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干细胞治疗炎症性肠病的研究进展

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【摘要】 炎症性肠病的患病人数在我国高速增长,传统药物治疗难以改变病程,且 2/3 的患者存在生物制剂失应答,亟需开发新疗法实现黏膜愈合。隐窝肠干细胞可分化成肠上皮细胞,并与肠上皮细胞协同修复肠道黏膜,维持肠道内稳态。炎症性肠病患者免疫功能紊乱,破坏肠道干细胞池自我更新,阻止黏膜修复再生导致黏膜屏障受损。近年来随着类器官共培养技术与单细胞测序技术的应用,免疫细胞与干细胞之间相关调控关系越加明确。干细胞移植有望重建黏膜屏障实现黏膜愈合,目前已开展多项干细胞临床研究并取得一定临床突破。本文综述免疫细胞与肠干细胞相关调控关系及干细胞临床研究前沿进展。

【关键词】 炎症性肠病;干细胞;移植
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Advances in stem cell therapy for inflammatory bowel disease

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【Abstract】 The population with inflammatory bowel disease is growing rapidly in China. Traditional treatments are difficult to change the course of disease, and 2/3 of patients have lost response to biological therapies. It is urgent to develop new therapies to achieve mucosal healing. Crypt intestinal stem cells can differentiate into intestinal epithelial cells, and cooperate with intestinal epithelial cells to repair intestinal mucosa and maintain intestinal homeostasis. The immune function of patients with inflammatory bowel disease is disordered, which destroys the self-renewal of intestinal stem cell pool and prevents the repair and regeneration of mucosa, resulting in the damage of mucosal barrier. In recent years, with the application of organoid co-culture technology and single-cell sequencing technology, the regulatory relationship between immune cells and stem cells has become more and more clear. Stem cell transplantation is expected to rebuild the mucosal barrier and achieve mucosal healing. At present, a number of clinical studies on stem cells have been carried out and some clinical breakthroughs have been made. This article reviewed the regulatory relationship between immune cells and intestinal stem cells and the advances in clinical research of stem cells.

【Key words】 Inflammatory bowel disease; Stem cell; Transplantation

炎症性肠病(inflammatory bowel disease,IBD)是一种病因未明的非特异性消化道炎症性疾病,包括克罗恩病(Crohn's disease,CD)及溃疡性结肠炎(ulcerative colitis,UC),其特征为慢性炎症导致消化道黏膜损伤。2017 年全球 IBD 总患病人数达 680 万[1],成为全球公共卫生事业巨大负担。社会因素造成 IBD 经历以下阶段转化:出现期、发病率加速期、患病率加速期、患病率平衡期,随着经济发展我国 IBD 患者迅速上升,预计 2025 年将达到 150 万[2-3]。IBD 主要治疗方式为包括生物制剂在内的内科治疗[4],发生并发症需外科干预[5]。氨基水杨酸盐、硫嘌呤和类固醇等非生物疗法可改善症状,但不改变 IBD 的总体病程[6]。生物制剂虽可改变 IBD 病程,但临床试验数据表明约 1/3 的 IBD 患者对生物制剂原发性失应答[7-10],1/3 的患者在生物制剂维持治疗期间发生继发性失应答[11],现有治疗方案难以达到满意临床疗效。随着生物学基础研究及临床试验深入,干细胞疗法有望拓宽 IBD 治疗方式。

1　干细胞动态维持肠道内稳态

肠道为人体最大器官,肠道隐窝使其在物理、化学及病原微生物侵害下仍维持内稳态。隐窝底部存在肠干细胞(intestinal stem cell,ISC),其不断分化及自我再生[12],以实现肠道上皮细胞更新。肠道隐窝结构图及 ISC 分化过程[13]如图 1 所示。Tian 等[14]发现储备 ISC 群位于隐窝底部"+4"位置,Bmi1[15]、mTert[16]、Hopx[17]和 Lrig1[18]为+4 ISC(即储备 ISC)标志物。活性 ISC 分化成祖细胞,沿肠道隐窝绒毛轴增殖及分化,Lgr5 为活性 ISC 重要标志物[13]。肠道受损刺激后+4 ISC 活化成 Lgr5+ISC 补充干细胞池[14],同时 Lgr5+ISC 具有分化补充+4 ISC 潜能[19]。肠道隐窝活性 ISC 及储备 ISC 动态平衡,维持肠道干细胞池自我更新,以助于实现黏膜修复。

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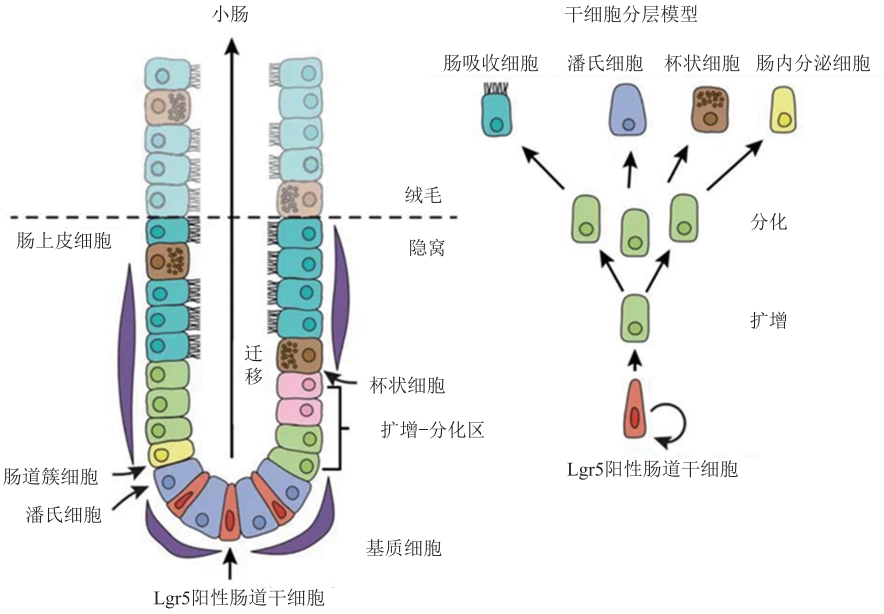

图 1 肠道隐窝结构图及 ISC 分化过程

Fig 1 Intestinal crypt structure and ISC differentiation

肠道隐窝为肠道发育时肠上皮细胞内陷所形成。Lgr5+ISC 位于隐窝底层,其迁移至扩增-分化区时分化成不同类型肠上皮细胞,保证肠道自我更新以维持肠道稳态。经典分化途径为 Lgr5+ISC 经有丝分裂先分化为肠吸收细胞、杯状细胞、肠内分泌细胞,最后分化潘氏细胞。潘氏细胞最终与肠干细胞交错分布于隐窝底部,分泌防御素、溶菌酶及细胞因子以支持保护肠干细胞。

肠道受到化学、物理、病原微生物侵害导致隐窝破损,ISC 与肠上皮细胞协同修复肠道黏膜,主要分为以下三步[20-21]:(1)破损隐窝分泌炎症因子刺激正常隐窝肠上皮细胞发生迁移。(2)正常隐窝底部 ISC 分化补充肠上皮细胞,并随肠上皮细胞发生迁移。(3)迁移后 ISC 及肠上皮细胞不断分裂、分化,形成通道样结构,并进一步内陷形成新隐窝以补充破损隐窝,最终实现损伤黏膜修复再生。

2 肠道免疫细胞调控 ISC 干预肠道内稳态

肠道免疫功能紊乱为 IBD 主要病因[22-23],然而其内在机制仍不明确。随着肠类器官(intestinal organoids,IOs)共培养技术和单细胞测序技术(single cell RNA sequencing,scRNA-seq)应用,发现免疫细胞通过调控 ISC 干预肠道内稳态,补充、维持肠道干细胞池可纠正免疫紊乱所致的肠道内稳态失调,进而实现黏膜修复及再生。

2.1 T 细胞直接调控 ISC CD 及 UC 患者均存在 Th1 及 Th2 免疫异常,Th1 免疫异常多见于 CD[24],巨噬细胞过度表达 IL-12、IL-18 及 TNF-α 并驱动 Th1 免疫应答,从而促进 IL-2 与 IFN-γ 分泌;Th2 免疫反应异常则多见于 UC[25],Th2 细胞因子家族成员 IL-5 与 IL-13 表达增加。同时 CD 与 UC 患者黏膜中均发现 Th17 细胞相关细胞因子 IL-17A 高表达[24-25],提示 IBD 患者亦存在 Th17 免疫异常。Biton 等[26]利用 scRNA-seq 发现 MHC Ⅱ在 Lgr5+ISC 中高表达,MHC Ⅱ通过与 T 细胞相互作用影响 ISC 分化,Th1-IOs 共培养促进 ISC 向潘氏细胞分化,Th2-IOs 共培养促进 ISC 向簇细胞分化。同时该研究发现 Th1-IOs 共培养、Th2-IOs 共培养、Th17-IOs 共培养或 IL-13、IL-17A 刺激均导致 ISC 池耗竭。移植物抗宿主病(graft versus host disease,GVHD)模型也表明异常活化 T 细胞靶向攻击 ISC[27],导致肠隐窝 ISC 及潘氏细胞数量显著减少[28]。以上研究证实 T 细胞通过直接抑制 ISC 再生、促进 ISC 分化、攻击 ISC 等方式调控肠道干细胞池,进而维持肠道内稳态及肠上皮屏障功能。

2.2 固有免疫细胞(innate lymphoid cells,ILC)分泌细胞因子间接调控 ISC ILC 为肠道免疫重要组成部分[29],类器官共培养发现黏膜损伤后 ILCs 分泌 IL-22[30]。IL-22 表达增加与 NLRP3 或 NLRP6 炎症小体轴相关,IL-22 已证实为 DSS 结肠炎[31-32]、GVHD 等肠炎保护因子[30, 33]。具体机制为 IL-22 诱导 Lgr5+ISC 发生 STAT3 磷酸化,独立经典分化途径诱导 ISC 维持及分化[33]。Lindemans 等[30]通过 ATOH1 缺陷类器官共培养发现 IL-22 可诱导 ISC 不分化潘氏细胞实现肠上皮再生,证实存在非经典干细胞分化途径。进一步研究表明 ISC 表达 IL-22 受体[13, 33],重组 IL-22 直接靶向促进 ISC 增殖、扩增,进而增强小鼠及人肠道类器官生长[30]。Hanash 等[33]发现,IL-22 治疗加速肠

干细胞池恢复,增加肠上皮再生,降低 GVHD 肠黏膜损伤。此外,ILC2s 分泌 IL-4、IL-13 可促进 ISC 分化上皮细胞[34-36],但 ILC2s 和 ISC 之间相互作用及分子机制仍需要进一步探索。

2.3 其余免疫细胞与 ISC 巨噬细胞与树突状细胞通过先天性免疫及适应性免疫以维持肠道内环境稳定。Noel 等[37]通过巨噬细胞-IOs 共培养发现巨噬细胞分泌细胞因子 IL-6、IL-8、IFN-γ 和 TGF-β1 促进肠上皮成熟。Sehgal 等[38]发现,巨噬细胞通过集落刺激因子 1(colony-stimulating factor 1,CSF1)维持 ISC 再生以修复损伤黏膜。Jones 等[39]通过树突状细胞-IOs 共培养发现树突状细胞分泌细胞因子 IL-1β、IL-6、IL-15 和 IL-17A 激活类器官 NF-κB2 信号通道,调节肠上皮细胞增殖及凋亡敏感性。

综上所述,T 细胞直接抑制再生、促进分化、攻击消耗等方式调控 ISC,固有免疫细胞通过细胞因子靶向促进 ISC 增殖、扩增,其他免疫细胞对维持 ISC 再生有重要作用。IBD 免疫功能紊乱,破坏肠道干细胞池自我更新,阻止黏膜修复再生导致黏膜屏障受损。干细胞移植或有望补充、修复 ISC 池,重建 IBD 上皮屏障。

3 干细胞相关临床研究

干细胞疗法应用前景巨大,目前已有诸多临床试验探索。干细胞来源如下:胚胎干细胞(embryonic stem cell,ES)、诱导多能干细胞(induced pluripotent stem cell,iPS)及体细胞。ES 与 iPS 细胞存在伦理问题、潜在致癌风险;体细胞无需基因重编程因而致癌风险低,且伦理争议少。目前主要使用造血干细胞(hematopoietic stem cell,HSC)或间充质干细胞(mesenchymal stem cell,MSC)开展 IBD 临床研究。

3.1 HSC 相关临床研究 HSC 可分化成髓系及淋巴系细胞,HSC 移植可重置免疫系统,多用于血液系统恶性肿瘤。HSC 移植或可减轻 IBD 患者异常免疫反应,上世纪 90 年代 Drakos 等[40]首次应用 HSC 移植治疗 CD。Burt 等[41]展开一项难治性 CD 自体 HSC 移植Ⅰ/Ⅱ期研究,发现移植后无药物缓解期 1 年时为 91%,2 年时为 63%,3 年为 57%,4 年为 39%,5 年为 19%。López-García 等[42]展开另一项难治性 CD 自体 HSC 移植单中心队列研究,证实移植后 5 年内患者出现复发,但 80%患者可恢复药物应答进而实现临床缓解,HSC 移植依然具有临床研究价值。多项难治性 CD 患者自体 HSC 移植研究表明[42-44]自体 HSC 移植无法解决遗传易感性导致疾病复发率较高,且存在频繁严重不良反应(serious adverse events,SAEs)。其临床应用受到严重应用限制,仍需深入研究探索改良 HSC 移植。

3.2 MSC 相关临床研究 MSC 具有免疫抑制作用,通过 PGE2 和 IL-10 极化 M2 巨噬细胞,减少树突状细胞和中性粒细胞[45];调节 T 淋巴细胞和 B 淋巴细胞的增殖和分化以降低其活性[46-47]。自 2003 年首次报道注射 MSC 成功治愈直肠阴道瘘[48]以来,多个Ⅰ期、Ⅱ期和Ⅲ期试验证明了 MSC 治疗 CD 肛瘘的安全性和有效性(见表 1)。此外,奥地利 Christopher 等 2018 年 10 月至 2021 年 4 月开展 MSC 治疗 CD 肛瘘前瞻、多中心临床研究(NCT05322057,暂未发表),相关研究数据暂未披露。

表 1 MSC 治疗 CD 相关临床试验

Tab 1 Clinical trials of MSC treatment for CD

研究	发表年份	国家	研究类型	病例数	给药方式	MSC 类型	MSC 来源	评效指标	结局	不良反应
García-Olmo 等[49]	2005 年	西班牙	Ⅰ期,开放标签,单臂	4	局部注射 3×10^6 MSC	自体	脂肪组织	瘘口皮肤上皮化	8 周时 75% 瘘管愈合	无
García-Olmo 等[50]	2009 年	西班牙	Ⅱb 期;开放标签;双臂;随机	14	分别局部注射纤维蛋白剂和 3×10^6 MSC 纤维蛋白剂	自体	脂肪组织	瘘口皮肤上皮化	8 周 MSC 组 71% 瘘管愈合 VS 纤维蛋白剂组 14%瘘管愈合	15 项 AE;4 项 SAE
Ciccocioppo 等[51]	2011 年	意大利	开放标签,单臂	10	每 4 周局部注射(1.5~3)$\times10^7$ MSC 直至黏膜好转或 MSC 不可获取	自体	脂肪组织	临床检查无引流,MRI 检查愈合	8 周时 67% 瘘管愈合;治疗后 1 年无复发	无
Cho 等[52]	2013 年	韩国	Ⅰ期,开放标签,单臂	10	基于瘘管大小,局部注射 1×10^7、2×10^7、4×10^7MSC	自体	脂肪组织	瘘口皮肤上皮化	8 周时 30% 瘘管愈合;治疗后 8 个月无复发	13 项 AE;3 项 SAE
Lee 等[53]	2013 年	韩国	Ⅱ期,开放标签,单臂	33	每 1 cm 瘘管长度予 3×10^7 或 6×10^7 MSC,若 8 周未愈合再次注射 1.5 倍以上剂量	自体	脂肪组织	瘘口皮肤上皮化	8 周时 82% 瘘管愈合;治疗后 1 年无复发	28 项 AE,1 项 SAE
de la Portilla 等[54]	2013 年	西班牙	Ⅰ/Ⅱa 期;开放标签,单臂	24	局部注射 2×10^6 MSC;若 14 周时未愈合再次注射 4×10^6	异体	脂肪组织	瘘口皮肤上皮化;临床检查无引流,MRI 检查愈合	24 周时 47% 患者愈合	4 项 SAE

续表 1

研究	发表年份	国家	研究类型	病例数	给药方式	MSC 类型	MSC 来源	评效指标	结局	不良反应
Gharibi 等[55]	2015 年	韩国	Ⅱ期	24	基于瘘管大小,局部注射 $(9\sim42)\times10^7$ MSC	自体	脂肪组织	瘘口皮肤上皮化	83%患者愈合;治疗后 2 年无复发	53 项 AE
Molendijk 等[56]	2015 年	荷兰	开放标签;四臂	21	局部注射,组 1:5 例 1×10^7 MSC;组 2:5 例 3×10^7 MSC;组 3:5 例 9×10^7 MSC;组 4:6 例安慰剂	异体	脂肪组织	临床检查无引流 MRI 检查< 2 cm 积液	12 周瘘管愈合,组 1:2/5;组 2:4/5;组 3:1/5;组 4:2/6	50 项 AE
Panés 等[57]	2016 年	以色列	Ⅲ期;随机对照试验	212	局部注射	异体	脂肪组织	临床检查无引流,MRI 检查< 2 cm 积液	24 周患者愈合率 MSC 50% *vs* 安慰剂 34%	MSC 组 68 项 AE,18 项 SAE 安慰剂 66 项 AE,14 项 SAE
Dietz 等[58]	2017 年	美国	Ⅰ期,开放标签,单臂	12	局部注射 GORE Bio A 枪头 20×10^7 MSC	自体	脂肪组织	临床检查无引流,MRI Van Assche 评分改善	6 个月时 83% 患者愈合	无

虽然局部注射脂肪组织来源 MSC 可促进 IBD 患者实现黏膜愈合,但关于最优 MSC 来源、给药剂量及频率以及是否需要长期注射 MSC 等仍需更多随机对照试验探索。

4 展望

实现黏膜愈合为 IBD 治疗目标,传统药物对 IBD 改善有限,2/3 患者对生物制剂失应答,亟需开发新疗法以促进 IBD 黏膜愈合。肠道隐窝通过干细胞池自我更新、分化,维持肠道内稳态。类器官共培养与单细胞测序表明免疫细胞直接或间接调控 ISC 进而干预肠道稳态,免疫细胞调控 ISC 具体机制仍需要进一步探索。IBD 免疫功能紊乱,阻止黏膜修复再生导致黏膜屏障受损,干细胞移植有望拓宽 IBD 治疗方式。目前已开展诸多干细胞临床研究,造血干细胞移植无法解决遗传易感性导致疾病复发率较高,且存在频繁严重不良反应,其临床应用受到严重应用限制,需改良优化造血干细胞移植方式。MSC 移植可促进 IBD 患者黏膜愈合,但是其最佳来源方式、给药剂量、频率及是否需要定期治疗等仍需更多随机对照试验探索。

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