基于巨噬细胞对肠黏膜愈合调控治疗炎症性肠病的药物研究现状

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摘要: 实现肠黏膜完整愈合是治疗炎症性肠病 (inflammatory bowel disease, IBD) 最理想的目标。患者肠黏膜愈合后不仅可以明显改变疾病进程、缓解临床症状, 还能显著减免并发症发生、防止疾病复发。由于消化道溃疡损伤伴有慢性炎症是IBD主要病理特点, 目前临床主要从抗炎入手治疗, 但此类疗法不能很好地促进患者肠黏膜愈合, 如何实现IBD长期缓解仍是亟待解决的难点。而在肠黏膜修复过程中, 巨噬细胞的极化重建维持着肠道微环境稳态, 是促进黏膜炎性修复的典型过程, 也是启动组织再生中不可轻视的关键一环。本研究通过查阅近十年的文献, 以促进IBD患者肠黏膜愈合为中心, 着重讨论目前临床用药的不足, 以及调控巨噬细胞促进肠黏膜修复的重要性、可行性, 并总结相关有促进肠黏膜修复潜力的药物及靶点, 以期为IBD的治疗提供有效的潜在药物以及治疗靶点。

关键词: 炎症性肠病; 肠黏膜愈合; 巨噬细胞; 极化平衡; 免疫修复

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Current drug research on intestinal mucosal healing in inflammatory bowel disease based on macrophage regulation

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Abstract: Complete healing of the intestinal mucosa is the most ideal goal in the treatment of inflammatory bowel disease (IBD). The intestinal mucosa healing not only significantly alters the course of the disease and relieves clinical symptoms, but also markedly reduces the occurrence of complications and prevents recurrence of IBD. As chronic inflammation associated with peptic ulcer damage is the main pathological feature of IBD, clinical treatment is mainly based on anti-inflammatory therapy, but such therapy cannot promote the healing of the intestinal mucosa of patients. Therefore, how to achieve long-term remission of IBD is still an urgent challenge. In the process of intestinal mucosal repair, the polarization of macrophages maintains the homeostasis of the intestinal microenvironment, which is a representative process that promotes mucosal inflammatory-repair. It is a key part of initiating tissue regeneration that should not be underestimated. In this paper, we reviewed the literature of the past decade, focusing on the promotion of intestinal mucosal healing in IBD. The discussion will highlight the importance and feasibility of regulating macrophages to promote intestinal mucosal repair. Following this thought, we discuss the shortcomings of current clinical treatments and summarize the relevant drugs which have potential to promote intestinal mucosal repair. The aim is to provide effective potential drugs and therapeutic targets for the

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treatment of IBD.

Key words: inflammatory bowel disease; intestinal mucosal healing; macrophage; polarization balance; healing through immune response

炎症性肠病 (inflammatory bowel disease, IBD) 是一种以消化道溃疡为显著特点的慢性自身免疫疾病[1]。近些年世界各地其发病率成倍增加[2,3], 患者长期遭受消化道出血、穿孔、肠梗阻等病痛的折磨。IBD主要包括溃疡性结肠炎 (ulcerative colitis, UC) 和克罗恩病 (Crohn's disease, CD)。对于病变位置, UC在结直肠, 一般呈连续的弥漫性分布, 大多数在乙状结肠和直肠, 可累及横结肠及降结肠, 甚至扩展至全结肠[4], 炎症仅限于黏膜和黏膜下层, 并伴有隐膜炎和隐窝脓肿[5]; CD的病变在胃肠道的任意位置, 且可以不连续[6], 在组织学上表现为黏膜下层增厚、透壁炎症、溃疡裂和肉芽肿[5]。

肠黏膜愈合被认为是治疗IBD的核心, 但目前临床用药不能实现IBD患者的完整黏膜愈合。在肠黏膜修复过程中, 巨噬细胞与多种肠道上皮细胞通过密切的胞间交互对话, 直接促进其增殖分化或创造出有利于上皮再生和黏膜愈合的微环境, 是实现修复不可或缺的参与者, 而IBD患者消化道内异常的巨噬细胞也是其自身黏膜修复出现障碍的关键之一[7]。基于此, 本综述通过文献查阅及总结, 明确调控巨噬细胞对于IBD患者肠黏膜愈合的重要性, 并总结其中具有代表性的治疗靶点, 以期为未来IBD的治疗提供方向。

1 促进肠黏膜愈合的必要性以及目前疗法的不足

1.1 促进肠黏膜愈合在IBD治疗中的意义 肠黏膜的愈合是IBD公认的治疗目标[8-10]。肠黏膜愈合能够明确改变IBD病程, 持续缓解临床症状, 显著改善临床结果以及降低患者的住院率和手术切除率。这就是为什么即使黏膜愈合可能不会根治IBD, 也被认为是CD和UC的治疗目标和临床试验的终点[11]。一项对于CD患者的临床分析表明, 使用英夫利息单抗达到肠黏膜愈合的患者, 在停药后14～78周内没有出现临床复发, 相比之下, 没有肠黏膜愈合的患者在0～8周内相继出现临床复发[1]。对于UC也有类似的结果, 相较于黏膜愈合的患者, 82例临床缓解但仍有黏膜炎症的患者在1年内复发风险增加了2～3倍[1]。肠黏膜愈合还能降低患者住院率和手术切除率。达到黏膜愈合的UC患者1年内结肠切除率仅为2% (3/178), 5年内结肠切除率为7% (13/176)[12]。达到黏膜愈合的CD患者5年内进行手术的概率为11% (6/53), 而未能愈合的患者1年内手术率为20% (18/88)[12]。因此, 实现肠黏膜愈合意味着患者大概率预后良好、长期缓解。

手术多为IBD患者药物治疗失败时的选择, 且术后的并发症以及疾病复发率较高[1]。对于UC而言, 患者手术后近期吻合口瘘和腹腔脓肿发生率为4.3%和7.5%。559例UC手术患者中, 术后90天并发症发生率为33.3%, 其中, 肠道相关并发症为59.7%, 感染性并发症为34.4%, 切口相关并发症为24.7%[13]。CD的手术治疗是在药物治疗失败时为缓解症状或为了治疗并发症所采取的治疗方法, 极少是治愈性的, 术后疾病常复发[14]。CD患者的回肠结肠切除后腹腔内感染性并发症 (intra-abdominal septic complications, IASC) 很常见, 一项回顾性试验分析, 6年内CD患者术后30天IASC的发生率为9.7%, 如果患者在手术前用皮质激素并伴有腹腔内脓肿, 术后IASC的发生率为40%[15]; 2 638例CD手术患者中, 术后90天内并发症发生率为23.8%, 其中, 肠道相关并发症为63.2%, 感染性并发症为33.9%, 切口相关并发症为19.9%[16]。CD患者10年后初次切除复发再次切除的累积概率为30%～44%[15]。由此看出, 手术是疾病进展到一定阶段的妥协治疗手段, 对于缓解患者长期身体痛苦作用有限。

综上所述, 促进IBD患者肠黏膜愈合能明显改善疾病进程, 减少疾病复发, 且相较于手术切除, 通过促进肠黏膜愈合实现IBD患者疾病的长期缓解能免除患者遭受手术后并发症的困扰, 更能提高患者的生活质量。

1.2 目前临床用药现状: 重点抗炎不能促进完全的肠黏膜愈合 目前治疗IBD的一线用药仍然以抗炎为主。根据世界胃肠病组织推荐的IBD全球实践指南 (2015年) 和中华医学会推荐的《炎症性肠病诊断与治疗的共识意见》(2018年, 北京)[14,17], 临床用药共有6类: 氨基水杨酸类、糖皮质激素类、免疫调节剂类、生物抑制剂类、抗生素类和益生菌。

除抗生素类和益生菌之外, 其他4类药物均以抗炎为主[18], 但这些药物对于促进肠黏膜愈合, 治疗IBD疗效有限, 尤其对于中重度的IBD患者, 目前临床约50%的中度至重度IBD患者不能达到黏膜愈合。一项CD临床试验表明, 即使抗肿瘤坏死因子 (tumor necrosis factor, TNF) 单抗和硫唑嘌呤药物联用, 并在生物标志物 (粪便钙卫蛋白和C反应蛋白) 的指导下进行早期积极药物治疗, 48周后, 患者内镜黏膜愈合比例仍低

于50%, 在同一研究的常规治疗组中这一比率更低, 仅为30%。2017～2019年UC进行的3项临床试验, 内窥镜下显示黏膜改善率分别为39.7%、27.7%和51.1% (使用药物分别为维多珠单抗、阿达木单抗和尤特克单抗)[19]。并且这些药物高发的不良反应和药物失效也给临床治疗带来极大困扰[18]。此外, IBD患者体内具有促炎特性的细菌菌株增多, 如变形杆菌、黏附性侵染性大肠杆菌和梭状芽孢杆菌, 相比之下, 能引起抗炎反应的细菌, 如克氏梭菌和费氏杆菌等细菌减少了, 而CD患者常用的抗生素辅助治疗会增加微生物的病害[20]。

目前, 主流的抗炎药物不能促进完全的肠黏膜愈合, 对于IBD疗效有限, 总结原因有3点: ① 仅为对症治疗。持续炎症只是IBD疾病的表观异常, 而IBD患者自身相关机制或细胞功能的异常则可能是疾病发生的根本原因, 故仅针对炎症的治疗无法改变疾病的本质; ② 治疗靶点单一。目前临床用药除益生菌类药物外, 其余5类药物作用靶点较为单一, 不能从多通路多靶点同时纠正或改善IBD的病理变化。但IBD是多因素共同作用的系统性疾病[5], 肠道内多个靶点均出现了异常, 故使用靶点单一的药物定会疗效欠佳; ③ 不良反应多发。目前临床所用化学药物, 一味针对某一靶点的激动或抑制, 容易导致机体与该靶点相关的生物学功能发生改变, 进而导致不良反应的发生[4]。因此, 当前这种重点靶向抗炎的治疗不能促进肠黏膜愈合, 改变IBD疾病进程。

2 巨噬细胞是促IBD患者肠黏膜再生的有效靶点

当肠道上皮屏障受损后, 巨噬细胞对于重建肠上皮屏障必不可少[7]。研究表明, 葡聚糖硫酸钠 (dextran sodium sulfate, DSS) 可损害结肠黏膜细胞之间连接引发结肠炎[21], 而经DSS处理过后的小鼠肠道破损处巨噬细胞聚集, 巨噬细胞集落刺激因子-1 (macrophage-colony stimulating factor-1, CSF-1) 缺乏的小鼠其肠道上皮屏障破坏后无法募集单核细胞, 其结肠上皮祖细胞也因此无法进行正常肠上皮损伤修复[22]。IBD患者体内异常的巨噬细胞影响了正常的修复过程。

2.1 肠道巨噬细胞在正常稳态环境中促进肠黏膜再生

炎症早期, 大量中性粒细胞进入组织, 单核细胞也被募集而来, 分化为炎性巨噬细胞, 表现为促炎作用, 对抗原产生适当的免疫反应。随后, 中性粒细胞吞噬杀菌后随即凋亡, 炎症进入消退阶段。而巨噬细胞专门检测和吞噬凋亡的中性粒细胞, 以防继发性坏死和炎症的进一步加剧。巨噬细胞经“find me”信号 (如溶血磷脂酰胆碱、鞘氨醇1-磷酸、趋化因子CX3CL1等) 被引导至凋亡细胞附近, 通过“eat me”信号 (如膜联蛋白-1、磷脂酰丝氨酸) 吞噬凋亡细胞, 而通过“don't eat me”抑制信号保护活细胞。一旦巨噬细胞经胞葬作用, 其表型发生转化, 多转变为消炎表型M2型[7], 使巨噬细胞主要发挥促进炎症消散和组织修复再生的作用: 第一, 经胞葬作用后, 巨噬细胞核受体激活, 使其通过旁分泌或自分泌抗炎介质来维持和促进抗炎反应[23], 如产生转化生长因子-β (transforming growth factor-β, TGF-β)、白细胞介素 (interleukin, IL)-10等抗炎细胞因子并抑制核因子κB (nuclear factor kappa-B, NF-κB) 等促炎信号[24]; 第二, 胞葬信号联合M2型巨噬细胞诱导信号激活的巨噬细胞, 能将再生信号传递至邻近的结肠上皮祖细胞, 促进损伤后上皮的愈合[22], 如M2型巨噬细胞产生的精氨酸酶1 (arginase-1, Arg-1) 可将*L*-精氨酸转化成多胺, 多胺通过c-Myc和p21分子促进附近隐窝中肠道干细胞增殖分裂, 参与伤口愈合[25], 且此过程依赖于TAM受体酪氨酸激酶受体家族中Axl/Mertk受体胞葬信号[26]; 第三, 巨噬细胞通过改变其代谢和激活大量的吞噬受体等方式[24], 增加MertK、Axl、CD36等受体分子转录, 进一步强化、延长胞葬作用[23,24]。由此可以看出, 在正常的肠道环境中, 具有特定促进肠黏膜修复的巨噬细胞为M2型巨噬细胞[27], 且胞葬作用与巨噬细胞促进修复信号表达紧密相关[28,29]。

除直接促进肠道干细胞再生外, 巨噬细胞辅助其他细胞功能以维持肠上皮屏障完整的作用也不容忽视, 研究表明, 如阻断单核细胞向巨噬细胞的分化、Paneth细胞产生抗菌肽能力减弱、富含亮氨酸重复序列的G蛋白偶联受体5阳性 (leucine rich repeat containing G protein-coupled receptor 5$^+$, Lgr5$^+$) 肠道干细胞和M细胞的分化均受到影响[30], 这更加表明巨噬细胞在肠道内修复微环境中多靶点的复杂作用和不可或缺的重要地位 (图1)。

2.2 IBD患者巨噬细胞异常影响黏膜修复

IBD患者表现出明显的促炎巨噬细胞增多, 且巨噬细胞的胞葬作用和其他细胞的联系均出现异常。单核细胞和促炎性M1巨噬细胞在IBD患者固有层中明显增加。侵入肠组织的固有层单核细胞和M1巨噬细胞通过破坏紧密连接蛋白和诱导上皮细胞凋亡直接促进上皮屏障破坏, 从而驱动IBD肠道炎症[31]。目前, 与IBD相关的至少163个易感基因位点已经确定[32], 而吞噬凋亡小肠上皮细胞的肠道巨噬细胞过表达的基因与IBD的41个易感基因重叠, 如*IL-12B*、淋巴细胞特异性蛋白1 (lymphocyte-specific protein 1, *LSP1*) 等基因, 这一事实表明, 巨噬细胞胞葬能力下降与IBD发病关联紧密[7]。另外, Paneth细胞功能异常在CD患者中很明显, 并且可能是单核细胞对Wnt-配体刺激不足的结果[30]。

综上所述, 由于IBD患者自身基因、环境等因素以

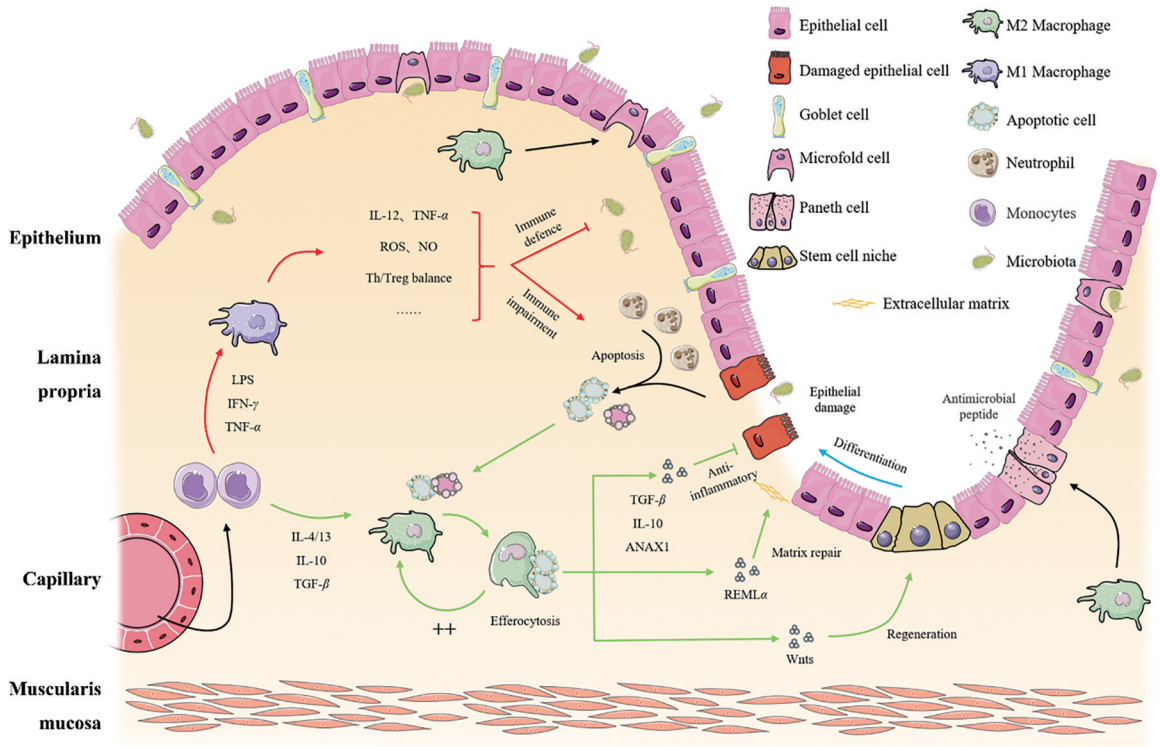

Figure 1 Multiple targets of macrophage in regulating inflammation and promoting mucosal healing. LPS: Lipopolysaccharide; IFN-γ: Interferon gamma; TNF-α: Tumor necrosis factor alpha; IL-4/13: Interleukin-4/13; IL-10: Interleukin-10; TGF-β: Transforming growth factor-beta; IL-12: Interleukin-12; ROS: Reactive oxygen species; NO: Nitric oxide; ANXA1: Annexin A1; Relmα: Resistin-like molecule alpha; WNTs: Wnt signaling pathway. Some elements of this figure were adapted from Servier Medical Art (http://smart. servier. com/), licensed under the Creative Commons Attribution 3.0 Unsupported License (https://creativecommons.org/licenses/by/3.0/)

及长期受炎症环境的影响, 患者自身肠道内, 以巨噬细胞为代表的黏膜修复过程或相关细胞机制出现异常, 故单纯的抑制炎症不可能实现良好的肠黏膜愈合, 而调控异常机制使其恢复正常稳态的生理过程则是当下之需。

3 基于调节巨噬细胞具有促进肠黏膜愈合潜在活性的药物及靶点

针对第二部分提到的异常, 国内外研究者都进行了广泛的探索。西医药能够精准地靶向治疗, 改变细胞的异常功能或细胞间的联系, 以促进IBD患者肠黏膜愈合[33]; 而中医药具有抗炎、黏膜修复和免疫调节多靶点药效同时进行的优势。另外, 长期经年的使用, 使得中药用法与剂量易于调控, 不良反应相对较低。因此中西医在促进肠黏膜修复、治疗IBD方面都具有独特的优势。

3.1 西医药基于巨噬细胞调节促进肠黏膜愈合 首先, 直接靶向巨噬细胞极化, 促进M2型巨噬细胞产生。IL-4作用于巨噬细胞的主要功能是使巨噬细胞极化为替代激活巨噬细胞[34]。IL-4激活的巨噬细胞可以修复肠黏膜, 减轻结肠炎炎症。IL-4可通过激活巨噬细胞中信号传导及转录激活蛋白6 (signal transducer and activator of transcription 6, STAT6) 促进肠道组织修复[35]。经IL-4处理的小鼠腹腔巨噬细胞以STAT6分子依赖的方式过表达Wnt2b、Wnt7b和Wnt10a, 激活Wnt信号通路促进2,4,6-三硝基苯磺酸 (2,4,6-trinitrobenzene sulfonic acid, TNBS) 处理的小鼠的黏膜修复[36]。体内外实验证明, 经IL-4处理的巨噬细胞能促进上皮细胞伤口修复[37], 且经冷冻保存后仍有抗结肠炎的作用[38]。第二, 靶向巨噬细胞胞葬, IL-4起到组织修复作用依赖于巨噬细胞胞葬信号Axl/Mertk, 故巨噬细胞Axl/Mertk可能是起治疗作用的潜在靶点[26,39]。第三, 靶向单核细胞/巨噬细胞与其他细胞的关系, 缺乏CSF-1的小鼠单核细胞不能正常分化为巨噬细胞, 同时, 小鼠肠隐窝内Paneth细胞、Lgr5$^+$肠干细胞和M细胞正常功能均受到影响, 表明CSF1具有在损伤、炎症或化学疗法后恢复上皮功能的潜力, 且这种作用已在其他器官中得到证实[30]。除以上所写之外, 表1[19,25,35,37,39-49]详细列出了一些药物或方法及其作用靶点。

3.2 中药促进肠黏膜愈合 大量研究表明, 中医药对于IBD肠黏膜愈合有良好作用。中医认为IBD病机复杂, 总属本虚标实, 虚为正气不足, 脾肾两虚, 机体免疫

Table 1 Examples of methods/drugs that promote mucosal repair and relative targets. CCR2: CC chemokine receptor-2; DSS: Dextran sodium sulfate; IBD: Inflammatory bowel disease; TNBS: 2, 4, 6-Trinitrobenzene sulfonic acid; Trem2: Triggering receptor expressed on myeloid cells 2; TLR9: Toll-like receptor 9; LXA_4: Lipoxin A_4; GM-CSF: Granulocyte-macrophage colony stimulating factor

Drug or method	Target	Model or experiment	Ref.
Inhibition of pro-inflammatory monocyte derivation into macrophages	Blocking CCR2	DSS-induced colitis in mice	[19,40,41]
Increasing the number of macrophages/ monocytes that promote mucosal healing	Increased adhesion of $\alpha4\beta7$ monocytes	Vedolizumab treatment for IBD	[19,42]
	Increased adhesion of $Ym1^+$ $Ly6C^{hi}$ monocytes	DSS-induced colitis in mice	[43]
IL-4	IL-4R in macrophage	DNBS-induced colitis in *Rag1*$^{-/-}$ mice	[35,37]
Promoting efferocytosis	Axl/Mertk in macrophage	DSS-induced colitis in *Axl*$^{-/-}$*Mertk*$^{-/-}$ mice	[39]
Resolvin E1	ChemR23 receptor	DSS-induced colitis in mice	[44]
Resolvin D1	LXA_4 receptor	DSS-induced colitis in mice	[45]
Maresin 1	M2 macrophage polarization	DSS/TNBS-induced colitis in mice	[46]
Krill oil	Promoting M2 polarization of macrophages; enhancing macrophage-mediated intracellular bacterial killing	Th2 cell imbalance induced colitis in pigs	[47]
GM-CSF	Reduction in neutrophil numbers and increasing accumulation of CD11b monocytic cells	DSS-induced colitis in mice	[48]
Trem2	Trem2 signaling	DSS-induced colitis in mice; *Trem2*$^{-/-}$ mice	[25]
TLR9 agonist	Promoting IL-10 secretion	DSS-induced colitis in mice	[49]

力低下; 实为毒邪久伏体内蕴结肠道, 使免疫系统异常, 炎症反应亢进, 损伤肠黏膜屏障, 本虚标实相互为害, 共同参与疾病的发生、发展过程[50]。故治疗IBD, 中医多补泻兼施、清温并用, 以解伏毒, 补脾肾为根本[51]。许多方药对于“巨噬细胞−肠黏膜修复”这一整合单元具有潜在的调控作用, 如常用的清热类和补益类方药, 多从调节免疫微环境和黏膜修复保护角度进行治疗。

在调节免疫微环境方面, 清热类方药效果突出。以巨噬细胞为代表, 黄连中的小檗碱可以抑制DSS模型小鼠的结肠巨噬细胞产生促炎细胞因子, 抑制其促炎功能, 并促进结肠中巨噬细胞凋亡, 促进DSS诱导的小鼠结肠炎的恢复[52]。黄芩苷可以上调干扰素因子4蛋白的表达并能逆转脂多糖 (lipopolysaccharide, LPS) 诱导的巨噬细胞激活, 通过调节巨噬细胞极化, 从而改善DSS诱导的结肠炎小鼠的炎症反应[53]。对于复方的使用, 王永强等[54]使用溃结2号方 (包括黄芪、太子参、白术、生地、鸡眼草、地锦草、桃仁、川芎), 可以降低M1型巨噬细胞水平, 从而达到促进溃疡性结肠炎创面愈合的作用, 且长时间用药较短期治疗具有明显优势。针对免疫微环境的调节, 目前中医药对其机制研究尚浅, 仍以抗炎保护为重点, 较少关注免疫细胞对肠黏膜修复的直接促进作用。

在促进肠黏膜再生修复中, 补益类方药具有潜在的功能。如黄芪中黄芪多糖通过降低UC模型大鼠结肠组织中的髓过氧化物酶 (myeloperoxidase, MPO) 活性及肿瘤坏死因子α (tumor necrosis factor alpha, TNF-α) 含量减轻肠道炎症反应, 从而减轻黏膜损伤[55,56]。四君子汤是健脾益气的经典方剂, 对于肠黏膜修复有良好作用, 研究表明, 其可通过维持肠上皮细胞的紧密连接以修复肠黏膜的机械屏障、促进杯状细胞分泌黏蛋白以修复肠黏膜的化学屏障[57]、抑制派伊尔结细胞的凋亡以修复肠黏膜的免疫屏障[58]、提高肠道优势菌群的数量以修复肠黏膜的生物屏障[59]。但对于补益方药通过调控免疫系统以实现炎性修复鲜有研究。

除上述实例外, 表2[4,55,56,60-75]详细列出了治疗IBD常用的中药、有效成分及靶点, 突出中医药用药特色和当前研究的局限性。

4 讨论

生理状态下, 免疫细胞与肠黏膜“损伤−愈合”平衡息息相关, 以维系肠道黏膜屏障稳态。针对IBD的治疗, 靶向免疫细胞不仅促进了炎症消散, 还能够在功能水平上使异常的肠上皮细胞趋向正常。以巨噬细胞为例, IL-4促进肠道黏膜修复依赖于巨噬细胞胞葬[39]; 巨噬细胞中Wnt信号通路对于激活肠道干细胞, 促进肠隐窝再生是不可或缺的[36,76,77]; 正常巨噬细胞对于Paneth细胞产生抗菌肽、M细胞的分化也必不可少[30]。

其他器官的修复与巨噬细胞也密切相关。腹腔中成熟的巨噬细胞在出现损伤时, 能够直接进入内脏器官中的损伤位点, 从而立即启动快速修复过程[78]。并且越来越多的研究表明, 以巨噬细胞表型及胞葬功能为靶点的治疗对修复愈合具有促进作用。如糖尿病模型小鼠其创面巨噬细胞存在从促炎型到修复型的表型转化障碍[79]。在修复后期创面周围聚集大量的巨噬细胞, 诱导型一氧化氮合酶 (inducible nitric-oxide synthase,

Table 2 Examples of traditional Chinese medicine for the treatment of IBD and its potential targets

Traditional Chinese medicine	Compound	Model	Target
Scutellariae Radix	Baicalin	DSS-induced colitis in mice	Anti-inflammation; promoting M2 polarization of macrophages[60,61]
Andrographis Herba	Andrographolide	*In vitro* A549/NF-κB-luc cells model; DSS-induced colitis in mice	Anti-inflammation[62]; induced autophagy in macrophages[63]
Coptidis Rhizoma; Cortex Phellodendri	Berberine	DSS-induced colitis in mice; TNBS-induced colitis in mice	Anti-inflammation[60]; promoting M2 polarization of macrophages[61]; maintain the intestinal residence of enteric glial cells (EGCs) and modulate the interactions between EGCs, epithelial cells and immune cells[64]
Artemisiae Annuae Herba	Artesunate	DSS-induced colitis in *Rag1*$^{-/-}$ mice; TNBS-induced colitis in rat	Inducing apoptosis in macrophages and dendritic cells of lamina propria[61,65]; modulating Th1/Th17 balance[66]
Ginseng Radix et Rhizoma	Ginsenoside	*In vitro* IEC-6 cells model	Promoting cell proliferation and migration; upregulating expression of E-cadherin and α-catenin[67]
	Panaxan	DSS-induced colitis in rat	Modulating the intestinal microflora; down-regulating the pro-apoptotic proteins; upregulating anti-apoptotic protein and tight junction protein expression[68]
Glycyrrhizae Radix et Rhizoma	Glycyrrhizic acid	DSS-induced colitis in mice	Upregulating tight junction protein expression[4]
Astragali Radix	Astragalus saponin	*In vitro* IEC-6 cells model	Promoting cell proliferation; upregulating expression of α-catenin[67]
	Astraglan	TNBS-induced colitis in rat	Anti-inflammation; upregulating EGF level, occludin and zonulaoccludens-1 (ZO-1) expression[55]; regulating the differentiation of T cells[60]; modulating the intestinal microflora[56]; promoting intestinal epithelial cells proliferation[69]
	Astragaloside IV	TNBS-induced colitis in rat	Promoting intestinal epithelial cells and stem cells proliferation[70]
Paeoniae Radix Alba	Paeoniflorin	*In vitro* Caco-2 cells model; TNBS-induced colitis in rat	Anti-inflammation[60]; upregulating Caco-2 cell tight junction proteins[71]; modulating Th1/Th17 balance[61]
Ophiopogonis Radix	Polysaccharide	*In vitro* IEC-6 cells model	Upregulating tight junction protein expression; inhibiting chemokine secretion of macrophage[72]
Pogostemonis Herba	Patchoulic alcohol	*In vitro* RAW264.7 cells model; DSS-induced colitis in mice	Decreasing the expression of pro-inflammatory cytokines of macrophages[73]; reducing ROS levels of macrophages[74]
Rhei Radix et Rhizoma	Rhuharb polysaccharide	TNBS-induced colitis in mice	Inhibition of epithelial cell apoptosis[75]

iNOS) 高表达, Arg-1 低表达, 而去除创面中 M1 型巨噬细胞, 能够启动糖尿病小鼠难愈创面的快速上皮化的过程, 促进创面愈合[80]。阻断巨噬细胞 Axl 和 Mertk 胞葬信号后, 肺损伤小鼠肺伤口愈合迟缓, 修复不良[39]。因此, 通过干预巨噬细胞表型转化及胞葬功能, 进而促进慢性创面的愈合, 将成为研究和临床治疗的有效手段。

中医药治疗 IBD 患者肠黏膜愈合效果明显, 且具有靶点多、安全性高的优势, 是开发治疗 IBD 药物的巨大宝库。如青黛中含有芳烃受体的配体, 可诱导 IL-22 的产生以介导黏膜的再生, 促进 UC 患者的黏膜愈合[81], 已广泛作为临床抗结肠炎的治疗药物。此外, 青黛还对类固醇依赖的 UC 患者和使用过抗 TNF-α 的患者也有治疗作用, 能够显著提高患者临床反应率和黏膜愈合率, 降低粪便钙卫蛋白水平[82]。虽然中医药研究越来越重视免疫微环境调节和促肠黏膜修复, 如清热类和补益类方药对于“巨噬细胞–肠黏膜修复”这一整合单元中关键环节有潜在的调控价值, 但目前多数研究都是从简单的抗炎角度去实现组织损伤的保护, 或从直接的修复再生角度去实现肠黏膜修复, 对依据完整的通路链条去实现组织再生关注不足。综上所述, 未来应该立足于炎性修复的全链条去关注药物的治疗策略, 才能真正发挥以 M2 型巨噬细胞为代表的、与组织再生修复有关的免疫细胞在炎症损伤性疾病中的关键作用, 也凸显出中医药“扶正祛邪”理论的科学性和优效性。

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