的FMT有效率远高于普通供体. 研究中发现该供体的肠道菌群组成在3年的随访过程中始终保持稳定, 研究者认为这是超级供体的肠菌特征之一, 但对于超级供体与普通供体在肠菌组成上的区别并未进一步探讨[23]. Mizuno等[108]发现有效供体肠道双歧杆菌的丰度显著高于无效供体, 但样本量较小, 尚需进一步验证. Wilson等[109]认为, 供体的选择应依据不同疾病的肠菌紊乱特点而定. 而IBS不同亚型、甚至同一亚型的不同个体的肠道菌群组成可能不尽相同. 因此, 针对IBS, 是否存在超级供体, 其肠道菌群特征如何, 以及是否存在特定物种或代谢物能反映IBS肠菌供体的优良程度, 都有待研究进一步探讨.

4.2 粪便处理流程 目前已发表的几篇国外RCT和部分国内研究多采用手工制菌[95,98,100,110], 而国内部分研究已

应用自动化设备代替手工操作[111]. 无论是手工还是机器, 粪菌分离的基本步骤一般是加入生理盐水、搅拌、过滤, 但操作过程中的具体细节, 比如粪便和生理盐水的配比、搅拌的转速及时间、滤网的孔径、是否加甘油作为冷冻保护剂、是否离心富集等, 都缺乏研究数据支持, 也无规范统一的标准. 此外, 操作过程中的环境因素如氧气含量、温度, 人为因素如操作污染也会影响分离出的肠菌的多样性和组成, 从而影响FMT的疗效. 再者, 虽然Johnsen等[93]发现新鲜菌液和冷冻菌液同样有效, 但粪便或菌液冷冻后复溶是否会影响分离出的菌群的含量和活性进而影响疗效, 尚需进一步研究证实. 不同研究的粪便处理流程不同, 导致研究结论可比性差.

4.3 FMT给药方法 FMT的给药途径有多种, 包括经上消化道(胃镜、鼻空肠管等)、经下消化道(结肠镜、结肠置管、保留灌肠等)、口服胶囊等[112]. 虽然不同给药途径对FMT治疗IBS的疗效差异尚无定论, 但以口服胶囊作为给药途径的两项RCT均得出FMT不优于安慰剂的结论[100,101]. 胶囊FMT疗效不佳的原因可能有以下几个方面: 首先, 人体肠道微生物有很大比例是专性厌氧菌, 而粪便排出体外后长时间暴露在有氧大气中将造成这部分微生物失活, 加之温度等外在条件的改变又使部分微生物大量繁殖, 导致最终的移植物和供体原本的菌群组成相差甚远. 而胶囊形式的移植物制作耗时较肠菌悬液长, 若不严格控制操作条件更易造成微生物组成改变, 导致疗效减弱. El-Salhy等[23]认为控制样品温度是FMT成功的重要因素之一. 该研究中粪便样本一经排出尽快冷藏, 移植当天在4 ℃下解冻、处理, 这样可以保证专性厌氧菌的活性[23]. 其次, 胶囊可能在上消化道分解, 使移植入的肠菌受到胃酸、胰酶的影响而失活[113]. Aroniadis等[101]为了减弱这种影响, 让患者在FMT治疗前三天每天口服质子泵抑制剂, 但这种做法的科学性有待进一步研究验证. 尽管如此, 口服肠菌胶囊作为FMT给药途径之一, 仍有便捷、创伤小、无需住院治疗等优点, 适用于内镜检查有禁忌的病人. 不同给药途径对疗效的影响, 也需要更多研究进一步探索.

此外, 不同研究的单次给药剂量、给药频率存在巨大差异. 有研究显示FMT的疗效呈现剂量依赖性, 高剂量组的有效率高于低剂量组[97]. 然而不同研究间单次给药剂量不具有可比性, 有的研究以初始的粪便质量为标准[95,97,100,101], 有的研究以肠菌悬液的体积为标准[98], 但对其中包含的微生物浓度及活菌比例没有详细描述. 再者, 对于肠菌移植前是否要使用泻药进行肠道准备、经下消化道途径给药时是否要在移植后使用止泻药以保留移植物不被排出, 这些临床实践中的问题尚无定论, 但都可能影响FMT的疗效.

4.4 其他 FMT治疗IBS的疗效具有较大个体差异性, 但潜在的影响因素不得而知. Halkjær等[100]分析治疗前后患者的肠道菌群, 发现FMT治疗组患者肠道菌群的α多样性增加, 菌群组成趋近于供体, 但症状无明显改善, 提示肠道菌群的变化和症状缓解并不平行. Schmidt等[114]通过分析316份FMT临床和宏基因组学数据, 发现FMT的疗效和供体菌株的定植、受体菌种的置换无关, 支持上述假说. 但也有研究得出相反的结论. Ianiro等[115]对涵盖了8种疾病、226组配对的FMT供体、受体(包括治疗前、后)的宏基因组数据进行了分析, 发现菌群植入率和临床疗效相关. Holvoet等[98]对比治疗有效的患者和无效者的肠道菌群, 发现有效者基线肠菌α多样性高于无效者, 且二者的菌群组成也存在显著差异. IBS患者治疗前的肠道菌群组成越接近其所接受的移植样本, 治疗效果越好[98]. 因此, 肠道菌群的变化和FMT疗效的关系、是否存在能够预测疗效的关键物种或代谢物, 这些问题都有待进一步探索.

5 结论

IBS患者存在肠道菌群紊乱, 导致下游多种代谢产物的含量发生变化, 并通过PAMP激活PRR, 扰乱促炎-抗炎平衡, 进而引起GBA互动异常、胃肠动力失调、肠屏障受损、内脏敏感性增高、肠道免疫激活等一系列病理生理改变, 最终驱动IBS的发生. 其中, 不同病理生理机制之间并非完全独立, 而是存在交叉. 值得注意的是, IBS作为一种异质性疾病, 不同亚型甚至不同个体的发病机制可能截然不同. 因此, 单一的物种丰度、代谢物含量或信号通路的变化往往不适用于所有患者, 这或许能解释为什么一些代谢物如SCFA在不同IBS患者中的变化趋势相反, 这也是靶向肠道菌群的治疗如益生菌、FMT的疗效具有很大个体差异的原因之一.

FMT作为现有逆转肠道菌群紊乱的最佳策略, 在国内外多个临床研究中显示出巨大的应用价值, 但仍然存在许多问题有待解决: 首先, FMT对于我国IBS患者的疗效及安全性尚需更大样本、高级别的研究证据支持, 尤其是不同亚型间的疗效差异. 其次, 不同粪菌提取方法、给入途径、给药剂量的选择需要研究证据加以指导, FMT的操作流程需要更加规范化、科学化, 这样才能增加不同研究间的可比性. 最后, FMT的远期疗效和安全性需要更长时间的随访数据支持. 解决这些问题将有助于今后临床实践中FMT的推广.

6 参考文献

1 Singh P, Lembo A. Emerging Role of the Gut Microbiome in Irritable Bowel Syndrome. *Gastroenterol Clin North Am* 2021; 50: 523-545 [PMID: 34304786 DOI: 10.1016/j.gtc.2021.03.003]

2 Mullish BH, Quraishi MN, Segal JP, McCune VL, Baxter M, Marsden GL, Moore D, Colville A, Bhala N, Iqbal TH, Settle C, Kontkowski G, Hart AL, Hawkey PM, Williams HR, Goldenberg SD. The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *J Hosp Infect* 2018; 100 Suppl 1: S1-S31 [PMID: 30173851 DOI: 10.1016/j.jhin.2018.07.037]

3 Franzosa EA, Sirota-Madi A, Avila-Pacheco J, Fornelos N, Haiser HJ, Reinker S, Vatanen T, Hall AB, Mallick H, McIver LJ, Sauk JS, Wilson RG, Stevens BW, Scott JM, Pierce K, Deik AA, Bullock K, Imhann F, Porter JA, Zhernakova A, Fu J, Weersma RK, Wijmenga C, Clish CB, Vlamakis H, Huttenhower C, Xavier RJ. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat Microbiol* 2019; 4: 293-305 [PMID: 30531976 DOI: 10.1038/s41564-018-0306-4]

4 Liu L, Liang L, Yang C, Zhou Y, Chen Y. Extracellular vesicles of Fusobacterium nucleatum compromise intestinal barrier through targeting RIPK1-mediated cell death pathway. *Gut Microbes* 2021; 13: 1-20 [PMID: 33769187 DOI: 10.1080/19490976.2021.1902718]

5 Chen Y, Chen Y, Cao P, Su W, Zhan N, Dong W. Fusobacterium nucleatum facilitates ulcerative colitis through activating IL-17F signaling to NF-κB via the upregulation of CARD3 expression. *J Pathol* 2020; 250: 170-182 [PMID: 31610014 DOI: 10.1002/path.5358]

6 Wei S, Zhang J, Wu X, Chen M, Huang H, Zeng S, Xiang Z, Li X, Dong W. Fusobacterium nucleatum Extracellular Vesicles Promote Experimental Colitis by Modulating Autophagy via the miR-574-5p/CARD3 Axis. *Inflamm Bowel Dis* 2023; 29: 9-26 [PMID: 35998069 DOI: 10.1093/ibd/izac177]

7 Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, Shulzhenko N. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine* 2020; 51: 102590 [PMID: 31901868 DOI: 10.1016/j.ebiom.2019.11.051]

8 Chu H, Duan Y, Yang L, Schnabl B. Small metabolites, possible big changes: a microbiota-centered view of non-alcoholic fatty liver disease. *Gut* 2019; 68: 359-370 [PMID: 30171065 DOI: 10.1136/gutjnl-2018-316307]

9 Dabke K, Hendrick G, Devkota S. The gut microbiome and metabolic syndrome. *J Clin Invest* 2019; 129: 4050-4057 [PMID: 31573550 DOI: 10.1172/JCI129194]

10 Richard ML, Liguori G, Lamas B, Brandi G, da Costa G, Hoffmann TW, Pierluigi Di Simone M, Calabrese C, Poggioli G, Langella P, Campieri M, Sokol H. Mucosa-associated microbiota dysbiosis in colitis associated cancer. *Gut Microbes* 2018; 9: 131-142 [PMID: 28914591 DOI: 10.1080/19490976.2017.1379637]

11 Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. *Gastroenterology* 2016 [PMID: 27144627 DOI: 10.1053/j.gastro.2016.02.031]

12 中华医学会消化病学分会胃肠功能性疾病协作组, 中华医学会消化病学分会胃肠动力学组. 2020年中国肠易激综合征专家共识意见. 中华消化杂志 2020; 40: 803-818 [DOI: 10.3760/cma.j.cn311367-20201116-00660]

13 Zhang F, Xiang W, Li CY, Li SC. Economic burden of irritable bowel syndrome in China. *World J Gastroenterol* 2016; 22: 10450-10460 [PMID: 28058026 DOI: 10.3748/wjg.v22.i47.10450]

14 Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. *Lancet* 2020; 396: 1675-1688 [PMID: 33049223 DOI: 10.1016/S0140-6736(20)31548-8]

15 Verdú EF, Bercik P, Verma-Gandhu M, Huang XX, Blennerhassett P, Jackson W, Mao Y, Wang L, Rochat F, Collins SM. Specific probiotic therapy attenuates antibiotic induced visceral hypersensitivity in mice. *Gut* 2006; 55: 182-190 [PMID: 16105890 DOI: 10.1136/gut.2005.066100]

16 Riba A, Olier M, Lacroix-Lamandé S, Lencina C, Bacquié V, Harkat C, Gillet M, Baron M, Sommer C, Mallet V, Salvador-Cartier C, Laurent F, Théodorou V, Ménard S. Paneth Cell Defects Induce Microbiota Dysbiosis in Mice and Promote Visceral Hypersensitivity. *Gastroenterology* 2017; 153: 1594-1606.e2 [PMID: 28865734 DOI: 10.1053/j.gastro.2017.08.044]

17 王腾飞. 酪酸梭菌调节感染后小鼠内脏高敏感的研究. 博士 2021 [DOI: 10.27272/d.cnki.gshdu.2021.005962]

18 Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, Singh S, Grover M. Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. *Gastroenterology* 2017; 152: 1042-1054.e1 [PMID: 28069350 DOI: 10.1053/j.gastro.2016.12.039]

19 Bai T, Xu Z, Xia P, Feng Y, Liu B, Liu H, Chen Y, Yan G, Lv B, Yan Z, Dai N, Long Y, Wei W, Shi Z, Li X, Fang X, Gao H, Qi L, Hou X. The Short-Term Efficacy of Bifidobacterium Quadruple Viable Tablet in Patients With Diarrhea-Predominant Irritable Bowel Syndrome: Potentially Mediated by Metabolism Rather Than Diversity Regulation. *Am J Gastroenterol* 2023; 118: 1256-1267 [PMID: 36717369 DOI: 10.14309/ajg.0000000000002147]

20 Maharshak N, Ringel Y, Katibian D, Lundqvist A, Sartor RB, Carroll IM, Ringel-Kulka T. Fecal and Mucosa-Associated Intestinal Microbiota in Patients with Diarrhea-Predominant Irritable Bowel Syndrome. *Dig Dis Sci* 2018; 63: 1890-1899 [PMID: 29777439 DOI: 10.1007/s10620-018-5086-4]

21 Hou Y, Dong L, Lu X, Shi H, Xu B, Zhong W, Ma L, Wang S, Yang C, He X, Zhao Y, Wang S. Distinctions Between Fecal and Intestinal Mucosal Microbiota in Subgroups of Irritable Bowel Syndrome. *Dig Dis Sci* 2022; 67: 5580-5592 [PMID: 35879512 DOI: 10.1007/s10620-022-07588-4]

22 Pittayanon R, Lau JT, Yuan Y, Leontiadis GI, Tse F, Surette M, Moayyedi P. Gut Microbiota in Patients With Irritable Bowel Syndrome-A Systematic Review. *Gastroenterology* 2019; 157: 97-108 [PMID: 30940523 DOI: 10.1053/j.gastro.2019.03.049]

23 El-Salhy M, Winkel R, Casen C, Hausken T, Gilja OH, Hatlebakk JG. Efficacy of Fecal Microbiota Transplantation for Patients With Irritable Bowel Syndrome at 3 Years After Transplantation. *Gastroenterology* 2022; 163: 982-994.e14 [PMID: 35709830 DOI: 10.1053/j.gastro.2022.06.020]

24 Pozuelo M, Panda S, Santiago A, Mendez S, Accarino A, Santos J, Guarner F, Azpiroz F, Manichanh C. Reduction of butyrate- and methane-producing microorganisms in patients with Irritable Bowel Syndrome. *Sci Rep* 2015; 5: 12693 [PMID: 26239401 DOI: 10.1038/srep12693]

25 杭露, 周盐, 孟杨杨, 冯雅, 王殷姝, 袁建业. 短链脂肪酸与肠易激综合征关系的研究进展. 世界华人消化杂志 2021 29; 1102-1109 [DOI: 10.11569/wcjd.v29.i19.1102]

26 Pimentel M, Lin HC, Enayati P, van den Burg B, Lee HR, Chen JH, Park S, Kong Y, Conklin J. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. *Am J Physiol Gastrointest Liver Physiol* 2006; 290: G1089-G1095 [PMID: 16293652 DOI: 10.1152/ajpgi.00574.2004]

27 Villanueva-Millan MJ, Leite G, Wang J, Morales W, Parodi G, Pimentel ML, Barlow GM, Mathur R, Rezaie A, Sanchez M, Ayyad S, Cohrs D, Chang C, Rashid M, Hosseini A, Fiorentino A, Weitsman S, Chuang B, Chang B, Pichetshote N, Pimentel M. Methanogens and Hydrogen Sulfide Producing Bacteria Guide Distinct Gut Microbe Profiles and Irritable Bowel Syndrome Subtypes. *Am J Gastroenterol* 2022; 117: 2055-2066 [PMID: 36114762 DOI: 10.14309/ajg.0000000000001997]

28 李宁宁, 王智凤, 费贵军, 朱丽明, 陈伟光, 李晓青, 郑家驹, 柯美云, 方秀才. 氢气结合甲烷气呼气试验检测肠易激综合征患者小肠细菌过度生长. 胃肠病学和肝病学杂志 2015; 24: 683-687 [DOI: 10.3969/j.issn.1006-5709.2015.06.012]

29 De Palma G, Lynch MD, Lu J, Dang VT, Deng Y, Jury J, Umeh G, Miranda PM, Pigrau Pastor M, Sidani S, Pinto-Sanchez MI,

Philip V, McLean PG, Hagelsieb MG, Surette MG, Bergonzelli GE, Verdu EF, Britz-McKibbin P, Neufeld JD, Collins SM, Bercik P. Transplantation of fecal microbiota from patients with irritable bowel syndrome alters gut function and behavior in recipient mice. *Sci Transl Med* 2017; 9 [PMID: 28251905 DOI: 10.1126/scitranslmed.aaf6397]

30 Margolis KG, Cryan JF, Mayer EA. The Microbiota-Gut-Brain Axis: From Motility to Mood. *Gastroenterology* 2021; 160: 1486-1501 [PMID: 33493503 DOI: 10.1053/j.gastro.2020.10.066]

31 张孝静, 潘飞, 杨云生, 彭丽华. 微生物-肠-脑轴研究与肠易激综合征. *胃肠病学和肝病学杂志* 2022; 31: 481-486 [DOI: 10.3969/j.issn.1006-5709.2022.05.001]

32 Mertsalmi TH, Aho VTE, Pereira PAB, Paulin L, Pekkonen E, Auvinen P, Scheperjans F. More than constipation - bowel symptoms in Parkinson's disease and their connection to gut microbiota. *Eur J Neurol* 2017; 24: 1375-1383 [PMID: 28891262 DOI: 10.1111/ene.13398]

33 Rao J, Xie R, Lin L, Jiang J, Du L, Zeng X, Li G, Wang C, Qiao Y. Fecal microbiota transplantation ameliorates gut microbiota imbalance and intestinal barrier damage in rats with stress-induced depressive-like behavior. *Eur J Neurosci* 2021; 53: 3598-3611 [PMID: 33742731 DOI: 10.1111/ejn.15192]

34 Rao J, Qiao Y, Xie R, Lin L, Jiang J, Wang C, Li G. Fecal microbiota transplantation ameliorates stress-induced depression-like behaviors associated with the inhibition of glial and NLRP3 inflammasome in rat brain. *J Psychiatr Res* 2021; 137: 147-157 [PMID: 33677218 DOI: 10.1016/j.jpsychires.2021.02.057]

35 Li N, Wang Q, Wang Y, Sun A, Lin Y, Jin Y, Li X. Fecal microbiota transplantation from chronic unpredictable mild stress mice donors affects anxiety-like and depression-like behavior in recipient mice via the gut microbiota-inflammation-brain axis. *Stress* 2019; 22: 592-602 [PMID: 31124390 DOI: 10.1080/10253890.2019.1617267]

36 Liu S, Guo R, Liu F, Yuan Q, Yu Y, Ren F. Gut Microbiota Regulates Depression-Like Behavior in Rats Through the Neuroendocrine-Immune-Mitochondrial Pathway. *Neuropsychiatr Dis Treat* 2020; 16: 859-869 [PMID: 32280227 DOI: 10.2147/NDT.S243551]

37 Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, Zink EM, Casey CP, Taylor BC, Lane CJ, Bramer LM, Isern NG, Hoyt DW, Noecker C, Sweredoski MJ, Moradian A, Borenstein E, Jansson JK, Knight R, Metz TO, Lois C, Geschwind DH, Krajmalnik-Brown R, Mazmanian SK. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. *Cell* 2019; 177: 1600-1618.e17 [PMID: 31150625 DOI: 10.1016/j.cell.2019.05.004]

38 Zhang M, Chu Y, Meng Q, Ding R, Shi X, Wang Z, He Y, Zhang J, Liu J, Zhang J, Yu J, Kang Y, Wang J. A quasi-paired cohort strategy reveals the impaired detoxifying function of microbes in the gut of autistic children. *Sci Adv* 2020; 6 [PMID: 33087359 DOI: 10.1126/sciadv.aba3760]

39 Liang Y, Cui L, Gao J, Zhu M, Zhang Y, Zhang HL. Gut Microbial Metabolites in Parkinson's Disease: Implications of Mitochondrial Dysfunction in the Pathogenesis and Treatment. *Mol Neurobiol* 2021; 58: 3745-3758 [PMID: 33825149 DOI: 10.1007/s12035-021-02375-0]

40 Wallen ZD, Demirkan A, Twa G, Cohen G, Dean MN, Standaert DG, Sampson TR, Payami H. Metagenomics of Parkinson's disease implicates the gut microbiome in multiple disease mechanisms. *Nat Commun* 2022; 13: 6958 [PMID: 36376318 DOI: 10.1038/s41467-022-34667-x]

41 Botschuijver S, Roeselers G, Levin E, Jonkers DM, Welting O, Heinsbroek SEM, de Weerd HH, Boekhout T, Fornai M, Masclee AA, Schuren FHJ, de Jonge WJ, Seppen J, van den Wijngaard RM. Intestinal Fungal Dysbiosis Is Associated With Visceral Hypersensitivity in Patients With Irritable Bowel Syndrome and Rats. *Gastroenterology* 2017; 153: 1026-1039 [PMID: 28624575 DOI: 10.1053/j.gastro.2017.06.004]

42 Koloski NA, Jones M, Talley NJ. Evidence that independent gut-to-brain and brain-to-gut pathways operate in the irritable bowel syndrome and functional dyspepsia: a 1-year population-based prospective study. *Aliment Pharmacol Ther* 2016; 44: 592-600 [PMID: 27444264 DOI: 10.1111/apt.13738]

43 Pinto-Sanchez MI, Ford AC, Avila CA, Verdu EF, Collins SM, Morgan D, Moayyedi P, Bercik P. Anxiety and Depression Increase in a Stepwise Manner in Parallel With Multiple FGIDs and Symptom Severity and Frequency. *Am J Gastroenterol* 2015; 110: 1038-1048 [PMID: 25964226 DOI: 10.1038/ajg.2015.128]

44 Raskov H, Burcharth J, Pommergaard HC, Rosenberg J. Irritable bowel syndrome, the microbiota and the gut-brain axis. *Gut Microbes* 2016; 7: 365-383 [PMID: 27472486 DOI: 10.1080/19490976.2016.1218585]

45 Black CJ, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. *Nat Rev Gastroenterol Hepatol* 2020; 17: 473-486 [PMID: 32296140 DOI: 10.1038/s41575-020-0286-8]

46 Hernandez LL, Limesand SW, Collier JL, Horseman ND, Collier RJ. The bovine mammary gland expresses multiple functional isoforms of serotonin receptors. *J Endocrinol* 2009; 203: 123-131 [PMID: 19654143 DOI: 10.1677/JOE-09-0187]

47 Liu N, Sun S, Wang P, Sun Y, Hu Q, Wang X. The Mechanism of Secretion and Metabolism of Gut-Derived 5-Hydroxytryptamine. *Int J Mol Sci* 2021; 22 [PMID: 34360695 DOI: 10.3390/ijms22157931]

48 Bulbring E, Lin RC. The effect of intraluminal application of 5-hydroxytryptamine and 5-hydroxytryptophan on peristalsis; the local production of 5-HT and its release in relation to intraluminal pressure and propulsive activity. *J Physiol* 1958; 140: 381-407 [PMID: 13514713 DOI: 10.1113/jphysiol.1958.sp005940]

49 Kerckhoffs AP, ter Linde JJ, Akkermans LM, Samsom M. SERT and TPH-1 mRNA expression are reduced in irritable bowel syndrome patients regardless of visceral sensitivity state in large intestine. *Am J Physiol Gastrointest Liver Physiol* 2012; 302: G1053-G1060 [PMID: 22323131 DOI: 10.1152/ajpgi.00153.2011]

50 Foley S, Garsed K, Singh G, Duroudier NP, Swan C, Hall IP, Zaitoun A, Bennett A, Marsden C, Holmes G, Walls A, Spiller RC. Impaired uptake of serotonin by platelets from patients with irritable bowel syndrome correlates with duodenal immune activation. *Gastroenterology* 2011; 140: 1434-43.e1 [PMID: 21315720 DOI: 10.1053/j.gastro.2011.01.052]

51 Faure C, Patey N, Gauthier C, Brooks EM, Mawe GM. Serotonin signaling is altered in irritable bowel syndrome with diarrhea but not in functional dyspepsia in pediatric age patients. *Gastroenterology* 2010; 139: 249-258 [PMID: 20303355 DOI: 10.1053/j.gastro.2010.03.032]

52 Hata T, Asano Y, Yoshihara K, Kimura-Todani T, Miyata N, Zhang XT, Takakura S, Aiba Y, Koga Y, Sudo N. Regulation of gut luminal serotonin by commensal microbiota in mice. *PLoS One* 2017; 12: e0180745 [PMID: 28683093 DOI: 10.1371/journal.pone.0180745]

53 Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015; 161: 264-276 [PMID: 25860609 DOI: 10.1016/j.cell.2015.02.047]

54 Fung TC, Vuong HE, Luna CDG, Pronovost GN, Aleksandrova AA, Riley NG, Vavilina A, McGinn J, Rendon T, Forrest LR, Hsiao EY. Intestinal serotonin and fluoxetine exposure modulate bacterial colonization in the gut. *Nat Microbiol* 2019; 4: 2064-2073 [PMID: 31477894 DOI: 10.1038/s41564-019-0540-4]

55 Reigstad CS, Salmonson CE, Rainey JF 3rd, Szurszewski JH, Linden DR, Sonnenburg JL, Farrugia G, Kashyap PC. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB*

J 2015; 29: 1395-1403 [PMID: 25550456 DOI: 10.1096/fj.14-259598]
56 Sugiyama Y, Mori Y, Nara M, Kotani Y, Nagai E, Kawada H, Kitamura M, Hirano R, Shimokawa H, Nakagawa A, Minami H, Gotoh A, Sakanaka M, Iida N, Koyanagi T, Katayama T, Okamoto S, Kurihara S. Gut bacterial aromatic amine production: aromatic amino acid decarboxylase and its effects on peripheral serotonin production. *Gut Microbes* 2022; 14: 2128605 [PMID: 36217238 DOI: 10.1080/19490976.2022.2128605]
57 Zhai L, Huang C, Ning Z, Zhang Y, Zhuang M, Yang W, Wang X, Wang J, Zhang L, Xiao H, Zhao L, Asthana P, Lam YY, Chow CFW, Huang JD, Yuan S, Chan KM, Yuan CS, Lau JY, Wong HLX, Bian ZX. Ruminococcus gnavus plays a pathogenic role in diarrhea-predominant irritable bowel syndrome by increasing serotonin biosynthesis. *Cell Host Microbe* 2023; 31: 33-44.e5 [PMID: 36495868 DOI: 10.1016/j.chom.2022.11.006]
58 Gu Y, Wang C, Qin X, Zhou B, Liu X, Liu T, Xie R, Liu J, Wang B, Cao H. Saccharomyces boulardii, a yeast probiotic, inhibits gut motility through upregulating intestinal serotonin transporter and modulating gut microbiota. *Pharmacol Res* 2022; 181: 106291 [PMID: 35690329 DOI: 10.1016/j.phrs.2022.106291]
59 Chen M, Ruan G, Chen L, Ying S, Li G, Xu F, Xiao Z, Tian Y, Lv L, Ping Y, Cheng Y, Wei Y. Neurotransmitter and Intestinal Interactions: Focus on the Microbiota-Gut-Brain Axis in Irritable Bowel Syndrome. *Front Endocrinol (Lausanne)* 2022; 13: 817100 [PMID: 35250873 DOI: 10.3389/fendo.2022.817100]
60 Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain Res* 2018; 1693: 128-133 [PMID: 29903615 DOI: 10.1016/j.brainres.2018.03.015]
61 Pokusaeva K, Johnson C, Luk B, Uribe G, Fu Y, Oezguen N, Matsunami RK, Lugo M, Major A, Mori-Akiyama Y, Hollister EB, Dann SM, Shi XZ, Engler DA, Savidge T, Versalovic J. GABA-producing Bifidobacterium dentium modulates visceral sensitivity in the intestine. *Neurogastroenterol Motil* 2017; 29 [PMID: 27458085 DOI: 10.1111/nmo.12904]
62 Laroute V, Beaufrand C, Gomes P, Nouaille S, Tondereau V, Daveran-Mingot ML, Theodorou V, Eutamene H, Mercier-Bonin M, Cocaign-Bousquet M. Lactococcus lactis NCDO2118 exerts visceral antinociceptive properties in rat via GABA production in the gastro-intestinal tract. *Elife* 2022; 11 [PMID: 35727704 DOI: 10.7554/eLife.77100]
63 Aggarwal S, Ahuja V, Paul J. Dysregulation of GABAergic Signalling Contributes in the Pathogenesis of Diarrhea-predominant Irritable Bowel Syndrome. *J Neurogastroenterol Motil* 2018; 24: 422-430 [PMID: 29852727 DOI: 10.5056/jnm17100]
64 Slattery SA, Niaz O, Aziz Q, Ford AC, Farmer AD. Systematic review with meta-analysis: the prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. *Aliment Pharmacol Ther* 2015; 42: 3-11 [PMID: 25913530 DOI: 10.1111/apt.13227]
65 Zhao L, Yang W, Chen Y, Huang F, Lu L, Lin C, Huang T, Ning Z, Zhai L, Zhong LL, Lam W, Yang Z, Zhang X, Cheng C, Han L, Qiu Q, Shang X, Huang R, Xiao H, Ren Z, Chen D, Sun S, El-Nezami H, Cai Z, Lu A, Fang X, Jia W, Bian Z. A Clostridia-rich microbiota enhances bile acid excretion in diarrhea-predominant irritable bowel syndrome. *J Clin Invest* 2020; 130: 438-450 [PMID: 31815740 DOI: 10.1172/JCI130976]
66 Ge X, Zhao W, Ding C, Tian H, Xu L, Wang H, Ni L, Jiang J, Gong J, Zhu W, Zhu M, Li N. Potential role of fecal microbiota from patients with slow transit constipation in the regulation of gastrointestinal motility. *Sci Rep* 2017; 7: 441 [PMID: 28348415 DOI: 10.1038/s41598-017-00612-y]
67 Traub RJ, Tang B, Ji Y, Pandya S, Yfantis H, Sun Y. A rat model of chronic postinflammatory visceral pain induced by deoxycholic acid. *Gastroenterology* 2008; 135: 2075-2083 [PMID: 19000677 DOI: 10.1053/j.gastro.2008.08.051]
68 Hollister EB, Oezguen N, Chumpitazi BP, Luna RA, Weidler EM, Rubio-Gonzales M, Dahdouli M, Cope JL, Mistretta TA, Raza S, Metcalf GA, Muzny DM, Gibbs RA, Petrosino JF, Heitkemper M, Savidge TC, Shulman RJ, Versalovic J. Leveraging Human Microbiome Features to Diagnose and Stratify Children with Irritable Bowel Syndrome. *J Mol Diagn* 2019; 21: 449-461 [PMID: 31005411 DOI: 10.1016/j.jmoldx.2019.01.006]
69 Edwinson AL, Yang L, Peters S, Hanning N, Jeraldo P, Jagtap P, Simpson JB, Yang TY, Kumar P, Mehta S, Nair A, Breen-Lyles M, Chikkamenahalli L, Graham RP, De Winter B, Patel R, Dasari S, Kashyap P, Griffin T, Chen J, Farrugia G, Redinbo MR, Grover M. Gut microbial β-glucuronidases regulate host luminal proteases and are depleted in irritable bowel syndrome. *Nat Microbiol* 2022; 7: 680-694 [PMID: 35484230 DOI: 10.1038/s41564-022-01103-1]
70 Xiao L, Liu Q, Luo M, Xiong L. Gut Microbiota-Derived Metabolites in Irritable Bowel Syndrome. *Front Cell Infect Microbiol* 2021; 11: 729346 [PMID: 34631603 DOI: 10.3389/fcimb.2021.729346]
71 Zhang J, Song L, Wang Y, Liu C, Zhang L, Zhu S, Liu S, Duan L. Beneficial effect of butyrate-producing Lachnospiraceae on stress-induced visceral hypersensitivity in rats. *J Gastroenterol Hepatol* 2019; 34: 1368-1376 [PMID: 30402954 DOI: 10.1111/jgh.14536]
72 Sun YY, Li M, Li YY, Li LX, Zhai WZ, Wang P, Yang XX, Gu X, Song LJ, Li Z, Zuo XL, Li YQ. The effect of Clostridium butyricum on symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *Sci Rep* 2018; 8: 2964 [PMID: 29445178 DOI: 10.1038/s41598-018-21241-z]
73 Ringel-Kulka T, Choi CH, Temas D, Kim A, Maier DM, Scott K, Galanko JA, Ringel Y. Altered Colonic Bacterial Fermentation as a Potential Pathophysiological Factor in Irritable Bowel Syndrome. *Am J Gastroenterol* 2015; 110: 1339-1346 [PMID: 26303129 DOI: 10.1038/ajg.2015.220]
74 Asano T, Tanaka KI, Tada A, Shimamura H, Tanaka R, Maruoka H, Mizushima T, Takenaga M. Ameliorative effect of chlorpromazine hydrochloride on visceral hypersensitivity in rats: possible involvement of 5-HT(2A) receptor. *Br J Pharmacol* 2017; 174: 3370-3381 [PMID: 28750135 DOI: 10.1111/bph.13960]
75 Shaidullov IF, Sorokina DM, Sitdikov FG, Hermann A, Abdulkhakov SR, Sitdikova GF. Short chain fatty acids and colon motility in a mouse model of irritable bowel syndrome. *BMC Gastroenterol* 2021; 21: 37 [PMID: 33499840 DOI: 10.1186/s12876-021-01613-y]
76 Luo M, Zhuang X, Tian Z, Xiong L. Alterations in short-chain fatty acids and serotonin in irritable bowel syndrome: a systematic review and meta-analysis. *BMC Gastroenterol* 2021; 21: 14 [PMID: 33407171 DOI: 10.1186/s12876-020-01577-5]
77 Gargari G, Taverniti V, Gardana C, Cremon C, Canducci F, Pagano I, Barbaro MR, Bellacosa L, Castellazzi AM, Valsecchi C, Tagliacarne SC, Bellini M, Bertani L, Gambaccini D, Marchi S, Cicala M, Germanà B, Dal Pont E, Vecchi M, Ogliari C, Fiore W, Stanghellini V, Barbara G, Guglielmetti S. Fecal Clostridiales distribution and short-chain fatty acids reflect bowel habits in irritable bowel syndrome. *Environ Microbiol* 2018; 20: 3201-3213 [PMID: 29749705 DOI: 10.1111/1462-2920.14271]
78 Lieberman P. The basics of histamine biology. *Ann Allergy Asthma Immunol* 2011; 106: S2-S5 [PMID: 21277530 DOI: 10.1016/j.anai.2010.08.005]
79 Sohn W, Lee OY, Lee SP, Lee KN, Jun DW, Lee HL, Yoon BC, Choi HS, Sim J, Jang KS. Mast cell number, substance P and vasoactive intestinal peptide in irritable bowel syndrome with diarrhea. *Scand J Gastroenterol* 2014; 49: 43-51 [PMID: 24256141 DOI: 10.3109/00365521.2013.857712]
80 Grabauskas G, Wu X, Gao J, Li JY, Turgeon DK, Owyang C. Prostaglandin E(2), Produced by Mast Cells in Colon Tissues From Patients With Irritable Bowel Syndrome, Contributes to

Visceral Hypersensitivity in Mice. *Gastroenterology* 2020; 158: 2195-2207.e6 [PMID: 32084424 DOI: 10.1053/j.gastro.2020.02.022]
81 Barbara G, Wang B, Stanghellini V, de Giorgio R, Cremon C, Di Nardo G, Trevisani M, Campi B, Geppetti P, Tonini M, Bunnett NW, Grundy D, Corinaldesi R. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* 2007; 132: 26-37 [PMID: 17241857 DOI: 10.1053/j.gastro.2006.11.039]
82 De Palma G, Shimbori C, Reed DE, Yu Y, Rabbia V, Lu J, Jimenez-Vargas N, Sessenwein J, Lopez-Lopez C, Pigrau M, Jaramillo-Polanco J, Zhang Y, Baerg L, Manzar A, Pujo J, Bai X, Pinto-Sanchez MI, Caminero A, Madsen K, Surette MG, Beyak M, Lomax AE, Verdu EF, Collins SM, Vanner SJ, Bercik P. Histamine production by the gut microbiota induces visceral hyperalgesia through histamine 4 receptor signaling in mice. *Sci Transl Med* 2022; 14: eabj1895 [PMID: 35895832 DOI: 10.1126/scitranslmed.abj1895]
83 Stanisor OI, van Diest SA, Yu Z, Welting O, Bekkali N, Shi J, de Jonge WJ, Boeckxstaens GE, van den Wijngaard RM. Stress-induced visceral hypersensitivity in maternally separated rats can be reversed by peripherally restricted histamine-1-receptor antagonists. *PLoS One* 2013; 8: e66884 [PMID: 23776699 DOI: 10.1371/journal.pone.0066884]
84 Wouters MM, Balemans D, Van Wanrooy S, Dooley J, Cibert-Goton V, Alpizar YA, Valdez-Morales EE, Nasser Y, Van Veldhoven PP, Vanbrabant W, Van der Merwe S, Mols R, Ghesquière B, Cirillo C, Kortekaas I, Carmeliet P, Peetermans WE, Vermeire S, Rutgeerts P, Augustijns P, Hellings PW, Belmans A, Vanner S, Bulmer DC, Talavera K, Vanden Berghe P, Liston A, Boeckxstaens GE. Histamine Receptor H1-Mediated Sensitization of TRPV1 Mediates Visceral Hypersensitivity and Symptoms in Patients With Irritable Bowel Syndrome. *Gastroenterology* 2016; 150: 875-87.e9 [PMID: 26752109 DOI: 10.1053/j.gastro.2015.12.034]
85 Sundin J, Rangel I, Kumawat AK, Hultgren-Hörnquist E, Brummer RJ. Aberrant mucosal lymphocyte number and subsets in the colon of post-infectious irritable bowel syndrome patients. *Scand J Gastroenterol* 2014; 49: 1068-1075 [PMID: 24919810 DOI: 10.3109/00365521.2014.926982]
86 Shukla R, Ghoshal U, Ranjan P, Ghoshal UC. Expression of Toll-like Receptors, Pro-, and Anti-inflammatory Cytokines in Relation to Gut Microbiota in Irritable Bowel Syndrome: The Evidence for Its Micro-organic Basis. *J Neurogastroenterol Motil* 2018; 24: 628-642 [PMID: 30347939 DOI: 10.5056/jnm18130]
87 He X, Cui LH, Wang XH, Yan ZH, Li C, Gong SD, Zheng Y, Luo Z, Wang Y. Modulation of inflammation by toll-like receptor 4/nuclear factor-kappa B in diarrhea-predominant irritable bowel syndrome. *Oncotarget* 2017; 8: 113957-113965 [PMID: 29371960 DOI: 10.18632/oncotarget.23045]
88 Nozu T, Miyagishi S, Nozu R, Takakusaki K, Okumura T. Altered colonic sensory and barrier functions by CRF: roles of TLR4 and IL-1. *J Endocrinol* 2018; 239: 241-252 [PMID: 30139928 DOI: 10.1530/JOE-18-0441]
89 Mallaret G, Lashermes A, Meleine M, Boudieu L, Barbier J, Aissouni Y, Gelot A, Chassaing B, Gewirtz AT, Ardid D, Carvalho FA. Involvement of toll-like receptor 5 in mouse model of colonic hypersensitivity induced by neonatal maternal separation. *World J Gastroenterol* 2022; 28: 3903-3916 [PMID: 36157543 DOI: 10.3748/wjg.v28.i29.3903]
90 Anitha M, Vijay-Kumar M, Sitaraman SV, Gewirtz AT, Srinivasan S. Gut microbial products regulate murine gastrointestinal motility via Toll-like receptor 4 signaling. *Gastroenterology* 2012; 143: 1006-16.e4 [PMID: 22732731 DOI: 10.1053/j.gastro.2012.06.034]
91 Gao J, Xiong T, Grabauskas G, Owyang C. Mucosal Serotonin Reuptake Transporter Expression in Irritable Bowel Syndrome Is Modulated by Gut Microbiota Via Mast Cell-Prostaglandin E2. *Gastroenterology* 2022; 162: 1962-1974.e6 [PMID: 35167867 DOI: 10.1053/j.gastro.2022.02.016]
92 顾湘. 具核梭杆菌参与肠易激综合征肠道菌群失调和内脏高敏感发生的相关机制研究. 博士 2020 [DOI: 10.27272/d.cnki.gshdu.2020.004083]
93 Johnsen PH, Hilpüsch F, Cavanagh JP, Leikanger IS, Kolstad C, Valle PC, Goll R. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *Lancet Gastroenterol Hepatol* 2018; 3: 17-24 [PMID: 29100842 DOI: 10.1016/S2468-1253(17)30338-2]
94 Lahtinen P, Jalanka J, Hartikainen A, Mattila E, Hillilä M, Punkkinen J, Koskenpato J, Anttila VJ, Tillonen J, Satokari R, Arkkila P. Randomised clinical trial: faecal microbiota transplantation versus autologous placebo administered via colonoscopy in irritable bowel syndrome. *Aliment Pharmacol Ther* 2020; 51: 1321-1331 [PMID: 32343000 DOI: 10.1111/apt.15740]
95 Holster S, Lindqvist CM, Repsilber D, Salonen A, de Vos WM, König J, Brummer RJ. The Effect of Allogenic Versus Autologous Fecal Microbiota Transfer on Symptoms, Visceral Perception and Fecal and Mucosal Microbiota in Irritable Bowel Syndrome: A Randomized Controlled Study. *Clin Transl Gastroenterol* 2019; 10: e00034 [PMID: 31009405 DOI: 10.14309/ctg.0000000000000034]
96 Hamazaki M, Sawada T, Yamamura T, Maeda K, Mizutani Y, Ishikawa E, Furune S, Yamamoto K, Ishikawa T, Kakushima N, Furukawa K, Ohno E, Honda T, Kawashima H, Ishigami M, Nakamura M, Fujishiro M. Fecal microbiota transplantation in the treatment of irritable bowel syndrome: a single-center prospective study in Japan. *BMC Gastroenterol* 2022; 22: 342 [PMID: 35836115 DOI: 10.1186/s12876-022-02408-5]
97 El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. *Gut* 2020; 69: 859-867 [PMID: 31852769 DOI: 10.1136/gutjnl-2019-319630]
98 Holvoet T, Joossens M, Vázquez-Castellanos JF, Christiaens E, Heyerick L, Boelens J, Verhasselt B, van Vlierberghe H, De Vos M, Raes J, De Looze D. Fecal Microbiota Transplantation Reduces Symptoms in Some Patients With Irritable Bowel Syndrome With Predominant Abdominal Bloating: Short- and Long-term Results From a Placebo-Controlled Randomized Trial. *Gastroenterology* 2021; 160: 145-157.e8 [PMID: 32681922 DOI: 10.1053/j.gastro.2020.07.013]
99 Yau YK, Su Q, Xu Z, Tang W, Ching JYL, Mak JWY, Cheung CP, Fung M, Ip M, Chan PKS, Wu JCY, Chan FKL, Ng SC. Randomised clinical trial: Faecal microbiota transplantation for irritable bowel syndrome with diarrhoea. *Aliment Pharmacol Ther* 2023; 58: 795-804 [PMID: 37667968 DOI: 10.1111/apt.17703]
100 Halkjær SI, Christensen AH, Lo BZS, Browne PD, Günther S, Hansen LH, Petersen AM. Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: results from a randomised, double-blind placebo-controlled study. *Gut* 2018; 67: 2107-2115 [PMID: 29980607 DOI: 10.1136/gutjnl-2018-316434]
101 Aroniadis OC, Brandt LJ, Oneto C, Feuerstadt P, Sherman A, Wolkoff AW, Kassam Z, Sadovsky RG, Elliott RJ, Budree S, Kim M, Keller MJ. Faecal microbiota transplantation for diarrhoea-predominant irritable bowel syndrome: a double-blind, randomised, placebo-controlled trial. *Lancet Gastroenterol Hepatol* 2019; 4: 675-685 [PMID: 31326345 DOI: 10.1016/S2468-1253(19)30198-0]
102 邢寒阳, 陈东风, 但凤. 粪菌移植治疗肠易激综合征的疗效: Meta分析. 胃肠病学和肝病学杂志 2022; 31: 1234-1240 [DOI: 10.3969/j.issn.1006-5709.2022.11.006]
103 Nanjing consensus on methodology of washed microbiota transplantation. *Chin Med J (Engl)* 2020; 133: 2330-2332 [PMID: 32701590 DOI: 10.1097/CM9.0000000000000954]

104 Cammarota G, Ianiro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, Sokol H, Arkkila P, Pintus C, Hart A, Segal J, Aloi M, Masucci L, Molinaro A, Scaldaferri F, Gasbarrini G, Lopez-Sanroman A, Link A, de Groot P, de Vos WM, Högenauer C, Malfertheiner P, Mattila E, Milosavljević T, Nieuwdorp M, Sanguinetti M, Simren M, Gasbarrini A; European FMT Working Group. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 2017; 66: 569-580 [PMID: 28087657 DOI: 10.1136/gutjnl-2016-313017]

105 Cammarota G, Ianiro G, Kelly CR, Mullish BH, Allegretti JR, Kassam Z, Putignani L, Fischer M, Keller JJ, Costello SP, Sokol H, Kump P, Satokari R, Kahn SA, Kao D, Arkkila P, Kuijper EJ, Vehreschild MJG, Pintus C, Lopetuso L, Masucci L, Scaldaferri F, Terveer EM, Nieuwdorp M, López-Sanromán A, Kupcinskas J, Hart A, Tilg H, Gasbarrini A. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* 2019; 68: 2111-2121 [PMID: 31563878 DOI: 10.1136/gutjnl-2019-319548]

106 Kump P, Wurm P, Gröchenig HP, Wenzl H, Petritsch W, Halwachs B, Wagner M, Stadlbauer V, Eherer A, Hoffmann KM, Deutschmann A, Reicht G, Reiter L, Slawitsch P, Gorkiewicz G, Högenauer C. The taxonomic composition of the donor intestinal microbiota is a major factor influencing the efficacy of faecal microbiota transplantation in therapy refractory ulcerative colitis. *Aliment Pharmacol Ther* 2018; 47: 67-77 [PMID: 29052237 DOI: 10.1111/apt.14387]

107 Fuentes S, Rossen NG, van der Spek MJ, Hartman JH, Huuskonen L, Korpela K, Salojärvi J, Aalvink S, de Vos WM, D'Haens GR, Zoetendal EG, Ponsioen CY. Microbial shifts and signatures of long-term remission in ulcerative colitis after faecal microbiota transplantation. *ISME J* 2017; 11: 1877-1889 [PMID: 28398347 DOI: 10.1038/ismej.2017.44]

108 Mizuno S, Masaoka T, Naganuma M, Kishimoto T, Kitazawa M, Kurokawa S, Nakashima M, Takeshita K, Suda W, Mimura M, Hattori M, Kanai T. Bifidobacterium-Rich Fecal Donor May Be a Positive Predictor for Successful Fecal Microbiota Transplantation in Patients with Irritable Bowel Syndrome. *Digestion* 2017; 96: 29-38 [PMID: 28628918 DOI: 10.1159/000471919]

109 Wilson BC, Vatanen T, Cutfield WS, O'Sullivan JM. The Super-Donor Phenomenon in Fecal Microbiota Transplantation. *Front Cell Infect Microbiol* 2019; 9: 2 [PMID: 30719428 DOI: 10.3389/fcimb.2019.00002]

110 郭世强, 刘春林, 吴清念, 张晓槟. 粪菌移植治疗感染后肠易激综合征的临床疗效. 临床药物治疗杂志 2021; 19: 63-66 [DOI: 10.3969/j.issn.1672-3384.2021.12.014]

111 王纯. 粪菌移植治疗帕金森病患者肠易激综合征样症状的有效性和安全性的临床研究. 硕士 2021 [DOI: 10.27001/d.cnki.gtjyu.2021.000112]

112 中华医学会肠外肠内营养学分会, 中国国际医疗保健促进交流会加速康复外科分会, 中国微生态治疗创新联盟, 上海预防医学会微生态专业委员会. 菌群移植途径的选择与建立临床应用中国专家共识. 中华胃肠外科杂志 2020; 23: 14-20 [DOI: 10.3760/cma.j.cn.441530-20200420-00228]

113 傅伟强, 黄才斌. 粪菌移植治疗腹泻型肠易激综合征研究进展. 实用临床医学 2022; 23: 122-127 [DOI: 10.13764/j.cnki.lcsy.2022.03.035]

114 Schmidt TSB, Li SS, Maistrenko OM, Akanni W, Coelho LP, Dolai S, Fullam A, Glazek AM, Hercog R, Herrema H, Jung F, Kandels S, Orakov A, Thielemann R, von Stetten M, Van Rossum T, Benes V, Borody TJ, de Vos WM, Ponsioen CY, Nieuwdorp M, Bork P. Drivers and determinants of strain dynamics following fecal microbiota transplantation. *Nat Med* 2022; 28: 1902-1912 [PMID: 36109636 DOI: 10.1038/s41591-022-01913-0]

115 Ianiro G, Punčochář M, Karcher N, Porcari S, Armanini F, Asnicar F, Beghini F, Blanco-Míguez A, Cumbo F, Manghi P, Pinto F, Masucci L, Quaranta G, De Giorgi S, Sciumè GD, Bibbò S, Del Chierico F, Putignani L, Sanguinetti M, Gasbarrini A, Valles-Colomer M, Cammarota G, Segata N. Variability of strain engraftment and predictability of microbiome composition after fecal microbiota transplantation across different diseases. *Nat Med* 2022; 28: 1913-1923 [PMID: 36109637 DOI: 10.1038/s41591-022-01964-3]

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