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专论与综述

丁酸梭菌及其代谢物丁酸对炎症性肠病影响的研究进展

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QIAN Yifan, ZHU Jianjun, DU Qinchao, ZHANG Runzan, ZHU Xiaobin, CHEN Hangping. Research advances in the effects of *Clostridium butyricum* and its metabolite butyrate on inflammatory bowel disease[J]. Microbiology China, 2025, 52(1): 114-126.

摘　要：炎症性肠病(inflammatory bowel diseases, IBD)发病机制复杂，缠绵难愈且易癌变，现有药物疗效未达预期且不良反应较多，亟须寻找新的治疗药物。而丁酸梭菌(*Clostridium butyricum*)及其代谢产物丁酸是近年来发现对肠黏膜屏障具有保护作用的一类益生菌及代谢物，但其具体作用机制有待归纳和总结。本文系统总结了 *C. butyricum* 和丁酸通过影响肠道屏障功能在 IBD 发病机制中作用的研究进展，以及其在炎症性肠病治疗中的潜在临床价值，以期为 IBD 发病机制的探究、治疗方式的创新提供新视角和思路。

关键词：丁酸梭菌；丁酸；炎症性肠病；肠道屏障

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Research advances in the effects of *Clostridium butyricum* and its metabolite butyrate on inflammatory bowel disease

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Abstract: Inflammatory bowel disease (IBD) is a complex and chronic inflammatory disease that is challenging to be cured and prone to carcinogenesis. Existing medications for IBD have limited efficacy and often come with adverse effects, which necessitates the development of new therapies. *Clostridium butyricum* and its metabolite, butyrate, have recently been identified as a probiotic and a metabolite, respectively, that offer protective benefits to the intestinal mucosal barrier. However, the specific mechanisms underlying their actions remain to be elucidated. Therefore, this article comprehensively reviews the research progress in the roles of *C. butyricum* and butyrate in the pathogenesis of IBD via influencing the intestinal barrier function, as well as their potential clinical values in the treatment of IBD. The findings will give novel insights into the research on the pathogenesis and innovation of the therapies of IBD.
Keywords: *Clostridium butyricum*; butyrate; inflammatory bowel disease; intestinal barrier

炎症性肠病(inflammatory bowel diseases, IBD)是一种慢性复杂的炎症性肠道病理状况，主要有溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD)这 2 个亚型[1]。UC 仅限于结肠，伴有浅表黏膜炎症，以连续的方式向近端结肠延伸，可致溃疡、严重出血和暴发性结肠炎。相反地，CD 可影响消化道的任何部分，病变呈多节段或跳跃性，不呈连续性，以透壁炎症为特征，可致纤维化狭窄、瘘管和脓肿等并发症[2]。流行病学研究表明，中国 IBD 的发病率呈逐年上升的趋势；预计到 2035 年，我国 IBD 患者将超过 200 万[3]。该类疾病迁延难愈，易反复且具有较高的癌变风险。目前，用于治疗 IBD 的临床药物及方法主要包括氨基水杨酸盐类、皮质类固醇、硫嘌呤类药物、免疫抑制剂和生物疗法，上述药物及措施的作用机制旨在减少肠黏膜炎症、缓解疾病进展及控制并发症等[4-5]，但无法实现治愈的目的，同时易产生耐药性、低反应性和不良反应性等[6]。因此，明确 IBD 具体发病机制，探索影响其发生发展进程中的关键因素，拓展治疗 IBD 的新思路、新方向和新靶点已成为相关领域的研究热点。

尽管 IBD 的具体发病机制尚不清楚，但肠道微生物群改变(微生态失调)、免疫反应失调、肠上皮屏障破坏、遗传易感性等因素被认为与该疾病的发生发展密切相关[7]。肠道屏障起着阻止有害物质进入肠壁并进入人体组织器官的作用[8]，主要包括机械、化学、免疫和生物屏障，而肠道屏障的破坏被认为是 IBD 最显著的特征之一。肠道微生物群作为一个复杂而动态的系统，其与宿主之间的相互作用有助于维持肠道上皮屏障和宿主免疫系统的正常功能[9]。研究表明，肠道微生态失衡可致黏膜反应失

调，从而导致遗传易感人群发生 IBD[10]。因此，通过补充某些特定菌株、药物干预或调整饮食结构来针对性调节肠道微生物群的组成和功能，以维持体内平衡免疫应答，目前被认为是治疗 IBD 的一种新兴治疗方法。丁酸梭菌(*Clostridium butyricum*)作为一种益生菌，于1933 年由 Chikaji Miyairi 博士首次从健康人群粪便中分离得到。其作为一类革兰氏阳性厌氧杆菌[11-12]，可消耗肠道内膳食纤维并产生短链脂肪酸(short chain fatty acid, SCFA)，对宿主发挥重要作用，如调节肠道免疫稳态[13]、改善胃肠道屏障功能[14-15]和减轻炎症[16-17]等。已有研究报道 *C. butyricum* 菌株对多种人类疾病如肠道获得性感染、肠道损伤、肠易激综合征、炎症性肠病、神经退行性疾病、代谢疾病和结直肠癌等具有潜在保护或改善作用[18]。本综述旨在总结 *C. butyricum* 改善 IBD 生物肠道屏障功能的机制，主要包括调节免疫反应、抑制氧化应激、改善肠道菌群组成等，以期为临床 IBD 治疗提供研究参考。

1 丁酸梭菌与肠黏膜屏障的作用关系

1.1 丁酸梭菌与肠黏膜机械屏障之间的作用

肠黏膜机械屏障是肠道内肠上皮细胞和它们之间的连接结构，为肠道提供了选择性通透和屏障功能的基础[19]。其中肠上皮细胞主要包括负责吸收功能的吸收细胞、分泌黏液的杯状细胞和少量内分泌细胞；此外，小肠中还具有潘氏细胞和未分化细胞，上述细胞处于不断地更新中，以保证对营养物质、电解质和水的吸收功能；同时维持对肠腔内各种毒素和抗原的抵御作用(图 1)[20]。肠上皮细胞通过形成复杂的蛋白质-蛋白质网络连接相邻细胞及细胞间隙，从而形成密集的屏障结构，限制细菌、蛋白质、脂质和微生物衍生物等物质的通过[21]。这一蛋白质网络主要形成包括紧密连接、桥粒和黏附连接在内的 3 种黏附复合物；以上复合物主要由跨膜蛋白组成，于胞外与邻近细胞相互作用，并与细胞内附着于细胞骨架的衔接蛋白相互作用[22]。研究发现紧密连接是由顶端多蛋白复合物组成的动态结构，可降低细胞旁通路的通透性[23-24]。紧密连接主要包括闭合蛋白(claudin)、咬合蛋白(occludin)、钙黏蛋白(cadherin)、带状闭合蛋白(zonula occludens, ZO)和连接黏附分子(junctional adhesion molecule, JAM)，对于维持屏障完整性至关重要。此外，桥粒是与角蛋白丝相连的局部致密斑块，具有强黏附作用，为肠黏膜屏障完整性提供机械支撑[22]。在肠黏膜机械屏障中，肠上皮细胞可通过分泌高度糖基化的聚合黏蛋白(mucin, MUC)、抗菌肽等生物活性物质，激活相应化学屏障和免疫屏障，从而提供了对肠道内各种毒素、病原体和其他小分子的清除作用，但当肠上皮屏障完整性被破坏，各种毒素、病原体和其他小分子损害肠上皮细胞，致上述生物活性物质分泌不足，进一步加重疾病病变程度。结肠和小肠部位的黏蛋白 2 (MUC2)可形成内环境中稳定的肠黏液层[25]。

研究表明，*C. butyricum* 能够显著提高紧密连接蛋白(如 claudin-1、claudin-2、occludin 和 ZO-1)的表达水平，减少肠道屏障的通透性，改善其机械屏障的完整性，从而维护肠道内环境稳态[26]。MUC2 是一种分泌型胃肠道黏蛋白，在维持黏膜屏障完整性和防御病原体侵袭方面起着关键作用。研究发现，MUC2 敲除小鼠易发展为自发性结肠炎，并且患结直肠癌的风险显著增加[27-28]，表明机械屏障对于免疫稳态和整体健康的重要性。*C. butyricum* 已被证

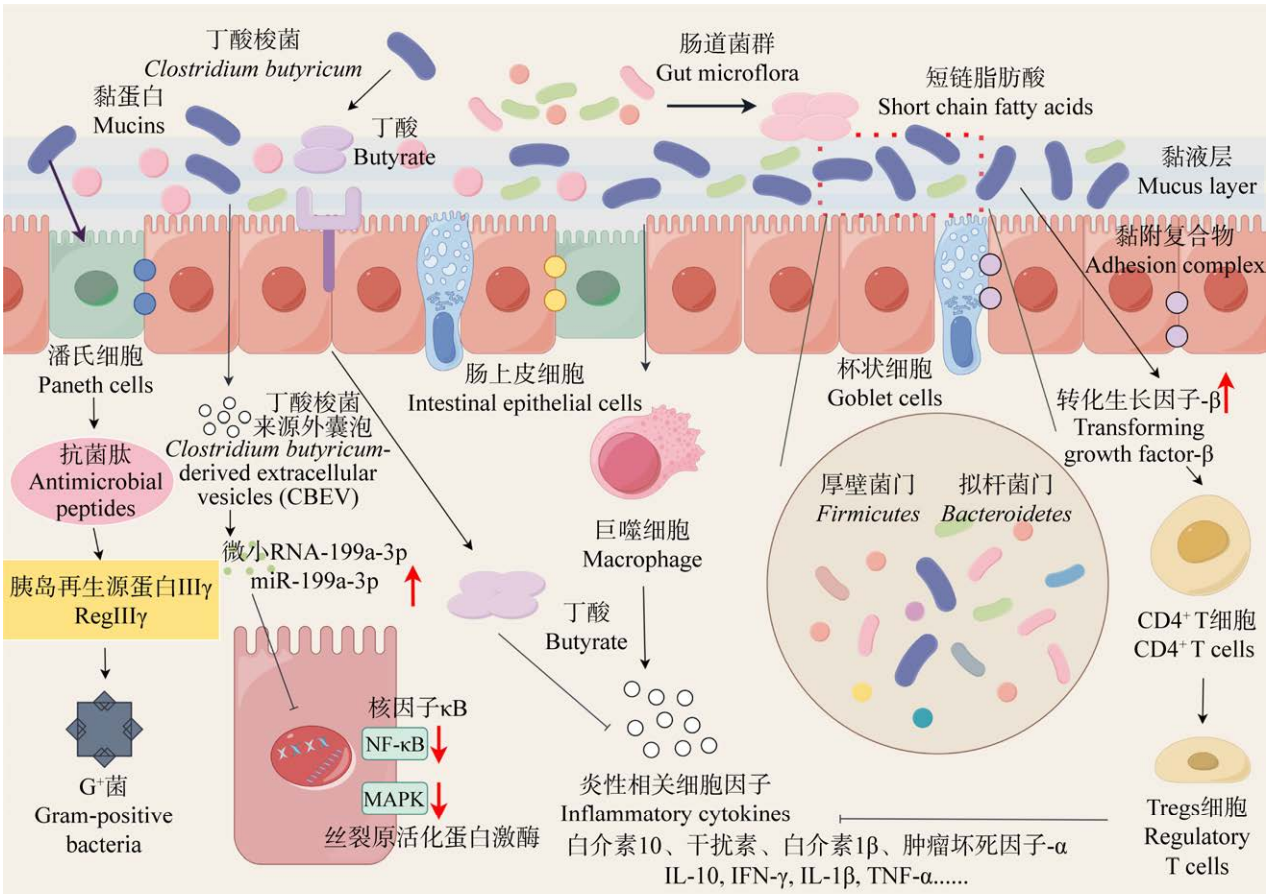

图 1　丁酸梭菌及其代谢物丁酸与肠道屏障关系图　病理损伤因子损害杯状细胞，导致黏液分泌减少和黏液层变薄。丁酸梭菌通过增加紧密蛋白和/或黏蛋白的表达水平，增加黏液层的厚度，从而改善肠道屏障的完整性。其定殖后刺激潘氏细胞分泌抗菌肽，直接杀灭革兰氏阳性菌，以维持肠道的稳态。丁酸梭菌促使幼稚 $CD4^+$ T 细胞分化为 Treg 谱系细胞，并与巨噬细胞互相作用，以调节免疫反应。丁酸梭菌来源的细胞外囊泡(CBEV)通过上调紧密连接蛋白的表达，减少炎症损伤，从而改善肠道屏障的完整性。丁酸梭菌代谢产物丁酸上调紧密连接蛋白的表达，增加黏液层的厚度，并调节氧化应激水平和免疫平衡，从而缓解病症。

Figure 1　Relationship between *Clostridium butyricum* and its metabolite butyrate and intestinal mucosal barrier. Pathological damage factors impair goblet cells, leading to reduced mucus secretion and thinning of the mucus layer. *Clostridium butyricum* enhances intestinal barrier integrity by increasing the expression levels of tight junction proteins and/or mucins, thereby thickening the mucus layer. Following colonization, *Clostridium butyricum* stimulates Paneth cells to secrete antimicrobial peptides, directly eliminating gram-positive bacteria to maintain intestinal homeostasis. Moreover, *Clostridium butyricum* promotes the differentiation of immature $CD4^+$ T cells into Treg cells and interacts with macrophages to regulate immune responses. *Clostridium butyricum*-derived extracellular vesicles (CBEVs) upregulate the expression of tight junction proteins, reduce inflammatory damage, and improve intestinal barrier integrity. The metabolic product of *Clostridium butyricum*, butyrate, upregulates the expression of tight junction proteins, increases the thickness of the mucus layer, and modulates oxidative stress and immune balance, thereby alleviating the symptoms.

明具有保护黏膜层的生理特性。一项针对肠道补充益生菌的小鼠研究试验结果表明，给予 *C. butyricum* Sx-01 菌株可显著提高结肠黏膜厚度，同时明显增加回肠绒毛长度[29]，而给予菌株 CBM 588 则可增加黏蛋白的产生(以 MUC2 表达的增加来衡量)，并显著减少结肠中的上皮损伤，如浅表上皮坏死和中性粒细胞浸润[30]。UC 伴有黏蛋白屏障功能障碍，同时伴有黏液层缺陷、杯状细胞耗竭及 MUC2 硫酸盐含量减少[31-32]。葡聚糖硫酸钠(dextran sulfate sodium, DSS)诱导 UC 小鼠模型中，发现其黏液层较对照组显著变薄，屏障渗透性增加，隐窝破坏程度上升伴有中性粒细胞相关标志物髓过氧化物酶(myeloperoxidase, MPO)表达增加，而给予 *C. butyricum* 后，MUC1、MUC2 和 MUC3 表达显著上调，表明受损黏液层得到修复[33]。多项临床研究使用 *C. butyricum* 联合传统药物美沙拉嗪治疗 UC，试验结果显示 *C. butyricum* 联合给药组患者治疗后疾病活动指数(包括腹泻、便血、黏膜表现与医师评估)、临床活动指数 Mayo 评分(包括排便次数、便血、内镜发现与医师总体评分)显著下降，内镜下病变严重度及病理评分明显降低并伴随血浆 D-乳酸、血清内毒素和 C 反应蛋白等检测指标水平下降，提示 *C. butyricum* 联合美沙拉嗪可明显改善临床症状，抵抗对肠黏膜屏障的损伤，抑制肠道炎症，从而改善 UC 患者临床症状[34-35]。进一步研究发现，*C. butyricum* 来源的细胞外囊泡(*C. butyricum*-derived extracellular vesicles, CBEV)作用与 UC 病变程度呈负相关，其可通过增加 miR-199a-3p 表达进而抑制促炎性 MAPK 和 NF-κB 信号通路，从而显著上调包括 occludin 和 claudin-1 等紧密连接蛋白的表达，并减少结肠组织中性粒细胞浸润，降低肠道黏膜屏障的通透性，改善肠道屏障完整性并抑制炎症反应[36]。因此，*C. butyricum* 能全面保护 IBD 肠黏膜的机械屏障，维护其结构和功能的完整性，从而减轻致病因子对肠道的损伤。

1.2 丁酸梭菌与肠黏膜化学屏障之间的作用

肠黏膜化学屏障与机械屏障在功能上相互协调，前者主要由黏液层组成，而黏液层主要由消化液、各种消化酶、溶菌酶、抗菌肽、胆汁酸和黏蛋白等组成，通过黏液层和黏蛋白，将肠腔内的微生物与肠上皮细胞分隔开来，有效阻止毒素和病原菌进入肠道，从而起到防止肠道菌群失调的作用(图 1)[37-39]。研究发现，肠上皮细胞(intestinal epithelial cell, IEC)表面的黏液层主要由杯状细胞产生的糖基化 MUC2 组成。这一黏液层形成双层结构，第一层黏液约 50 μm，几乎没有细菌存在，起到将微生物群远离上皮屏障、限制炎症的作用；第二层黏液层中存在微生物群并参与其降解，这一过程每天都在不断变化[40]。MUC2 覆盖肠上皮细胞表面，是肠道黏液层形成的主要成分：它不仅可以改善食物吸收，为共生肠道细菌提供附着位点，还能抑制病原体与 IEC 的结合[41]。同时，构成肠道化学屏障的各种物质具有一定的功能。溶菌酶可以水解细菌细胞壁中的肽聚糖发挥抗菌作用[42]，消化酶可以将食物中的大分子物质分解成小分子物质以便于消化和吸收[43]，胆汁酸可影响胃肠动力、感觉、分泌、功能调节、肠屏障通透性和炎症反应[44]，而抗菌肽是潘氏细胞分泌的肽，具有防腐、抗炎、增强免疫和组织修复作用[45]。因此，肠黏液层在保护肠道免受机械、化学和生物因素影响方面发挥着主要作用，并有助于维持肠道稳态[41]。

多种肠道疾病中均发现杯状细胞功能下降、肠黏液层的组成和厚度发生改变。UC 患者的黏液层被破坏，呈高度渗透性，厚度明显减少，同时 MUC2 的产生和表达也下降，这导致继发炎

症反应，进一步加快疾病发生发展进程[46-47]。同时，敲除 MUC2 基因小鼠更易发生结肠发炎，并与实验性结肠炎的发生和持续病程相关，由此可以说明 MUC2 在肠道化学屏障中起着不可或缺的作用[27]。在给予 *C. butyricum* 作用后，UC 小鼠结肠隐窝杯状细胞数量显著提高，肠道中的 MUC2 蛋白分泌率显著提高，导致黏液层厚度显著上升，进而降低结肠细胞凋亡率[33,48]。以上结果表明 *C. butyricum* 能够通过增强上皮紧密连接和黏膜屏障完整性来避免 DSS 作用所致的肠道损伤。相关研究报道称，潘氏细胞是 IBD 等肠道炎症的起源部位，在疾病发生发展进程中其结构受损、数量减少。潘氏细胞通过释放抗菌肽、溶菌酶和其他生物活性肽来调节炎症反应[49-51]。潘氏细胞所分泌的抗菌肽被认为是黏液层中最重要的抗菌物质之一[52]，其经诱导释放的抗菌肽胰岛再生源性 3γ (RegIIIγ)可与细胞壁肽聚糖结合，起到直接杀灭革兰氏阳性菌的作用。研究表明 RegIIIγ 的缺失可致小鼠自发性结肠炎的产生[53-55]，提示 UC 可能与肠道中潘氏细胞的数量与功能存在关联。人体中唯一一种组织蛋白酶抑制剂(cathelicidin)抗菌肽 LL-37 在 IBD 患者炎症黏膜中的表达显著上调，其可增强机体抗菌和抗脂多糖活性，保护肠道组织免受细菌感染和过度炎症反应[56]。尽管目前尚无相关研究表明 *C. butyricum* 直接刺激肠道内潘氏细胞分泌抗菌肽及促进其生物活性，但已有研究发现牡丹皮中的丹皮酚可以修复受损肠道屏障并缓解病症，这一作用与 *C. butyricum* 在相应部位定殖增强屏障完整性并激活抗菌肽有关[57]。因此，肠黏膜化学屏障的结构与功能完整性与 *C. butyricum* 之间的紧密联系值得深入研究。

1.3 丁酸梭菌与肠黏膜免疫屏障之间的作用

肠道免疫屏障在肠道抵御各种致病因子侵袭过程中起到关键作用。免疫屏障主要由肠上皮、肠道相关淋巴组织(gut-associated lymphatic tissue, GALT)和固有层中的不同免疫细胞亚群组成。肠上皮层不仅可作为肠道的机械屏障，也是最重要的先天免疫屏障之一，它通过产生免疫相关分子，参与免疫细胞的相互作用，对维持肠道免疫功能具有重要影响。在肠道上皮黏膜中，固有层包括潘氏斑(peyer's patches, PP)、免疫细胞、抗菌肽及免疫球蛋白 A (immunoglobulin A, IgA)，共同参与保护宿主免受外来病原体的入侵，维持肠道环境的稳定(图 1)[58-59]。当肠黏膜屏障受损时，革兰氏阴性菌可能会侵袭肠黏膜，但肠道中广泛存在的 IgA 可以通过与这些菌相互作用，有效抵抗其侵袭和破坏，从而发挥保护肠黏膜屏障的作用[60]。PP 作为免疫应答的诱导和活化部位，在肠道免疫中起到重要作用。其数量和形态可在一定程度上反映黏膜免疫功能的状态。肠黏膜中成熟的树突状细胞具有促 B 细胞成熟分化为浆细胞的能力，而浆细胞可分泌 IgA，并能有效激活初始 T 细胞分化为功能群，如 Th1、Th2、Th9、Th17 或 Treg 细胞[61]，进而发挥相应促炎或抗炎作用。先天淋巴细胞(innate lymphoid cell, ILC)作为免疫应答的调节与效应位点[62]，可产生 IFN-γ、IL-5、IL-13、IL-17 和 IL-22 等[63]，当肠道屏障被破坏，ILC 就可能被异常激活进而导致疾病的发生[64]。

已有研究表明，IBD 患者肠道黏膜中 IL-17A$^+$ CD161$^+$效应 T 细胞、IL-17A$^+$调节性 T 细胞(regulatory T cell, Treg)、HLA-DR$^+$ CD56$^+$粒细胞增加，III型 ILC 减少[65]。因此，以抗炎细胞因子的减少和促炎细胞因子的增加为代表的免疫屏障受损与 IBD 病程进展密切相关。研究表明，*C. butyricum* 能够增加肠系膜淋巴结中的 Tregs 丰度，从而提高肠道免疫耐受度，

并减轻免疫损伤[66-67]。同时 *C. butyricum* 通过增加转化生长因子-β 的产生，促使幼稚 $CD4^+$ T 细胞分化为 Treg 谱系细胞，从而调节免疫反应[68]。化学诱导 UC 小鼠腺体排列不规则，隐窝结构紊乱，可见大量中性粒细胞、淋巴细胞、嗜酸性粒细胞浸润，而经规范给予 *C. butyricum* CBM588 菌株可激活结肠树突状细胞中 Toll 样受体 2 (Toll-like receptor 2, TLR2)依赖的转化生长因子-β 的表达，从而有效缓解 UC 小鼠结肠组织中的黏膜缺失、杯状细胞减少及炎性浸润[69]。在 UC 中 *C. butyricum* 可与肠 $F4/80^+$ $CD11b^+$巨噬细胞相互作用促进抗炎因子 IL-10 的表达，从而调节肠道免疫功能，降低炎症反应[70]。同时，研究显示 *C. butyricum* 可与相关炎症信号通路相互作用减轻炎性病理损伤，如 *C. butyricum* 能够抑制 TLR2 信号通路和 IL-17 分泌，对 DSS 诱导的肠道炎症发挥保护作用[71]。NF-κB 信号通路的激活诱导 TNF-α 和 IL-1β 的分泌并加剧炎症，但 *C. butyricum* 可通过抑制 NF-κB 信号通路降低促炎细胞因子(IFN-γ、IL-1β、IL-8、TNF-α)水平，从而降低肠上皮细胞的炎症反应，有效逆转 DSS 作用肠道结构的损伤，如杯状细胞、腺体和隐窝大面积消失[72-73]。此外，CBEV 通过抑制 MAPK-NF-κB 信号通路介导的炎症反应，降低炎症因子水平，恢复细胞因子稳态，降低 UC 病损严重程度[34]。因此，*C. butyricum* 可从抑制炎症相关细胞因子生成、调节细胞因子平衡、介导相关信号通路等多方面、多靶点来维持肠黏膜免疫屏障，减轻 IBD 肠道炎症-免疫反应，进而缓解相关病理损伤。

1.4 丁酸梭菌与肠黏膜生物屏障之间的作用

肠道微生物屏障主要由肠道中的微生物(包括细菌、真菌和病毒)和微生物代谢产物组成。正常生理状态下，肠道内环境中的益生菌和致病菌处于动态平衡状态，但这一平衡易受到外源和内源因素的影响。肠道菌群主要由厚壁菌门(*Firmicutes*)和拟杆菌门(*Bacteroidetes*)组成(图 1)，它们主要定殖于肠黏膜表面，并在肠道营养物质代谢、通透性和免疫等方面发挥重要作用，对维持肠道健康至关重要[74]。肠道菌群黏附在黏膜表面，与致病菌在肠道内竞争黏附和定殖，对肠道免疫反应具有抗菌和调节作用；同时可分泌乳酸和短链脂肪酸等次生代谢物，降低机体肠道 pH 值和氧化还原电位，抑制致病菌的生长，并分泌细菌素，抑制外来细菌的定殖和生长；并且可作为优势菌群与致病菌争夺营养，抑制致病菌的生长，形成微生物屏障，抵御机会致病菌的定殖，维持肠道内稳态。*C. butyricum* 作为一种益生菌，其生长代谢基质主要以碳水化合物、蛋白质和脂肪为主。通过发酵代谢，*C. butyricum* 产生的 SCFAs 是结肠细胞的主要能量来源，可促进其正常生理活动，并维护肠道菌群的数量与种类多样性[75]。因此，当 IBD 致使 *C. butyricum* 菌群丰度和数量下降，无法为其他肠道正常菌群提供能量，会导致内源性的菌群失衡，这与已有研究得出的 IBD 严重程度与 *C. butyricum* 菌群丰度和数量呈负相关的结论一致[76]。与此同时，实验研究发现肠道细菌产生的毒素脂多糖可诱导 HEK-TLR4 细胞以 TLR4 依赖途径产生 NF-κB 和 IL-8，从而导致 IBD 的发生[77]。而通过补充 *C. butyricum* 抑制 TLR4/NF-κB/MAPK 信号通路的激活，调节炎症相关因子，改善 UC 症状及结肠形态，同时增加短链脂肪酸含量，提高机体抗炎作用[72]。表皮生长因子受体(epidermal growth factor receptor, EGFR)激活可维持肠道屏障的完整性，促进细胞增殖，调节免疫平衡及肠道菌群，已有研究表明实验性 UC

小鼠饲喂 *C. butyricum* 对结肠上皮细胞系呈浓度依赖性和时间依赖性地激活 EGFR，从而保护紧密连接，增加小鼠杯状细胞数量和 MUC2 的产生，减轻 UC 病理损伤[48]。此外，口服 *C. butyricum* 后评估肠道细菌群落结构发现，*C. butyricum* 组显著增加了厚壁菌门(*Firmicutes*)的丰度及数量，但下调了拟杆菌门(*Bacteroidetes*)的丰度，这表明 *C. butyricum* 的定殖与肠道内环境稳态的重新建立紧密相关，进而对肠道健康产生积极影响[78]；*C. butyricum* 还可通过促进自身在相应部位定殖来作为丹皮酚治疗 UC 的“驱动菌”[57]。因此，作为一种对 IBD 有益的益生菌，*C. butyricum* 可通过调节炎性因子、稳定供能、维护肠道微生物种群平衡等多种机制，从不同的黏膜保护角度保护肠黏膜屏障结构和功能的完整性，有助于减轻 IBD 引起的肠道损伤。

2 丁酸梭菌代谢产物丁酸与肠道屏障之间的关系

在探讨 *C. butyricum* 与肠道屏障的关系之后，进一步深入分析其主要代谢产物丁酸的作用。丁酸不仅通过直接作用于肠道屏障的机械、化学、生物和免疫层面来维持肠道稳态，还在调节肠道微生物群和免疫反应中扮演着关键角色。因此，丁酸的作用是对 *C. butyricum* 影响肠道屏障机制的补充和扩展，两者共同构成了维持肠道内环境稳态的重要因素(图 1)。SCFA 是碳链少于 6 个碳组成的有机酸，以乙酸、丙酸和丁酸为主要代表。丁酸盐可通过上调编码 claudin-1、occludin 和 ZO-1 蛋白的基因表达来增加紧密连接，从而提高肠道黏膜屏障的完整性[79]。此外，丁酸也可通过增加 MUC2 的表达来增加肠上皮黏液层厚度[80]。在大鼠研究中，盲肠和粪便中丁酸浓度与黏液层厚度呈正相关[81]。

肠道的动态免疫平衡主要由肠道微生物区系和/或其衍生的 SCFA 调节。丁酸盐可调节 IBD 中先天性和获得性免疫细胞的生成、成熟、运输和功能，表明其在肠道炎症中的调节作用[82]。中性粒细胞浸润是肠道验证部位先天免疫反应的第一道防线，SCFA 与中性粒细胞相互作用，参与其募集并调节其趋化性。研究表明，丁酸和/或丙酸通过增加细胞因子诱导的中性粒细胞趋化剂 2αβ 的分泌，从而增强中性粒细胞向炎症细胞的迁移，从而促进抗炎反应并改善病理炎性损伤[83]。与此同时，丁酸能有效调节树突状细胞的功能和发育，降低树突状细胞对 T 细胞的刺激能力，减少促炎因子(IFN-γ, IL-12)的产生[84]。IL-10 在肠道炎症期间通过限制炎症反应和减少组织损伤维持免疫系统稳态；丁酸可上调 IBD 患者 T 细胞中 IL-10 水平，这表明丁酸在调节免疫反应中起着重要作用，有助于维持免疫系统的稳态[75]。同时，体内和体外 IBD 模型中，丁酸也表现出抗炎潜力，表明丁酸可用于预防炎症损伤并保护肠上皮屏障[79]。通过补充外源性丁酸，DSS 诱导的 UC 小鼠结肠生物样本中炎症相关因子(IL-1β、IL-6、TNF-α)含量水平显著下降；而 UC 小鼠结肠中产丁酸菌布氏丁酸梭菌(*Butyricicoccus*)、瘤胃球菌(*Ruminococcus*)等丰度、肠道菌群代谢物短链脂肪酸(丁酸和丙酸)较对照组小鼠明显降低，以上结果提示丁酸在 UC 疾病进程中起着重要作用[85]。这些研究结果表明，丁酸可通过减少促炎因子和增强抗炎因子来调节炎症状况和免疫。

研究发现，氧化应激参与 IBD 的发生[9]。在生理条件下，氧代谢产生活性氧(reactive oxygen species, ROS)，机体可承受一定水平的活性氧，维持肠道正常的内稳态。IBD 发病时，ROS

可由炎症、组织病理学和组织损伤产生，其过量将增加肠黏膜通透性，加速炎症反应。氧化应激具有多种危害，如脂质过氧化、DNA 损伤、蛋白质羰基化、上皮细胞损伤、肠屏障功能障碍等。因此，氧化应激可损伤肠道黏膜的机械屏障功能，显著增强肠道通透性。丁酸参与氧化应激的调节，降低丙二醛(malondialdehyde, MDA)和 ROS 水平[85]；还可通过降低 H_2O_2 诱导 DNA 氧化损伤程度，恢复抗氧化剂谷胱甘肽的水平[86]，从而降低机体氧化应激水平，进而减轻氧化应激对肠黏膜的损伤。由此可见，*C. butyricum* 的代谢产物丁酸可多角度影响肠黏膜屏障的结构和功能，但其调节机制有待于进一步研究探讨。

3 结论与展望

肠道共生菌 *C. butyricum* 与 IBD 关系密切，研究表明 *C. butyricum* 及其代谢产物丁酸通过上调紧密蛋白、黏蛋白的表达、上调抗炎因子并抑制促炎因子的产生、调节肠道菌群组成、抑制氧化应激反应等多种途径发挥有益作用。因此，*C. butyricum* 被认为是一种对肠道黏液层和肠黏膜屏障结构功能有益的且在改善宿主代谢功能和免疫应答方面具有重要价值的益生菌。

C. butyricum 的应用可以为 IBD 患者带来希望。然而，就其应用层面而言仍有许多问题亟须解决。例如，研究主要集中在小鼠动物模型上，具体应用于临床的研究较少，人体试验的证据更加有限。同时缺乏标准方案，有效性研究的实验设置和质量存在差异。因此，为了正确评价 *C. butyricum* 在 IBD 中的疗效，有必要进行更严格的随机、双盲、对照临床试验来进一步深入研究其保护机制。未来，肠道微生物学、胃肠病学流行病学与肠道菌群、代谢物、分子信号和基因工程快速分析的有机结合也有望为 IBD 治疗提供新的见解和方向。*C. butyricum* 及其代谢产物作为益生菌的重要组成部分，从整体、器官、组织、细胞、分子和基因水平的进一步研究和开发将为开发新型的肠道微生物治疗方法提供重要的理论和实践基础。

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