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封面故事

秧茂盛, 教授, 博士, 吉首大学药学院, 曾研究过癫痫、精神分裂症、儿童自闭症、II型糖尿病等的遗传背景和分子病理机制, 对哮喘、血脂异常、心血管疾病、肠道菌群失调等的病理基础和临床药物治疗也有一定的研究. 曾担任国内外七本杂志编委以及30多本杂志审稿人, 迄今为止, 在国内外学术期刊发表论文108篇(国际论文26篇). 掌握分子生物学、遗传学、药理学、流行病学、医学统计学和循证医学等学科的研究技术.

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文献综述 REVIEW

MSCs–肠道菌群相互调控关系在IBD治疗中的作用

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Effects of interaction between mesenchymal stem cells and gut microbiota in treatment of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is considered a chronic recurrent non-specific enteropathy whose etiology and pathology have yet been fully elucidated. Abnormal immune regulation between gut microbiota and the intestinal mucosa plays a crucial role in the development of IBD. Accordingly, intestinal microecological therapy to correct the imbalance of gut microbiota has important clinical significance. The application of mesenchymal stem cells (MSCs) in IBD has shown a promising therapeutic prospect based on its ability of immunosuppression and tissue repair, and more importantly, MSCs contribute to restoring the diversity and abundance of gut microbiota. And in the same way, gut microbiota produces indispensable effects in regulating the functional activities of MSCs. Therefore, the combined application of MSCs and intestinal microecological therapy may lead to higher clinical remission rates in the context of IBD. This paper reviews the characteristics of gut microbiota in IBD, the current status of microbe-targeted therapies, the gut microbiota-intestinal mucosal epithelium interaction, and the effects of interaction between MSCs and gut microbiota interaction in the treatment of IBD, with an aim to provide meaningful guidance for the further investigation of MSCs-gut microbiota interaction in this new field.

Key Words: Inflammatory bowel disease; Gut microbiota; Mesenchymal stem cells; Intestinal mucosa epithelium

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摘要

炎症性肠病(inflammatory bowel diseases, IBD)是一种慢性复发性非特异性肠道疾病, 其病因和发病机制尚未完全阐明. 研究证实肠道菌群与肠粘膜之间

异常的免疫调控在IBD的发生发展中起着决定性作用, 纠正菌群失调的肠道微生态疗法对IBD的治疗有着重要的临床意义. 间充质干细胞(mesenchymal stem cells, MSCs)在IBD的应用中显示出积极的治疗前景, 其有望成为IBD的新兴治疗手段. MSCs除了免疫抑制、组织修复的作用以外, 还有助于恢复正常肠道菌群的多样性及丰度, 同时, 肠道菌群对MSCs的功能活动同样起着重要的调控作用. 因此在IBD的环境背景下, MSCs与肠道微生态疗法的联合应用可能会取得更好的临床治疗效果. 本文就IBD肠道菌群特征及菌群靶向治疗现状, 肠道菌群与宿主肠粘膜上皮之间以及MSCs与肠道菌群之间的相互调控关系在IBD治疗中的作用做一综述, 可为探究MSCs-肠道菌群相互作用提供重要指导意义.

关键词: 炎症性肠病; 肠道菌群; 间充质干细胞; 肠黏膜上皮

核心提要: 肠道菌群失调是炎症性肠病(inflammatory bowel diseases, IBD)发病的重要因素, 微生态疗法对IBD治疗有重要意义. MSCs除了免疫调控还有助于重塑肠道菌群, 同时菌群对MSCs也起着重要调控作用. 因此在IBD环境背景下, MSCs与微生态疗法的联合应用可能会取得更好的临床效果.

文献来源: 刘爱茹, 杨少鹏, 张晓岚. MSCs-肠道菌群相互调控关系在IBD治疗中的作用. 世界华人消化杂志 2021; 29(6): 312-318
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0 引言

炎症性肠病(inflammatory bowel diseases, IBD)是一种慢性复发性非特异性肠道疾病, 其病因尚不十分明确, 主要包括克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC). 该病病程长, 复发率高, 容易出现局部及全身并发症, 严重影响患者的生活质量. 目前, 肠道菌群在IBD的免疫发病机制中的作用已经被广泛证实. 肠道菌群失调是肠屏障功能受损、免疫稳态破坏的重要促发因素, 还可能是IBD发生以及慢性化的决定性事件[1]. 因此以纠正菌群失调为基础的微生态疗法如益生菌、益生元、粪菌移植(fecal microbiota transplantation, FMT)等均显示出一定的积极疗效[2], 但仍面临着严峻的挑战. MSCs因其强大的免疫抑制、组织修复等作用, 在IBD中的治疗前景越来越被证实. 近年来研究发现MSCs有助于恢复正常肠道菌群, 重建肠道微生态, 促进疾病缓解, 同时肠道菌群对MSCs的功能活动同样起着重要的调控作用[3]. 因此, MSCs与肠道微生态疗法的联合应用可能会引起IBD患者更高的临床缓解率[3].

1 肠道菌群-肠粘膜上皮相互调控作用

肠道微生物主要包括细菌、病毒、真菌、寄生虫, 其中细菌数量巨大, 约为10^{14} CFUs/mL, 在与IBD发病关系中的研究最为广泛[4]. 肠道菌群主要包括四大菌门, 即厚壁菌门、拟杆菌门、放线菌门和变形菌门. 生理情况下, 肠道菌群和肠粘膜上皮之间保持着互利共生的关系, 共同维持着肠道稳态的平衡.

1.1 肠道菌群对肠粘膜上皮功能的调控 肠道菌群对宿主肠道呈现出重要的代谢、免疫和肠上皮保护功能. 在代谢方面, 菌群分解低聚糖, 合成短链脂肪酸(short chain fatty acids, SCFAs), 如丁酸盐、丙酸盐和乙酸盐, 为肠上皮细胞提供丰富的能量来源[5]. 同时, 肠道菌群还能合成维生素B、维生素K、烟酸、生物素和叶酸, 以及促进胆汁酸的肠肝循环, 调控物质代谢[6]. 在免疫方面, 肠道菌群通过产生微生物相关分子模式, 被肠粘膜上皮细胞和免疫细胞特异性受体识别, 如Toll样受体(toll-like receptors, TLR)和Nod样受体(nod-like receptors, NLR), 参与肠道的固有免疫和适应性免疫调节[7]. 肠道共生菌群及其相关代谢产物, 如SCFAs、吲哚等可以诱导树突状细胞分泌转化生长因子β(transforming growth factor-β, TGF-β)、白介素10(interleukin-10, IL-10)等细胞因子, 进而调控肠道调节性T细胞(regulatory T cells, Tregs)的增殖分化, 维持Tregs/Th17细胞之间的动态平衡, 抑制肠道免疫炎症反应的发生, 同时诱导B细胞向产生免疫球蛋白A(immunoglobulin A, IgA)的浆细胞的转换, 参与细胞免疫和体液免疫调节[2]. 在肠粘膜上皮保护方面, 肠道菌群通过影响上皮细胞的再生、凋亡以及紧密连接(tight junction, TJ)的表达和功能, 维护肠粘膜上皮的完整性. 多项研究表明[8,9], 肠道菌群可以引起无菌动物肠上皮形态和结构的改变. 无菌实验动物口服非致病性大肠杆菌和其他共生菌, 可以诱发隐窝上皮细胞的增殖, 肠绒毛的凋亡, 并促进损伤肠上皮的增生修复[9,10]. 同时肠道共生菌群对TJ屏障显示出积极的保护作用, 从而增强上皮对病原体的抵抗力, 降低病原体的肠道通透性, 减少菌群移位, 预防炎症反应的发生[11]. 在DSS诱导的结肠炎实验动物模型中, 益生菌可通过上调TJ蛋白的表达, 恢复肠道屏障功能, 降低肠道菌群的通透移位率[12]. 此外, 体外研究表明, 细菌代谢产物SCFAs也可以通过活化蛋白激酶途径调节TJ的合成, 从而增加肠粘膜上皮的完整性[13].

1.2 肠粘膜上皮对肠道菌群的调控 宿主为了与肠道菌

群维持稳态的关系, 需通过多种机制限制菌群与肠粘膜上皮表面的接触, 减少病原体的通透移位, 预防炎症反应的激活.

宿主肠粘膜通过粘液分泌, 释放抗菌肽和免疫球蛋白等机制限制潜在的有害病原体接触肠粘膜上皮表面[14,15]. 肠粘膜上皮表面分布着主要由杯状细胞分泌的粘蛋白2(mucin 2, MUC2)构成的粘液凝胶层[16]. 在大肠的肠上皮表面存在着两层明显不同的黏液层: 外层包含大量黏液寄生菌, 而靠近上皮的内层则几乎处于无菌状态[17]. 内黏液层为肠粘膜上皮提供了一个强大的物理屏障, 也成为了抗菌肽和免疫球蛋白的重要依附支架[18]. 小肠则缺乏界限清楚的内黏液层, 但含有大量的潘氏(Paneth)细胞, 其位于隐窝的底部, 富含抗菌分子. 在细菌信号的刺激下, Paneth细胞可以向肠腔释放抗菌分子, 如防御素, 以抑制细菌的聚集黏附[19]. 同时, 小肠的上皮细胞尚可分泌抗菌凝集素, 积聚在黏液层, 以阻止菌群和肠粘膜上皮表面的接触[20].

分泌型IgA在维持肠道微生态平衡中发挥着重要作用. IgA主要通过T细胞依赖性和非依赖性的调控方式由消化道相关淋巴组织(gut-associated lymphoid tissues, GALTs)中的浆细胞产生. 大量的多聚体IgA穿过上皮细胞分泌进入肠腔, 通过包裹细菌并与其抗原及毒素相结合, 抑制病原菌的生长, 稳定共生菌的丰度, 维护菌群多样性[21]. Forkhead家族的转录因子Foxp3是Tregs表达的特征性标志分子, Foxp3+Tregs在调控IgA的分泌中起着重要作用. 研究发现肠黏膜Foxp3+Tregs可通过TGF-β促进GALTs(尤其PP淋巴结)对IgA的选择性分泌[22], 高亲和力分泌型IgA可以特异性结合致病菌抗原靶位抑制其生长, 并阻止其对肠粘膜上皮的黏附, 降低细菌的穿透率[23], 上调有益菌丰度, 尤其厚壁菌群的增加又可以促进Foxp3+Tregs的增殖分化以调节免疫稳态, 因此Tregs-IgA 轴在维持肠道免疫和菌群稳态平衡中扮演着重要角色[24]. 同时, 肠腔内大部分共生菌可通过与T细胞非依赖性IgA结合以维持其在肠腔内的稳定定植[21].

此外, IL-22在介导肠粘膜上皮屏障和宿主抗菌防御功能上也发挥着重要作用[25]. IL-22可由固有免疫和适应性免疫细胞分泌, 通过诱导抗菌肽的表达抑制产碱杆菌属[26]、分节丝状菌等有害菌的增殖扩张, 同时在预防Th17细胞介导的结肠炎的发生中也发挥着重要作用[27].

因此, 肠道菌群和肠黏膜上皮之间相互调控, 彼此制约, 共同维持着宿主的稳态平衡. 该平衡一旦被打破, 将出现肠道微生态紊乱, 粘膜免疫系统激活, 进而导致IBD等多种炎症相关疾病的发生与发展.

2 IBD肠道菌群特征及菌群靶向治疗现状

目前的证据普遍支持菌群失调是引起IBD发生与发展的重要促发因素. 尽管尚无特异病原菌被普遍认为是IBD的病因, 但以往的研究结果指出, 与健康对照组相比, IBD患者肠道菌群失调, 细菌多样性降低, 正常存在于健康肠道中的拟杆菌门和厚壁菌门丰度下降, 而放线菌门和变形菌门等有害菌群显著升高[4]. 黏附性侵袭性大肠杆菌激活免疫炎症反应、损伤肠上皮的机制已经被明确, 大约30%-40%的回肠CD患者的肠道中可发现该菌[28]. 同时, 研究发现IBD患者肠道内耶尔森菌和艰难梭菌的比例明显上调[29,30], 且活动性CD患者外周血中副结核分枝杆菌的阳性率可高达68%[31]. 对肠黏膜标本研究结果显示, 与UC相比, CD肠道有益菌群的减少更为明显[32], 尤其回肠CD患者粪普拉梭杆菌显著减少[33], 这种细菌与手术后复发呈负相关, 而将该菌移植至慢性实验性结肠炎小鼠肠道内, 可减轻结肠炎症反应. 此外, 在IBD患者中尚观察到产生SCFA、吲哚等代谢产物的有益菌的数量明显减少, 如梭状芽孢杆菌、消化性链球菌等[34,35].

鉴于肠道菌群变化与IBD发生发展关系的重要性, 纠正菌群失调、改善肠道微生态对IBD患者的补救治疗具有重要临床意义. 目前以纠正菌群失调为靶标的微生态疗法如抗生素、益生菌、益生元、合生元等均显示出一定的辅助效果, 但其长期疗效和安全性并不确切[36]. FMT作为新兴的肠道微生态疗法, 为IBD患者的治疗也带来积极的前景, 在治疗活动期UC中疗效确切, 但远期耐受性和安全性仍不清楚, 且目前尚缺乏在CD中的治疗证据[36,37]. 因此, 如何重建肠道微生态仍是IBD治疗领域面临的重要问题.

3 MSCs-肠道菌群相互调控在IBD治疗中的作用

目前, 干细胞移植是IBD治疗领域的研究热点, 其中MSCs因其具有抑制炎症反应、调节免疫紊乱及促进黏膜组织修复等作用, 在IBD的基础和临床研究中均显示出积极的治疗效果[38-40], 有望成为IBD的新兴治疗手段. 目前MSCs在IBD中的机制研究主要集中在免疫调控方面, 其主要通过促进Tregs的增殖分化、抑制Th17的活性及促炎因子的分泌来维持肠黏膜免疫稳态, 抑制粘膜炎症反应的发生[41]. 近年来研究发现[3]MSCs有助于改善肠道菌群多样性及丰度, 重建肠道微生态, 而肠道菌群也可以调控MSCs的功能活动, 共同影响宿主免疫稳态的恢复.

3.1 MSCs对肠道菌群的影响

Yan等[42]研究表明, 人脐

间充质干细胞(human umbilical mesenchymal stem cells, HUMSCs)可以通过恢复肠道共生菌的多样性和丰度, 尤其是产短链脂肪酸的S24-7和毛螺菌科, 改善食物过敏小鼠的症状. 在急性肝损伤老鼠模型中, MSCs的植入可以改变厚壁菌门/拟杆菌门的比值, 上调乳杆菌属丰度, 增加上皮TJ蛋白ZO-1的表达, 且菌群基因功能预测分析提示MSCs移植小鼠的功能性生物标志物涉及了细胞运动、信号转导、膜转运以及脂类、辅因子、维生素等的代谢, 进一步表明MSCs的植入有利于维持肠道粘膜的生物学和内稳态, 减少细菌移位, 促进急性肝损伤的恢复[43]. Sun等[44]发现在脓毒症大鼠中, 肠道内产生脂多糖的埃希-志贺氏菌属比例增加, 而与调节肠黏膜厚度和维持肠道屏障功能相关的阿克曼菌丰度下降. 这些肠道微生物群的变化破坏了能量平衡, 加重了炎症反应, 降低了肠道屏障功能, 促进了肠道细菌的移位. 而脂肪来源的MSCs的植入使肠道有益菌比例增加, 有害菌比例减少, 恢复了肠道菌群多样性, 有利于脓毒症的改善, 从而为MSCs在脓毒症中的应用提供了潜在的治疗机制. 另一项研究发现HUMSCs的应用改善了小鼠关节炎症, 同时上调了肠道拟杆菌属与芽孢杆菌的丰度, 促进了色氨酸的代谢, 相关代谢产物吲哚等的增加可进一步调控Tregs/Th17细胞的平衡, 抑制免疫炎症反应, 此外尚观察到肠粘膜B细胞和IgA分泌增加, 进而对肠道菌群的调控又发挥重要作用[45]. 最新一项研究表明[46]在非酒精性脂肪性肝炎(Non-alcoholic steatohepatitis, NASH)小鼠模型中, MSCs的应用可以维持拟杆菌属的水平, 上调梭状芽孢杆菌的丰度, 纠正肠道菌群失调, 同时改善菌群代谢紊乱, 因此MSCs可能通过调控肠道菌群影响肝-肠轴促进NASH的恢复. Tsuruhara等[47]发现脂肪来源的MSCs移植到老龄小鼠体内, 可以通过增加抗原特异性分泌型IgA的产生, 影响肠道菌群的构成, 促进小鼠粘膜免疫状态的恢复, 其可能与树突状细胞的功能调控有关. Nagashima等[48]最近发现肠上皮下间充质细胞可以调控分泌型IgA的产生, 诱导菌群多样性, 维持肠道微生态平衡, 即间接反应了MSCs调节肠道菌群的潜能.

此外, 在IBD的疾病模型中, 目前也有文献报道MSCs对肠道菌群的调控影响[49,50]. 2014年Mar等[49]在DSS诱导的结肠炎小鼠模型中指出, 与DSS未治疗组相比, MSCs的应用对肠道菌群多样性的影响并不显著, 而益生菌VSL#3或联合MSCs可以明显改善肠道菌群多样性及构成. 而2018年另一项在DSS诱导的结肠炎小鼠模型中的研究指出, 结肠炎小鼠肠道菌群发生了显著的改变, 变形菌门和拟杆菌属明显增加, 厚壁菌门显著减少, 诱导的多能干细胞或脂肪来源的MSCs应用后, 结肠炎小鼠肠道菌群的构成接近于健康正常小鼠水平, 肠道炎症明显缓解. 然而, 肠道菌群的改变是肠粘膜愈合改善的结果, 亦或肠粘膜愈合是肠道菌群改善的结果, 目前还不清楚[50]. 此外, 有研究表明[51], MSCs可增加致病菌的清除, 显著降低菌血症的发生率. 在慢性金黄色葡萄球菌感染的老鼠模型中, MSCs的静脉输注可以有效地控制炎症感染, 并发现其可通过分泌抗菌肽增加杀菌作用[52]. 而在大肠杆菌诱发的急性肺损伤或肺炎模型中, MSCs气管内移植后可以通过上调β-防御素2或抗菌蛋白lipocalin 2的分泌, 增加细菌的清除率[53,54]. Harman等[55]体外研究发现, 马来源的MSCs可以抑制金黄色葡萄球菌和大肠杆菌的生长, 并通过分泌抗菌肽破坏细菌细胞膜的完整性. 另一项研究表明[56], HUMSCs可以增加巨噬细胞的吞噬活性, 降低致病菌的负荷, 增加新生脓毒症鼠的存活率. 然而MSCs对肠道菌群的影响是否与细菌的清除增加有关值得进一步探索. 因此明确MSCs对肠道微生态的影响及机制将为其在IBD中的有效应用提供更加重要的理论依据.

3.2 *肠道菌群对MSCs的影响* MSCs可以通过表达功能性模式识别受体(TLR, NLR)感知微生物信号, 进而对其刺激做出反应[57-59]. 同时, MSCs在IBD等多种疾病治疗的应用中, 肠道菌群对MSCs的增殖分化、迁移和免疫调控等功能的发挥具有重要影响[59]. Xiao等[60]的研究指出无菌小鼠的骨髓MSCs的干性发生了明显变化, 将无特定病原体小鼠的肠道微生物移植入无菌小鼠, 发现骨髓MSCs的增殖分化能力恢复正常. 此外, 正常肠道菌群可以通过诱导T细胞凋亡和细胞因子的分泌来维持骨髓MSCs的免疫调控能力, 而在DSS诱导的实验性结肠炎小鼠模型中, 无菌小鼠来源的骨髓MSCs的植入对疾病无治疗作用[60]. Kol等[59]研究发现, 沙门氏菌可以显著抑制MSCs的迁移, 上调细胞表面分子CD54的表达以及IL-6、IL-8和前列腺素E2(Prostaglandin E2, PGE2)等细胞因子的分泌, 但并不影响MSCs的活性和增殖能力, 也并不诱导其抗原呈递表型的转换. 而其他体外研究报道, 感染了金黄色葡萄球菌[61]或幽门螺旋杆菌[62]的胃肠上皮细胞可以促进MSCs的炎症靶向迁移. 另有研究表明, 慢性缺氧可以引起慢性紫绀性心脏病儿童患者肠道菌群失调, 乳杆菌属丰度降低, D-半乳糖积聚, 诱发骨髓MSCs的早衰. 而在缺氧大鼠模型中, 补充干酪乳杆菌有助于MSCs功能的恢复[63]. 在酒精性肝炎的小鼠模型中, 与单独疗法相比, 鼠李糖乳杆菌联合骨髓MSCs疗法可以显著抑制肝脏炎症反应, 调节淋巴细胞亚群平衡, 改善肝炎的症状[64]. 在肠道菌群失调的1型糖尿病小鼠模型中, 脂肪来源的MSCs治疗糖尿病的作用减弱, 而应用抗生素纠正菌群失调, 上调双歧杆菌的丰度后可明显增强MSCs的治疗作用[65]. 此外, 肠道细菌代谢产物也

可以影响MSCs的功能, 如细菌代谢产物氧化三甲胺可以显著促进骨髓MSCs的成脂功能, 而降低骨生成, 加重骨质疏松的发生[66]; 而SCFAs则可以抑制绒毛膜来源MSCs的成脂分化功能, 减少脂肪的积聚[67]. 因此, 在接受MSCs进行治疗的疾病中, 肠道菌群可能与其他介质一起参与调节MSCs的功能表型, 影响MSCs的治疗作用, 但其直接的调控机制尚不清楚. 因此, 探究肠道菌群对MSCs功能的调控机制, 将为MSCs在IBD等疾病中的有效应用保驾护航.

综上, 肠道菌群与MSCs之间可相互调控, 影响彼此功能的发挥. 同时, 在IBD的治疗中, 肠道微生态疗法与MSCs对肠黏膜上皮均显示出相似的调控作用: 如恢复肠黏膜免疫稳态, 修复肠上皮屏障, 调节肠道菌群多样性等. 可见二者联合治疗可能会改善IBD患者的临床治疗反应率, 为患者的治疗提供新的思路[3].

4 结论

肠道菌群与肠黏膜上皮之间相互调控, 互利共生, 共同维持肠道微生态和免疫稳态的平衡. 肠道菌群失调与IBD发生发展的关系已经被证实. 靶向肠道菌群的微生态疗法, 已成为IBD重要的补救治疗措施, 但其尚处于起步阶段, 仍存在许多未知. MSCs在IBD中的积极治疗效果引起了广泛的关注. MSCs-肠道菌群的相互关系的研究更是作为一个新的、具有积极前景的研究领域崭露头角. MSCs可重建肠道微生态, 而肠道微生物可作为协同因子增强MSCs的功能活动, 尽管具体的调控机制以及特定调控菌群尚未明确, 但有研究显示, 在IBD的环境背景下, MSCs与肠道菌群疗法的联合应用可引起更高的临床缓解率. 因此, MSCs-肠道菌群的相互调控关系作为一个新的领域值得深入探索和研究.

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