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文献综述 REVIEW

# 短链脂肪酸介导的菌群–宿主互动与肠易激综合征的研究进展

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## Short chain fatty acids mediated flora-host interaction and irritable bowel syndrome

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## Abstract

Intestinal flora has proved to be closely related to the onset of irritable bowel syndrome (IBS). Short chain fatty acids (SCFAs) are the main product of flora metabolism as well as important messenger molecules in the gut, playing a role in maintaining the stability of microorganism community structure and in regulating intestinal immune response, motility and the epithelial barrier. Flora imbalance in IBS patients has a direct impact on the microbiota-SCFAs-intestinal epithelial cells signal pathway, which results in low-grade inflammation, increased intestinal permeability and abnormality of motility. Studying the role SCFA plays in the pathogenesis of IBS can expand our understanding of this disease and provide a new strategy for therapy.



Key Words: Intestinal microbiota; Irritable bowel syndrome; Short-chain fatty acids; Immune

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**背景资料**
肠易激综合征(irritable bowel syndrome, IBS)是一种以腹痛、腹部不适伴排便习惯改变为特点的功能性胃肠病, 病因和发病机制尚不清楚. 肠道菌群与IBS发病机制的联系近年来备受关注, 有研究认为功能性胃肠病可能在肠道菌群领域实现突破.

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**研发前沿**

近年来研究集中在观察IBS患者肠道菌群结构、多样性的异常改变及其意义. 并以此为依据指导IBS患者饮食、生活习惯及医务人员的临床实践. 当前肠道菌群的研究多通过分析粪便样本完成, 依附于肠黏膜的肠道菌群及其在肠黏膜表面与宿主细胞产生的相互作用尚待进一步研究.


## 摘要

肠道菌群和肠易激综合征(irritable bowel syndrome, IBS)发病密切相关, 短链脂肪酸是菌群代谢的主要产物和重要信息分子, 不仅起到稳定菌群结构的作用, 还参与肠道免疫、动力和肠上皮屏障的调节. IBS患者肠道菌群失调, 直接影响了肠道菌群-短链脂肪酸-肠上皮细胞的正常信号路径, 最终导致低度炎症反应、肠上皮屏障通透性增加和动力异常. 研究短链脂肪酸与IBS发病机制的关系对全面认识IBS并指导临床具有重要意义.




**关键词: 肠道菌群; 肠易激综合征; 短链脂肪酸; 免疫**

**核心提示**: 本文综述显示短链脂肪酸(short-chain fatty acids, SCFAs)介导的肠道菌群-肠上皮细胞相互作用对于肠道免疫、动力和肠黏膜屏障等功能有重要意义. 肠道菌群失调影响SCFA的产生和利用, 造成免疫紊乱、动力异常和肠上皮屏障通透性增加, 最终导致IBS发生.

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## 0 引言

肠易激综合征(irritable bowel syndrome, IBS)是最常见的功能性胃肠病之一, 以腹痛或腹部不适伴排便习惯改变和/或大便性状异常为特征[1]. 流行病学数据显示, 在世界范围内约15%-20%的成人受其影响, 欧美国家IBS发病率为10%-20%, 中国IBS发病率为4.60%-5.67%[2]. IBS机制尚未完全阐明, 其病理生理学基础主要包括胃肠动力失调和内脏感知异常两方面. 早期生活压力、社会心理因素、食物不耐受、抗生素滥用、肠道感染等因素均能导致肠易激综合征的发病[3]. 肠道菌群对于维持肠道消化、营养、免疫、内分泌功能具有重要意义, 还影响机体的生长发育、代谢、情绪反应等方面. 越来越多证据表明肠道菌群在IBS的发病机制中起重要作用[4-7]. 短链脂肪酸(short-chain fatty acids, SCFAs)是肠道菌群的主要代谢产物, 是肠道菌群实现对肠道功能调节的关键信息分子.

## 1 SCFA概述

SCFAs是一组由6个及以下碳原子组成的饱和脂肪酸, 包括乙酸、丙酸、异丁酸、丁酸、异戊酸、己酸和异己酸等. 其中分布于肠道的SCFA主要有乙酸、丙酸、丁酸, 是由纤维和抗性淀粉(resistant starch, RS)(指在健康成人小肠中难以被消化的淀粉及其降解产物)在结肠中经厌氧菌发酵产生. SCFAs能被肠道快速吸收, 其中丁酸是肠上皮细胞重要的能量来源, 其大部分被吸收用于供能, 乙酸和丙酸到达门静脉循环, 丙酸被肝脏吸收, 参与糖异生并抑制胆固醇合成[8], 乙酸随血液进入全身循环, 仅有少量SCFAs(约占总量5%-10%)逃脱吸收并在粪便样本中被检出(图1).

SCFAs被肠道吸收的方式有两种. 非游离SCFAs可以通过简单扩散方式通过肠上皮屏障, 游离SCFAs则需要通过转运体运输[9], 两种主要的转运体分别是单羧酸转运蛋白1(monocarboxylate transporter1, MCT-1)和钠耦联单羧酸转运蛋白1(sodium-coupled monocarboxylate transporter1, SMCT-1). SCFAs作用于其受体发挥生物学效应. 目前已知的SCFAs的受体主要有G蛋白偶联受体41(G protein-coupled receptor 41, GPR41)、GPR43和GPR109, 这些受体广泛分布于肠上皮细胞和嗜酸性粒细胞、嗜碱性粒细胞、中性粒细胞等免疫细胞, 参与肠道动力、内分泌和免疫等功能的调节[10].

## 2 SCFAs是肠道菌群-宿主交互作用的重要信息分子

2.1 SCFAs与肠道微环境 肠道菌群在肠黏膜表面与宿主细胞的相互作用影响肠道微环境[11]. 细菌发酵产生的SCFAs是肠道中主要的阴离子, 浓度达到50-150 mmol/L. SCFAs可降低肠道pH, 达到促进益生菌的生长增殖并抑制特定病原菌定植的目的[12-14]. SCFAs抑制病原菌定植的机制尚不清楚, 研究[15,16]认为SCFA能损伤病原菌细胞膜和导致氧化应激, 还发现SCFA具有抑制病原菌某些毒性因子表达的作用[17]. 综上推断, SCFA是肠道菌群之间用于信息交

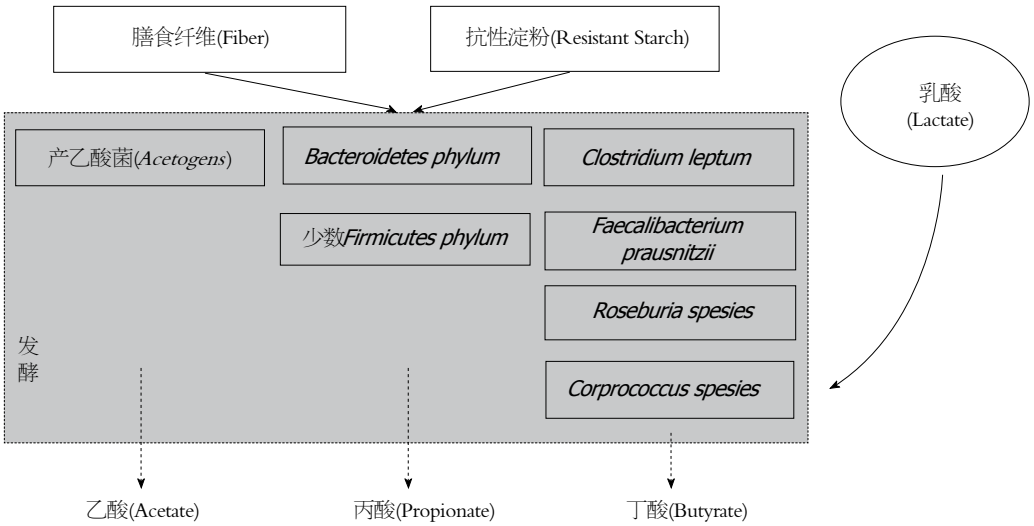


**图 1　3种主要SCFA在体内的产生过程.** SCFA: 短链脂肪酸.

**相关报道**
Hiso等研究显示肠道菌群以短链脂肪酸(short-chain fatty acids, SCFAs)为介质作用于肠嗜铬细胞, 影响肠道重要信息分子5-HT的合成和释放. Ringel-Kulka通过对比IBS患者和健康志愿者肠道通过时间、胃肠道pH及粪便SCFA指出肠道细菌发酵过程异常及短链脂肪酸含量改变可能导致IBS发生.

流的感应分子, 对菌群内部结构的稳定起到决定作用. 同时, SCFA还是菌群传递信号给宿主细胞的重要介质, 影响肠内分泌细胞、免疫细胞和神经末梢[18], 间接影响肠腔内稳态.

SCFAs对肠上皮细胞有营养和促增殖、分化作用, 对维持肠黏膜屏障完整性、稳定肠道微环境具有积极意义. 最新研究[19-22]表明SCFA具有促进黏蛋白生成、增强肠黏膜屏障的作用. SCFA通过激活肠上皮细胞内低氧诱导因子(hypoxia inducible factor, HIF), 刺激肠黏膜屏障重要蛋白-黏蛋白的释放. 同时, SCFA具有促进白介素(interleukin, IL)-18释放, 加速肠黏膜屏障修复的作用[23]. SCFA缺乏导致肠黏膜变薄、保护作用下降, 细菌及抗原进入黏膜下层损伤肠细胞[24].

2.2 SCFAs参与肠道内免疫调节 SCFA作用于肠上皮细胞、单核吞噬细胞、先天淋巴细胞、B淋巴细胞、T淋巴细胞和Treg细胞, 是沟通肠道菌群和肠免疫系统的重要分子[25]. 既往资料显示, SCFA在免疫调节中主要发挥抗炎的作用. Maslowski等[26]发现DSS炎症模型中, 无菌小鼠(Germ-Free, GF小鼠)呈现更严重的炎症程度, 乙酸干预后GF小鼠模型炎症程度减轻, 趋近于普通小鼠; 其进一步研究发现, 与野生型小鼠相比, *GPR43*基因敲除小鼠($Gpr43^{-/-}$)的炎症程度更为严重, 提示GPR43参与SCFA对免疫反应的调节. SCFA促进T细胞分化为Treg细胞, 诱导其释放IL-10从而抑制效应T细胞Th1和Th17的激活和炎症反应的发生[27]. 最新研究发现, SCFAs在不同肠内免疫环境下对免疫起双向调节作用. 如炎症初期SCFAs作用肠上皮细胞表面的GPR41和GPR43[28]、激活细胞内的激动蛋白1(activator protein-1, AP-1)通路, 促进细胞因子和趋化因子释放, 增强免疫应答[24,29,30]. 这种保护性免疫反应帮助机体快速清除病原, 缩短炎症反应时间.

2.3 SCFAs影响肠道动力 大量临床和实验数据证明SCFA参与调节肠道动力. 1988年, 梅奥诊所医生Kamath[31,32]在研究中发现SCFA具有增强犬类回肠动力的作用, 这一结论在随后的临床观察中得到验证. 而关于SCFA调节结肠动力的研究得出了不同的结果: Soret等[33]研究表明SCFA能够诱导肠肌层神经元可塑性并促进结肠运动. Cherbut等学者的研究[34-36]则显示SCFA有抑制结肠动力的作用. SCFA对结肠动力的调节可能受其浓度影响, 低浓度(10-100 mmol/L)的SCFA增强肠动力或无影响, 而高浓度(>100 mmol/L)条件下, SCFA抑制结肠动力[34,37]. 研究[36]显示进食抗性淀粉的大鼠结肠中的丁酸含量明显上升而结肠收缩受到抑制. 临床上根据抗性淀粉这一特性将其用于治疗霍乱患者腹泻症状并取得显著疗效[38].

肠动力调节机制复杂. 5-羟色胺(5-hydroxytryptamine, 5-HT)是肠道中广泛存在的关键动力调控分子, 除影响肠道动力外, 还与内分泌、血管收缩以及肠神经系统有密切联系. Yano等[39]的研究显示肠道菌群以SCFA为介质作用于肠嗜铬细胞, 调控5-HT的合成和释放. 这一过程可能与SCFAs促进肠上皮细胞中Tph1转录有关[40]. Grider等[37]的研究

**创新盘点**

全面总结了关于短链脂肪酸与IBS发病相关性的最新研究成果, 将肠道菌群、短链脂肪酸及宿主细胞作为统一整体, 从SCFA参与调控肠道免疫、肠道动力、肠黏膜屏障等方面进行分析, 提出了短链脂肪酸介导的肠道菌群-宿主互动异常可能导致IBS症状, 为IBS发病机制提供合理假设.

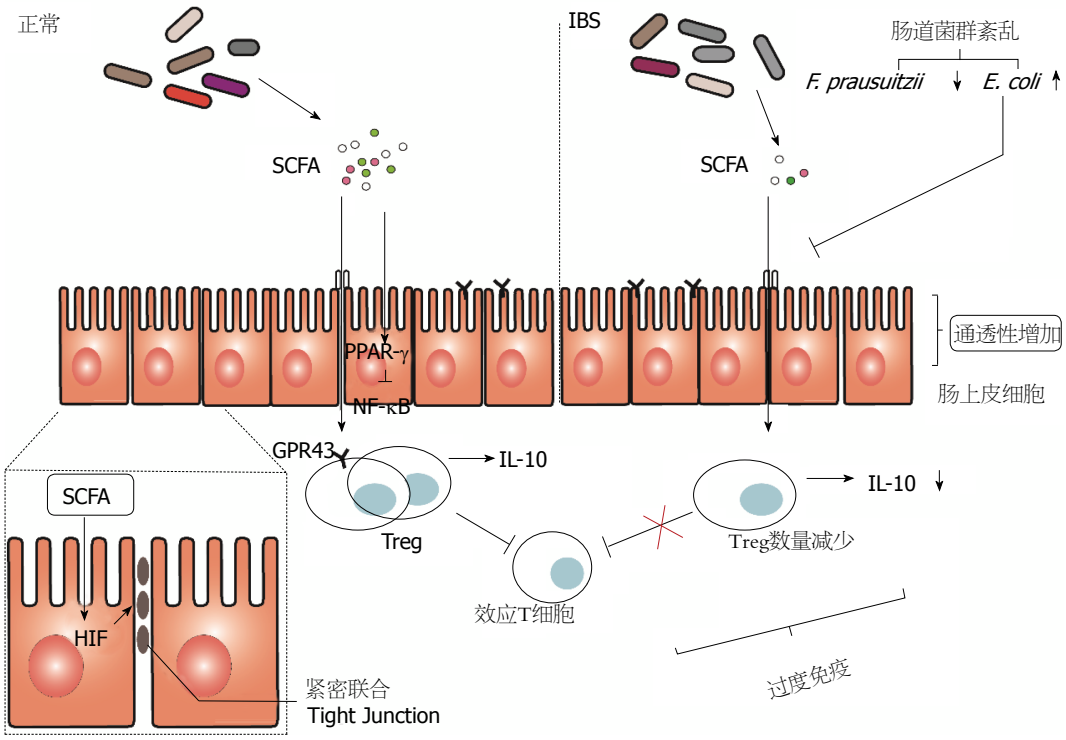


**图 2 IBS中肠道菌群-SCFA-肠上皮细胞信号路径异常**. SCFA: 短链脂肪酸; IL: 白介素; GPR: G蛋白偶联受体; HIF: 低氧诱导因子; IBS: 肠易激综合征; NF-κB: 核因子-κB; PPAR-γ: 过氧化物酶体增殖物激活受体γ.

显示SCFA促进5-HT和CGRP的释放, 并诱发蠕动反射. 上述证据表明, SCFA在是肠道动力分子调控网络里的重要一环.

## 3 SCFAs和肠易激综合征

3.1 IBS患者肠道菌群变化 临床和动物研究证实IBS患者的肠道菌群存在结构和功能异常改变. Carroll等[41]将IBS患者和健康人的肠道菌群进行分析比较, 结果提示IBS患者菌群中*F. prausnitzii*减少、*Enterobacteriaceae*增加, Rajilić-Stojanović[42]发现IBS患者粪便中双歧杆菌、柔嫩梭菌数量减少, 瘤胃球菌属、梭状芽胞杆菌种数量增加. Chassard等[43]的研究显示IBS-C患者中呈现多菌种及其功能产物的失调, 产乳酸菌、耗氢细菌、产烷细菌、还原产乙酸菌及大肠罗氏杆菌(*Roseburia-E.*)较健康人减少. 其中*F. prausnitzii*和*Roseburia-E.*是两种重要的产丁酸菌, 其减少可能直接导致肠道中SCFA缺乏(图2).

3.2 IBS患者的SCFA改变 早在1987年, Mortensen等[44]就发现SCFA在腹泻型和便秘型IBS患者的粪便中分别呈上升和下降趋势. Kang等[45]发现IBS-C患者粪便中丁酸浓度升高. Treem等[46]对IBS-D患者粪便细菌培养后再予底物发酵, 发现总SCFA浓度的下降和丁酸浓度的升高. 研究结果的不一致性提示粪便中SCFA受多因素影响. 影响粪便中SCFA的首要因素是结肠传输时间(colonic transit time, CTT), 粪便SCFA吸收率与CTT存在呈正相关, CTT>50 h的粪便中SCFA无法检出[47]. 肠道菌群结构对粪便SCFA含量也有一定影响, 如大肠杆菌(*E. coli*)感染能够显著减少肠上皮细胞对SCFA的摄入, 造成SCFA生物利用度降低[48]. 据此可推断, 至少在IBS-D型患者中存在SCFA吸收障碍, 这可能是粪便检出SCFA含量增加的重要原因之一[49,50](表1).

3.3 SCFAs参与IBS肠道免疫过度激活 肠道感染使IBS发病风险增加6-7倍[51,52], 部分细菌性肠炎患者6 mo内存在持续的消化系症状, 其中少部分患者出现类似IBS的临床症状[53]. 感染所致的肠道菌群改变可能是免疫反应过度激活状态长期存在的根源[54]. 在IBS患者肠道内以大肠杆菌为代表的机会致病菌过度生长破坏了肠道菌群间的平衡[55], 阻碍肠上皮细胞对SCFA的吸收[48,56]. 而SCFA吸收、利用降低直接导致Treg细胞分化过程出现障碍, 抗炎因子IL-10释放减少, 最终造成免疫过度激活.

3.4 SCFAs和肠黏膜通透性改变 肠黏膜屏障包

表 1 关于IBS患者肠道SCFA的研究

| 研究者 | 研究对象 | | 总SCFA | 乙酸 | 丙酸 | 丁酸 |
|---|---|---|---|---|---|---|
| Mortensen等[44]1987 | IBS($n$ = 18) | D | ↑ | – | – | – |
| | | C | ↓ | – | – | – |
| Treem等[46]1996 | IBS-D($n$ = 5) | | ↓ | ↓ | ↓ | ↑ |
| Kang等[45]2015 | IBS-C($n$ = 9) | | ns | ns | ns | ↑ |
| Tana等[49]2010 | IBS($n$ = 26) | | ↑ | ↑ | ↑ | ns |
| Ringel-Kulka等[50]2015 | IBS($n$ = 114) | D | ns | – | – | – |
| | | C | | ↓ | ↓ | ↓ |

–: 未比较; ns: no significant, 差异不显著. SCFA: 短链脂肪酸.

**应用要点**

通过肠道中短链脂肪酸含量判断肠道菌群的状态和发酵情况, 以此指导饮食结构、抗菌素、益菌素及SCFA制剂的使用, 为IBS治疗提供新的思路.

括肠肌层和表面的肠上皮细胞层, 肠上皮细胞层与肠道菌群直接接触, 是菌群-宿主发生交互作用的重要场所. 肠上皮细胞通过紧密联合(tight junction)相互连接, 构成肠上皮屏障, 在异常情况下, 紧密连接蛋白合成减少, 上皮细胞间间隙增加, 即所谓的“肠通透性增加”. 肠道菌群对肠上皮屏障具有生长促进作用, 正常菌群释放SCFA抑制肠黏膜的通透性, 对维持肠黏膜屏障的完整性具有积极意义[14,57]. 但肠道菌群异常改变的IBS患者由于肠上皮细胞对SCFA摄入不足, 直接影响紧密连接蛋白的分布, 是导致其肠黏膜通透性增加的重要原因之一[6].

3.5 SCFAs与内脏的高敏感 Kamath等[32]在研究发现健康人回肠灌入SCFA导致腹痛, Fukudo等[58]进一步研究证实IBS-D患者粪便中SCFAs的异常改变与IBS症状具有相关性, 推测SCFA可能通过激活某类酸受体诱发内脏高敏感. 另一研究证实丁酸能够上调脊髓中酸敏感离子通道(ASIC1A)的含量, 诱发脊髓神经可塑性改变并引发内脏痛[59]. 丁酸灌肠在不改变组织结构的条件下可导致内脏痛阈降低, 故被应用于建立IBS内脏高敏模型. 然而临床研究结果与动物实验相悖, Burger-van Paassen等[20]研究显示丁酸结肠给药能够减轻健康志愿者的内脏痛, SCFA相关制剂常被临床用于治疗IBS和IBD[60]. 据此, 考虑SCFA致内脏高敏可能是肠道自身的一种预警机制, 是机体预防炎症和器质性疾病发生的保护性生理反应[61].

## 4 结论

综上研究, 得出以下假说: (1)IBS患者肠道菌群失调引起肠道内SCFA的改变; (2)肠道菌群的紊乱导致异常的肠道菌群-SCFA-肠上皮细胞信号传导, 引起肠道低度炎症反应、动力异常和肠黏膜通透性增加; (3)SCFA对肠道起到保护和促修复作用, SCFA的异常改变与IBS症状存在关联. SCFA在调节肠动力、肠道免疫及肠黏膜通透性等方面发挥重要作用, 其机制有待更深入研究. SCFA在具体环境下具有不同作用, 如SCFA对肠道免疫起到双向调节作用. 下一步研究可着眼于SCFA与交感神经、肠神经系统、脑-肠轴的联系, 了解其在IBS发病的信号网络的作用. 针对IBS患者肠道菌群失调的治疗方法主要有益生素、抗生素治疗和菌群移植. 前者应用不当可能加剧菌群失调[62], 而后者方法尚不成熟、成功率低. SCFA对于肠道微环境、免疫方面的调节作用使其成为潜在的治疗靶点. 临床试验发现SCFA制剂的应用能够改善IBS症状, 如发现丁酸钠能缓解腹痛症状[45,63]. 但其作用机制较为复杂, 需要继续探索. 总之, 研究SCFA介导的菌群-宿主互动有利于对IBS病理生理机制的深入探讨, 为今后IBS的诊断和治疗开辟了新的思路.

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**同行评价**

作者对短链脂肪酸和肠道菌群的相互作用, 以及其与IBS发病机制进行了综述和总结. 总结较全面, 引用文献较新, 具有较强学术价值.


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