益生菌治疗炎症性肠病的研究进展

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摘要：炎症性肠病（IBD）是一种慢性肠道炎症疾病，发病率逐年上升，但病因尚不明确，缺少针对性好、安全性高的治疗药物。近年来，益生菌作为一种潜在的治疗策略，在IBD的预防和治疗中展现出巨大潜力。文章详细阐述了益生菌治疗IBD的机制，汇总了用于治疗IBD的常见益生菌属，并对益生菌的应用做了展望，以期为益生菌治疗IBD的研究奠定基础。

关键词：益生菌；炎症性肠病；治疗机制；研究进展
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Research Progress of Probiotics in the Treatment of Inflammatory Bowel Disease

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ABSTRACT: Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory disease with an increasing incidence rate year by year, but its etiology is still unclear. And there is a lack of well-targeted and safe therapeutic drugs. In recent years, probiotics have shown large potential as a potential treatment strategy for the prevention and treatment of IBD. This paper elaborates on the mechanism of probiotics in the treatment of IBD, summarizes common probiotic species used in the treatment of IBD, and looks forward to the application of probiotics, aiming to lay a foundation for the research on probiotics in the treatment of IBD.

Key Words: probiotics; inflammatory bowel disease; therapeutic mechanism; research progress

炎症性肠病（inflammatory bowel disease，IBD）累及回肠、直肠、结肠，有肠道和大脑相互作用的特征[1]，临床表现为黏液血便、腹痛等[2]。IBD基于临床参数可分为2个亚型：溃疡性结肠炎（ulcerative colitis，UC）和克罗恩病（Crohn disease，CD）。UC病变主要集中在结肠，以黏膜炎症为特征，具有连续性。而CD的病变范围涉及整个胃肠道，以透壁炎症为特征，具有不连续性[3]。近几十年，亚洲人IBD的发病率和患病率呈增加趋势[4]。IBD的发病机制尚不明确，业界倾向于认为其是由环境、遗传等因素引发宿主异常免疫反应及微生物群之间的相互作用所驱动。IBD中存在的肠道代谢紊乱现象，与已知的肠道菌群生态失调一致[5]。

传统的IBD治疗药物有5-氨基水杨酸、免疫抑制剂等，但一些患者服用后会出现严重不良反应[6]，且具有吸收少、生物利用度低等问题[7]。益生菌是活的微生物菌株，适量服用有益处[8]。研究[9]显示，益生菌引发的不良反应较少，不会造成吸收减少等问题。并且部分益生菌可分泌抗炎细胞因子[10]，有望成为治疗包括IBD在内的慢性炎症性疾病的有效手段。目前应用较多的益生菌是细菌（如嗜酸乳杆

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菌、双歧杆菌等）[11]。

本文综述了益生菌治疗 IBD 的机制及常用的益生菌属，期望为 IBD 的临床治疗提供参考。

1　益生菌治疗 IBD 的机制

1.1　调节肠道菌群

菌群失调是 IBD 发病的关键因素 [12]。研究 [13—14] 显示，IBD 可使致病菌［如大肠埃希菌（*Escherichia coli*，*E. coli*）］增加，并使有益菌（如乳酸杆菌）大幅减少。此外，微生物群破坏导致的宿主 - 微生物相互作用不匹配，会促进 IBD 发展 [15]。

益生菌可恢复肠道生态失调、重建微生物组成 [16]，还能塑造肠道微生物群、控制多种肠道疾病、促进整体健康 [17]。粪菌移植（fecal microbiota transplant，FMT）可能恢复 UC 患者的菌群失衡。一项 Meta 分析 [18] 显示，包含 8 种不同菌株的强效生物活性菌剂，即混合益生菌 VSL#3，在 UC 的临床缓解和临床反应中均取得良好效果，比 FMT 安全性更好。乳酸菌是常用的益生菌，可调节肠道微生物群、维持宿主健康，被用于治疗包括 IBD 在内的多种疾病 [19]。YAN 等 [20] 报道将 *E. coli* Nissle 1917（EcN）改造，用于在结肠炎大鼠的肠腔持续合成（*R*）-3- 羟基丁酸乙酯［（*R*）-3-hydroxybutyrate，3HB］。3HB 促进了益生菌（尤其是阿克曼菌）的生长，使微生物组占比从 2% 增至 31% 以上。GU 等 [21] 研究显示，鼠李糖乳杆菌 GG 通过调节 5- 羟色胺受体 4（5-hydroxytryptamine receptor 4，5-HT4R）和肠道微生物而促进肠道黏蛋白产生。在 Toll 样受体（Toll-like receptors，TLR）1 缺失的炎症小鼠中，罗伊乳杆菌可通过抑制有害菌的生长和改善四硫酸盐的代谢而改善肠道代谢功能 [22]。梭状芽孢杆菌丰度在健康者和 IBD 患者间存在差异。普氏栖粪杆菌可改善肠道菌群失调，缓解 CD 患者症状 [23]。研究 [24—25] 显示，益生菌除可缓解肠道菌群失调以外，还可减少肠道细菌脂多糖（lipopolysaccharide，LPS）的产生。也有研究 [26] 讨论了益生菌对肠道菌群和人体免疫力的影响，强调通过益生菌调节肠道菌群可增强人体免疫力。

1.2　调节肠道免疫系统，减少炎症反应

肠道稳态需要免疫系统和微生物群的共同维持。免疫系统能确保有益微生物群的组成、控制特定菌生长、增强上皮屏障功能，并对肠道屏障相关的致病菌或分子做出反应 [27—28]。免疫系统功能障碍通常会导致疾病发生，如 TLR 介导的先天免疫功能障碍可能是 IBD 的重要发病机制。多数单基因 IBD 患者均表现出潜在的原发性免疫缺陷，说明免疫系统失调在极早发性 IBD 中的重要性 [29]。益生菌的免疫调节作用为 IBD 的治疗提供了新的临床策略 [30]。GONCIARZ 等 [31] 研究显示，Janus 酪氨酸激酶 / 信号转导和转录激活剂（Janus tyrosine kinase/signal transducer and activator of transcription，JAK/STAT）在调节免疫功能中发挥关键作用，其功能障碍与自身免疫疾病和炎症疾病相关，可作为治疗 IBD 的新靶点。且益生菌可通过 JAK/STAT 信号传导调节免疫功能。有研究 [32] 通过随机、双盲、对照试验探究了含 6 种不同的乳杆菌和双歧杆菌、菌浓度为 300 亿 CFU 的多菌株益生菌（MCP® BCMC® 菌株）的作用，结果显示该类菌株具有稳定黏膜免疫的功能，可保护患者免受肠道通透性增加的影响。

益生菌的抗炎作用反映了宿主与微生物群间的免疫耐受性。$CD4^+$ T 细胞是 IBD 等免疫炎症性疾病的关键靶点。JIA 等 [33] 通过酶联免疫法研究致病菌和益生菌如何影响 2 种 $CD4^+$ T 细胞亚型［即辅助性 T 细胞 17（helper T cell 17，Th17）和调节性 T 细胞（regulatory T cell，Treg）］的平衡，以缓解炎症。结果显示，益生菌可通过不同的 TLR 直接调节 Th17 与 Tregs 之间的平衡。肠道平衡需要通过维持潜在的促炎细胞［分泌干扰素（interferon-g，IFN-g）的辅助性 T 细胞（helper T cell，Th）、分泌白细胞介素 -17（interleukin-17，IL-17）的 Th17 细胞］和抗炎 $Foxp3^+$ 受体 T 细胞之间的平衡而达成。经益生菌治疗后，肠道菌群失调的情况可以得到缓解，炎症标志物及不必要的免疫系统激活将会减少 [34]。XU 等 [35] 制备了以 EcN 衍生的膜（EcN-derived membrane，EM）为表面，以可生物降解的二硒化物桥接的介孔二氧化硅纳米粒（diselenide-bridged mesoporous silica nanoparticles，SeM）为核心的益生菌纳米药物 SeM@EM，在葡聚

糖硫酸钠（dextran sulfate sodium，DSS）诱导的小鼠肠炎模型中，该制品可牢固黏附在黏膜层，恢复肠道氧化还原平衡并调节免疫稳态。此外，EM 和 SeM 能分别通过增加细菌多样性和将微生物组特征转变为抗原表型，协同地将肠道微生物组改变为有利状态。研究[36]显示，益生菌植物乳杆菌 HNU082（*Lactobacillus plantarum* HNU082，Lp082）可通过优化生物屏障、免疫屏障等，改善 UC 患者的肠道黏膜屏障，缓解炎症。双歧杆菌及其制剂可作用于炎症通路，从而调节免疫系统，发挥抗炎作用[37]。

益生菌可促进人工酶的靶向性和滞留时间，以持续清除升高的活性氧（reactive oxygen species，ROS），减少炎症因子及人工酶引起的炎症，重塑肠道屏障功能并恢复肠道微生物群。采用人工酶修饰的益生菌可避免不良反应，治疗效果已在动物模型中得到证实[38—39]。BIAGIOLI 等[40]研究显示，由 4 种益生菌（嗜热链球菌、干酪乳杆菌、短双歧杆菌、动物双歧杆菌乳亚种）与 1 种革兰阳性菌（枯草芽孢杆菌）组成的复合益生菌可缓解 2,4,6- 三硝基苯磺酸（2,4,6-trinitrobenzenesulfonic acid，TNBS）或 DSS 诱导的小鼠 IBD，并可减少促炎因子的表达、增加 IL-10 mRNA 的表达和 Treg 的数量。研究[41]显示，将益生菌装载在酵母膜内，膜上嵌入的 β- 葡聚糖可促进微皱褶细胞的吞噬作用，激发黏膜免疫并调节肠道菌群，维持肠道稳态。

表 1 列出了几种益生菌的相关免疫及抗炎作用[42—51]。

1.3 降低肠道通透性，增强肠道屏障功能

肠道是人体最大的免疫器官[52]。肠道屏障（图 1）受损会导致微生态系统失衡（微生物多样性和丰度降低）[53]。研究[54]显示，经双歧杆菌处理可增加 LPS 刺激的人结直肠腺癌细胞（Caco-2 细胞）的跨上皮电阻值，降低其细胞旁路通透性。益生菌通过对 TLR2 的刺激来调节 TJ 蛋白的表达和定位，通过促进上皮中 TJ 蛋白的上调和重新定位来恢复肠道屏障[55]。此外，益生菌 VSL#3 可通过降低 IBD 小鼠的氧化应激和肠道通透性来缓解 IBD[56]。

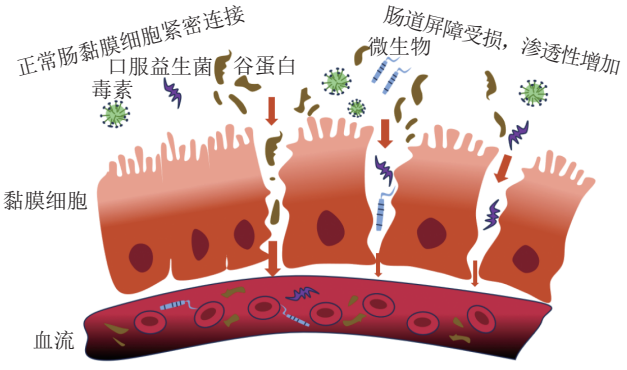


图 1 肠道屏障示意图

Fig.1 Schematic Diagram of Intestinal Barrier

1.4 增加机体抗氧化能力

IBD 患者体内的 ROS 水平升高[57]，而 ROS 的积累会破坏肠道组织[58]。合生元（益生菌和益生元）可通过降低 ROS 和提高抗氧化酶水平来减轻结肠炎症[59]，降低 ROS 积累的风险[60]。口服经基因工程改造的 EcN，可过表达抗氧化酶，从而抑制肠道炎症[61]。HUANG 等[62]开发了一种 ROS 响应性水凝胶，靶向递送罗伊乳杆菌以缓解 IBD。结果表明，该水凝胶可一定程度上清除 ROS 并保护人结肠癌细

表 1 益生菌的相关免疫及抗炎作用

Tab.1 Related Immune and Anti-inflammatory Effects of Probiotics

益生菌	免疫作用	抗炎作用	参考文献
植物乳杆菌	诱导和活化免疫应答、调节肠道内抗原、启动 IgA 免疫	抑制促炎因子如 IL-β、TNF-α 和 IL-6 的表达，稳定肠道菌群并抑制病原菌生长	[42—43]
干酪乳杆菌	调节细胞因子和趋化因子受体的平衡，提高上皮内淋巴细胞的数量，从而显著提高肠黏膜的免疫力	通过改善组织学评分、降低宿主炎症因子水平、调节肠道菌群、增强囊性纤维化跨膜转导调节因子的表达等来预防肠黏膜炎症	[44—45]
双歧杆菌	提高 IgG、IgA 水平	增加水通道蛋白和紧密连接（tight junction，TJ）蛋白的表达，抑制 TLR4/ 核因子 κB（nuclear factor κB，NF-κB）信号通路的激活，从而显著提高抗炎细胞因子的水平，降低促炎细胞因子的水平	[46—47]
嗜酸乳杆菌	改善肠道屏障功能并维持免疫稳态	抑制相关促炎因子，促进抗炎因子的表达	[48—49]
枯草芽孢杆菌	增加抗炎免疫细胞群对体外 LPS 刺激外周血单核细胞（peripheral blood mononuclear cell，PBMC）的反应	通过改善粪便代谢和增强结肠屏障来减轻结肠氧化应激和炎症	[50—51]

胞（HT-29 细胞）免受氧化损伤。

ROS 在 IBD 的发展中起关键作用。益生菌通过减少 LPS 诱导的 ROS 来缓解结肠炎症，对防治 IBD 至关重要[63]。

2 常见的治疗或缓解 IBD 的益生菌

2.1 乳酸菌

乳酸菌通过结合蛋白与上皮细胞相互作用，起到调节免疫反应的作用[64]。多项研究[65]已证明乳酸菌可缓解 IBD。LEBLANC 等[66]研究显示乳酸菌，特别是产叶酸和核黄素的菌株，可作为 IBD 患者的辅助治疗。

2.1.1 乳杆菌

干酪乳杆菌通过抑制 NF-κB 通路，可恢复 IBD 小鼠的疾病活动指数（disease activity index，DAI），并促进抗炎因子表达[67]。HAO 等[68]研究显示植物乳杆菌 Q7 衍生的细胞外囊泡（extracellular vesicle，EV）可改善肠道菌群失调。罗伊乳杆菌衍生的 EV 可抑制由活化巨噬细胞介导的炎症反应，在肠道免疫调节中发挥重要作用[69]。ZHANG 等[70]研究了加氏乳杆菌 G098 对结肠炎的缓解作用和机制，结果显示 G098 通过调节宿主免疫和肠道微生物，可有效逆转结肠炎症状。由于鼠李糖乳杆菌和副干酪乳杆菌对胃肠道疾病具有高抵抗力，被认为可作为潜在的益生菌[71]。

2.1.2 粪肠球菌

粪肠球菌是兼性厌氧革兰阳性乳酸菌。研究[72]证明，热灭活粪肠球菌 EF-2001 对二硝基苯磺酸（dinitrobenzene sulfonic acid，DNBS）诱导的 IBD 具有保护作用。并且，IBD 小鼠经 EF-2001 治疗后，发炎的结肠中有多种细胞因子的表达降低，组织破坏被抑制。粪肠球菌可减弱 NLRP3（可介导 IBD 的炎症小体）激活所需要的吞噬作用，保护小鼠免受 IBD 损伤[73]。粪肠球菌还能预防 IBD 的抑郁样行为。TAKAHASHI 等[74]报道粪肠球菌逆转了小鼠直肠和海马中 TNF-α 和 IL-6 的过表达，且增强了小胶质细胞中 NFκB p65 的表达和海马中 X 连锁凋亡抑制蛋白的表达。

2.1.3 凝结芽孢杆菌

“孢子形成菌”凝结芽孢杆菌具有稳定性和益生作用，可调节炎症细胞因子和 C 反应蛋白，促进肠道屏障的恢复[75]。SASAKI 等[76]研究显示，凝结芽孢杆菌对 IBD 患者肠道内的有害微生物表现出抑制作用，具有改善肠道微环境的作用。凝结芽孢杆菌还可与绿香蕉抗性淀粉的合生素补充剂协同作用，改善 IBD 的炎症状况[77]。

2.2 双歧杆菌

双歧杆菌可通过防止屏障破坏和促进受损细胞修复来维持肠上皮屏障稳定[78]，还可通过促进短链脂肪酸的产生而发挥抗炎作用[79]。两歧双歧杆菌 BGN4-SK-pBESIL10 菌株可产生抗炎细胞因子，抑制促炎细胞因子。与结肠炎小鼠模型相比，BGN4-SK 治疗可提高小鼠的抗氧化酶水平，证明 BGN4-SK 能减轻结肠炎症状[80—81]。双歧杆菌还能调节 C-Jun 氨基末端激酶细胞内通路，减轻 IBD 的上皮屏障损伤[82]。

2.3 芽孢杆菌

芽孢杆菌在 IBD 中具有抗炎和抗氧化作用，代谢物能单独或与免疫球蛋白和氨基酸结合，影响 IBD 模型的免疫反应，展现了在 IBD 防治中的重要作用[83]。

2.3.1 非致病性芽孢杆菌

枯草芽孢杆菌可在体外抑制炎症反应并增强肠道屏障的完整性，还能调节肠道免疫并缓解 IBD 症状[84—85]。口服枯草芽孢杆菌发酵乳可显著降低患者的 DAI，减轻肠黏膜损伤。此外，枯草芽孢杆菌可平衡肠道菌群，增加有益菌丰度，降低 *E. coli* 和拟杆菌的丰度[86]。CHUNG 等[87]报道，枯草芽孢杆菌 J92 中富含的胞外多糖可改善 IBD 小鼠的免疫功能，维持肠道屏障的完整性。LIU 等[88]评估了口服枯草芽孢杆菌对 IBD 的缓解作用。口服枯草芽孢杆菌 6 周的 IBD 小鼠与口服 2 周及未口服的相比，小鼠体质量和结肠长度增加，DAI 降低，上皮完整性和肠道菌群结构得到改善，TJ 蛋白也有所增加。另外，富含解淀粉芽孢杆菌的骆驼乳对 IBD 具有预防作用，能平衡炎症细胞因子[89]。

2.3.2 兼性厌氧型地衣芽孢杆菌

地衣芽孢杆菌是兼性革兰阳性厌氧菌，因具有

益生菌特性和抗炎作用，在 IBD 模型中有一定的治疗潜力[90—91]。由于其具有重塑肠道微生物群的能力，可用于治疗肠道菌群紊乱引起的疾病及肠道炎症[92]。地衣芽孢杆菌缓解了 IBD 的症状及粪便微生物丰度降低的现象[93]。此外，补充地衣芽孢杆菌后，一氧化氮的产生相对减少，炎症标志物水平降低，证明地衣芽孢杆菌可缓解 IBD 症状[94]。

3 结论与展望

综上所述，IBD 病因取决于多种因素，需进一步研究其发病机制。益生菌在调节肠道菌群、肠道免疫等方面可发挥重要作用，弥补常规药物的治疗缺陷。尽管该类药物的监管标准有限，但益生菌相对安全，不良反应或禁忌证较少。由于合并用药没有得到充分控制、数据库薄弱等因素，导致益生菌治疗 IBD 积累的证据不够确凿。现有证据能支持益生菌对轻 / 中度 UC 的疗效，但在 CD 中却不然。目前的试验尚未对特定患者使用适当的菌株或剂量。因此，益生菌治疗 IBD 的方法仍需探索，需要更多的临床试验来评估产品益处，探索最佳的菌株、剂量、配方等。由于在致病菌群已存在的情况下应用益生菌干预的治疗时机太晚等原因，益生菌治疗 IBD 的效果并不理想；还需针对 IBD 的表型进行个体化治疗，进一步发掘益生菌在 CD 中的效用。未来的研究应把优化菌株放在首位，识别和组合使用不同菌株，充分发掘它们的协同作用。

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