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炎症性肠病的发生发展关键环节及其干预药物

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摘要 近年来, 炎症性肠病(inflammatory bowel disease, IBD)的发病率显著上升, 但是仍然缺乏有效的治疗策略. IBD通常是环境因素干扰、遗传易感和肠道微生物异常等相互作用的结果. 鉴于其发病机制的复杂性, 确定IBD的关键发展阶段将成为突破当前临床药物使用瓶颈的重要环节. 基于此, 本文详细综述了多种因素对IBD发生的影响, 重点阐述了氧化应激介导的肠上皮细胞异常死亡引起的肠上皮细胞屏障的受损, 肠道免疫微环境失调导致的免疫屏障损害等几个关键环节, 同时, 根据上述关键环节探讨了IBD的新治疗策略, 为用于临床药物干预的新药物递送系统提供新思路.

关键词 炎症性肠病, 发病因素, 关键环节, 新治疗策略, 干预药物

炎症性肠病(inflammatory bowel disease, IBD)是一种慢性肠道炎症性疾病, 主要包括克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC). 近年来全球的IBD发病率不断上升, 在北美、大洋洲和欧洲等地区高达0.3%[1]. IBD的临床用药存在部分患者对药物不敏感、易产生药物不良反应等问题导致其尚无法治愈. 大量临床研究表明, IBD是环境因素干扰、遗传易感与肠道微生物异常等相互作用的结果[2]. 由于IBD发生发展涉及的病理过程十分复杂, 发病机制至今不明. 肠上皮细胞屏障与肠免疫屏障受损是其中两个关键环节: (ⅰ) 氧化应激介导的肠细胞异常死亡, 如凋亡、铁死亡与焦亡, 引起肠上皮细胞屏障受损[3]; (ⅱ) 中性粒细胞、巨噬细胞(macrophages, Mφ)、树突状细胞(dendritic cell, DC)与辅助性T细胞(T helper cell, Th)等免疫细胞的异常活化导致肠免疫屏障受损[4]. 恢复氧化还原平衡、调控肠道微生态以及修复肠上皮细胞屏障等新策略的提出有望给患者带来新的选择. 恢复氧化还原平衡策略旨在通过减少活性氧(reactive oxidative species, ROS)的产生, 以及加速ROS的清除, 来调节IBD肠道环境稳态; 而肠道菌群疗法与肠黏膜损伤修复疗法, 一方面调控微生物的生长以恢复肠道微生态, 另一方面诱导肠上皮细胞增生, 防止肠黏膜损伤, 以修复肠上皮细胞屏障. 此外, 新型生物制剂与小分子药物的发现以及药物递送系统的设计开发, 有望开启IBD治疗的新篇章. 因此, 本文基于IBD发病因素之间的复杂关系, 探讨关于IBD发生发展

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的关键环节及治疗策略和药物的最新进展.

1 IBD的发病因素

除环境因素外, IBD的发病主要受到遗传易感性和肠道微生物群改变之间的相互作用的影响[2](图1). 因此充分了解各因素与IBD发病机制之间的关系, 同时深入研究其相互作用的网络效应, 将有助于寻找治疗IBD的潜在靶点.

1.1 遗传易感性

遗传学早期研究发现IBD的发生存在家庭聚集现象, IBD患者的一级亲属患病的相对风险为正常人群的5倍以上[5], 其中CD的遗传风险比UC更高[6]. 2001年发现第一个易感基因*NOD2*/*CARD15*以来, IBD易感基因研究取得了重大突破[7]. 随着全外显子测序和全基因组关联研究(genome wide association study, GWAS)等基因组技术的飞速发展, 陆续有超过240个基因座被证明与IBD易感性密切相关[8]. 例如, 编码细胞内模式识别受体的*NOD2*/*CARD15*基因与编码Toll样受体4的*TLR4*基因, 都是与细菌识别相关的IBD易感基因[9]; 编码TLIA的*TNFSF15*基因是与IL23/Th17信号途径相关的易感基因, 其单核苷酸多态性突变会增加CD患病风险[10]; 除*TNFSF15*基因外, 编码IL23受体(IL23R)的基因也被证明可通过激活TYK2、Janus激酶(Janus Kinase, JAK)和STAT3等显著降低IBD发病率[11]. 因此IL23/Th17信号途径中*TNFSF15*, *IL23R*, *TYK2*, *JAK2*和*STAT3*等相关基因与IBD易感性密切相关. 此外, 研究人员已证实*ATG16L1*, *IRGM*, *ULK1*, *LRRK2*和*MTMR3*是与自噬相关的IBD易感基因, 其在固有免疫与获得性免疫中发挥重要作用, 同时研究显示CD发病风险与患者携带的自噬相关基因成正比[12]; *LAMB1*, *HNF4A*, *CDH1*及*GNA12*基因被证实与UC患者肠上皮细胞屏障的完整性破坏有关[13]. 东亚地区IBD患者的GWAS分析, 与欧洲IBD患者数据联合分析对比, 鉴定出16个新的IBD基因位点[14]. 因此定位易感基因遗传序列, 阐明不同个体之间的共同作用机制, 探究基因与环境等其他致病因素之间的内在联系, 将有利于完善新药研究设计理论基础.

1.2 肠道微生物异常

肠道微生物作为外部环境和肠道黏膜联系的枢纽, 在宿主体内发挥病原体防御、免疫发育等作用[15]. 肠道微生物对于维持机体健康与介导疾病也具有重要意义, 且通常受到宿主本身与环境因素的影响[16]. IBD患者的肠道微生物群与健康人群有异. 首先, IBD患者

图 1 IBD各发病因素之间的相互作用
Figure 1 The interaction between pathogenic factors of IBD

肠道中微生物组多样性降低. 氧化应激的增强, 使专性厌氧菌拟杆菌门、厚壁菌门和需氧菌放线菌门等有益菌种减少, 兼性厌氧菌和变性菌门等促炎菌种增加, 使得肠黏膜易受损引发肠道炎症[16]. 此外, 患者肠道微生物异常也会影响一系列代谢物的产生/转化, 如短链脂肪酸(Short-chain fatty acid, SCFA)、胆汁酸和色氨酸等. SCFA是肠道细菌发酵碳水化合物的产物, 有助于调节宿主免疫系统和维持宿主健康[17]. 研究发现, UC患者的粪便SCFA水平有不同程度的降低[18]. 胆汁酸是一种餐后被分泌到胃肠道辅助消化的物质, 可经肠道微生物代谢为3-酮胆汁酸等次级胆汁酸进一步调节宿主免疫反应[19]. IBD患者中存在3-酮胆汁酸与异石胆酸基因水平的显著降低[20]. 色氨酸是一种必需氨基酸, 经菌群代谢后产生的吲哚及其衍生物可通过激活多环芳烃受体等方式调节黏膜免疫[21]. 与在UC患者中的研究结果一致, 葡聚糖硫酸钠(dextran sulfate sodium salt, DSS)诱导的小鼠结肠炎模型血清中吲哚、吲哚丙酸水平均下调[22]. 在诸多因素共同作用下, 机体内多个致病机制将被启动, 加快IBD的发展, 故进一步探究IBD病理过程中关键环节有助于全面了解IBD.

2　IBD病理过程中关键环节

2.1　氧化应激介导的肠细胞异常死亡

早期研究指出, 在IBD患者与结肠炎动物模型的肠内存在ROS累积, 其与IBD的严重程度相关[23]. ROS指由线粒体有氧呼吸电子传递链或氧化酶代谢产生的超氧阴离子($O_2^{\bullet-}$)、过氧化氢(H_2O_2)和羟基自由基(•OH)等活性分子. 在IBD中ROS可激活细胞内转录因子、蛋白质复合物和激酶介导的信号通路(如NF-κB, MAPK与NLRP3)诱导炎症加剧[24]. 这表明ROS累积引起的氧化应激在IBD的进展中扮演重要角色, 但目前氧化应激参与IBD的病理机制仍然未得到很好的解释, 越来越多研究表明, ROS累积介导的细胞异常死亡是IBD的关键病理过程, 主要包括凋亡、铁死亡以及焦亡(图2).

细胞凋亡是最常见的细胞死亡方式, ROS可通过线粒体途径诱导肠道上皮细胞凋亡[25], 这可能与长期暴露于氧化环境引起的DNA损伤有关[26]. Bax/Bak形成低聚物复合体可由DNA损伤诱导形成, 随后插入到线粒体外膜孔隙, 导致线粒体渗透压改变, 跨膜电位丢失, 从而促使细胞色素C(cytochrome C, Cyt C)从线粒体释放到细胞质, 并与细胞凋亡激活因子1结合形成凋亡复合体, 活化Caspase-9前体, 进而激活Caspase-3和Caspase-7, 从而诱发细胞凋亡. 此外, DNA损伤还会激活Bcl-2家族促凋亡因子, Bcl-2改变膜电位使线粒体通透性增加, 从而线粒体内促凋亡因子Cyt C释放到胞质中, 启动Caspase级联反应, 最终导致细胞凋亡[27].

铁死亡是近年来发现的一种依赖铁与ROS的细胞氧化性死亡方式[28], Mayr等人[29]发现, 在IBD中也有铁死亡的发生且通常伴随有铁过量以及ROS、谷胱甘肽(glutathione, GSH)、谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPx4)的异常. 新证据表明, 在UC患者和

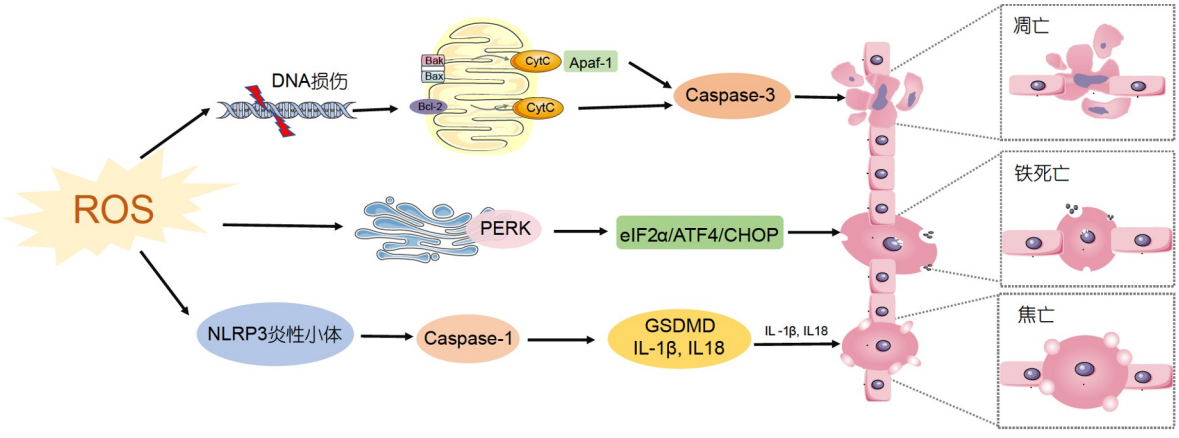

图 2　氧化应激在肠上皮中介导的异常死亡方式

Figure 2　Abnormal deaths mediated by oxidative stress in intestinal epithelium

结肠炎小鼠结肠上皮细胞中，胞内蛋白激酶样内质网激酶通过激活并调控eIF2α/ATF4/CHOP信号通路，介导铁死亡的发生[30].

细胞焦亡又称为炎性坏死，是一种高度炎性形式的程序性细胞死亡[31]. NLRP3炎症小体的组装和激活是细胞焦亡发生的关键环节, 研究显示, 过量的ROS累积可通过激活NLRP3-Caspase-1信号通路促进炎性因子IL-1β和IL18的生成，进一步裂解胃泌素D蛋白启动经典焦亡途径[32]. ROS介导的经典细胞焦亡途径在IBD的发生发展中扮演不可或缺的角色，因此进一步阐明其信号转导机制对后续治疗IBD具有指导意义.

肠细胞异常死亡会导致肠上皮细胞屏障障碍，一方面致病菌或抗原等有害物质可通过肠上皮细胞屏障缺口入侵肠壁，进而诱导过度的免疫应答[33]；另一方面细胞来源的物质，在有关细胞死亡后也会继发性缺失, 致使肠道通透性增加. 例如, 杯状细胞可分泌黏蛋白2(mucin2, MUC2), 其缺失可在小鼠模型中诱发自发性结肠炎[34]; Paneth细胞可分泌α-防御素, 研究发现Paneth细胞分泌异常会导致抗菌相关的自噬缺陷[35]. 因此，恢复氧化还原平衡并阻断肠细胞异常死亡有利于维持肠上皮细胞屏障，这可能成为阻止IBD进程的重要策略.

2.2 肠道免疫微环境失调

肠道中过度激活的免疫应答引发的肠黏膜炎症是IBD显著的病理特征. 肠道在炎症早期存在中性粒细胞浸润，血液中存在白细胞水平上升，它们通过介导氧化反应和蛋白水解损伤肠上皮细胞屏障，并释放多种炎症介质来加剧炎症[4]; 一般情况下, 中性粒细胞凋亡而后炎症消退, Mφ则通过表达鞘氨醇-1-磷酸(sphingosine 1-phosphate，S1P)等“找到我”信号找到并吞噬凋亡的中性粒细胞，从促炎型M1转化为抗炎型M2发挥清除作用，帮助机体消除炎症[36,37]. 但据报道，吞噬凋亡肠上皮细胞的肠Mφ过表达41个与IBD易感基因重叠的基因[38], 这提示Mφ吞噬凋亡细胞作用的缺陷可能与IBD的发生密切相关. 与健康人相比，CD与UC患者结肠中多存在M1的富集[39]，M1可分泌大量IL-23, IL-1β, 肿瘤坏死因子α(tumor necrosis factor α, TNF-α)等促炎因子[40], 其中IL-1β具有诱导致病性Th17细胞转化和扩增的能力[41]；M2产生脂氧素A4(lipoxin A4, LXA4)可限制中性粒细胞进一步进入损伤部位，但在严重UC患者中发现脂氧素的生物合成存在缺陷[42], 且通过激活LXA4受体发现炎性Mφ可被抑制从而改善结肠炎，这进一步说明LXA4与IBD发生或发展确有一定的相关性.

肠道微环境中DC可作为固有免疫和适应性免疫的桥梁，识别并呈递抗原，与T细胞、B细胞和肠上皮细胞相互作用, 维持黏膜稳态或诱导机体免疫耐受[43]. IBD患者体内潜在的耐受性树突状细胞缺乏，这与炎症程度显著相关[44]. 相较于正常黏膜(通常只表达TLR3，TLR5)，CD和UC患者DC中TLR2和TLR4表达水平显著升高，其中CD患者黏膜上DC还存在CD40分子的表达上调，分泌更多的IL-12和IL-6[45]. CD患者的DC表达趋化因子受体CCR7，CCR7可以与趋化因子CCL19和CCL21结合辅助DC黏附于炎症黏膜中，进一步促进炎症[46]. 模式识别受体(如TLR4)的异常表达与异常受体反应可能是DC错误地识别共生细菌, 并诱导针对病原体的Th1和Th17炎性免疫反应的重要基础[47,48]. CD通常被认为是Th1和Th17细胞的产生和激活加剧的结果, 存在主要细胞因子IL-12，IL-23，IFN-γ和IL-17的升高，而UC则被认为受Th2和Th9细胞及其主要细胞因子IL-13，IL-5和IL-9驱动[49,50]. 此外，肠道黏膜中也存在Th17细胞浸润[51]，主要是外周血中Th17细胞数量增多，炎症黏膜中IL-17，IL-21，IL-23等几种主要的Th17细胞因子含量丰富[52]. 目前基于免疫失调的治疗在改善患者生活方面取得了重要进展，但免疫微环境是动态的而非静止的，治疗仍未达到治愈的目标. 参与IBD病理生理的细胞类型以及其动态变化有待进一步更详细地探究.

3 新治疗策略探索与新药进展

现有药物无法根治IBD，只能针对患者病症达到缓解症状、预防复发的用药目的. IBD发病率的持续增加，不仅严重影响患者生活质量与心理健康[53]，同时给国家与社会医疗造成严重的负担，因此基于现有发病机制开发治疗IBD的新药物是当前研究热点. 首先，近年来，基础和临床科学的最新进展极大地改变了人们对肠道微生物在IBD中的作用的认识, 另外IBD患者在长期接受免疫抑制药物的治疗后，其感染率和肿瘤易感性明显提高[54]，故通过调控肠道微生物以及应用“非免疫疗法”，来恢复肠道微生态、修复肠上皮

细胞屏障策略的提出已引起广泛关注. 其次, 氧化应激作为IBD发生发展中的关键环节被大量研究, 恢复氧化还原平衡治疗IBD的潜力也被逐渐挖掘. 最后, 在过去的十年里可用于IBD治疗的活性成分不断涌现, 但其存在消化道稳定性不足、生物利用率低以及药物不良反应较大等局限性, 因此寻找潜在治疗药物及改良药物制剂成为研发治疗IBD新药物的突破点. 下面将基于以上三方面展开讨论.

3.1　新治疗策略

(1) 调控肠道微生态, 重建/修复肠上皮细胞屏障. IBD是一种多菌性疾病, 微生物组可以通过诱导的细胞信号转导、增殖和神经递质生物合成在细胞水平上改变宿主生理状态, 导致肠黏膜和机体改变, 从而影响体内平衡、肠上皮细胞屏障功能、先天和适应性免疫反应和代谢[16]. 故恢复肠道微生物群对修复肠黏膜与恢复机体稳态意义重大.

恢复肠道微生物群主要在于通过不同方式调控肠道微生物的生长, 比如, 直接调控某一菌种的生长. Zhu等人[55]研究发现, 在厌氧条件下抑制肠杆菌科兼性厌氧菌呼吸和使用钨酸盐抑制硝酸盐还原酶可以控制其过度生长. CD患者的回肠黏膜被黏附侵袭性大肠杆菌(adherent invasive *Escherichia coli*, AIEC)异常定植, 这些大肠杆菌能够黏附并侵入肠上皮细胞, 据报道*FimH*基因产物可通过宿主CEACAM6受体促进AIEC与小肠上皮结合, 使AIEC抵抗免疫系统的清除. 基于此, 有学者提出, 开发一种利用与*FimH*结合进行对接的噬菌体并递送特异性剪切*FimH*基因组的CRISPR以去除AIEC定植[56], 这一创新策略为IBD治疗提供思路, 但仍需要具体的研究来支撑. 粪便微生物移植(fecal microbiota transplantation, FMT), 又称粪菌移植, 是一种通过将来自健康志愿者粪便中的菌落转移到患者肠道中以恢复肠道菌群的方法. 在四项随机对照实验中, 28% UC患者在接受FMT治疗后实现了临床缓解[57], 近年来FMT具有治疗UC的潜力逐渐成为一个共识. 饮食对肠道菌落有直接的影响, 通过控制饮食也有助于恢复肠道菌群和修复肠道黏膜. 与高脂肪、高糖的西方饮食相比[58], 富含水果与蔬菜、全谷物及海鲜的地中海饮食有利于增加肠道菌群多样性, 维持肠上皮细胞屏障的完整[59].

“非免疫疗法”也有望成为治疗IBD的新策略. 肠黏膜的修复依赖于上皮细胞的增殖分化, 首先损伤部位周围的肠上皮细胞迁移到病灶部位, 随后肠上皮细胞开始增殖分化以修复肠黏膜损伤缺口[60]. 基于上述过程, 修复肠上皮细胞屏障主要通过补充必需营养物或其他物质, 帮助肠黏膜愈合与抑制炎症减少肠道损伤这两个方向进行. 全肠内营养(exclusive enteral nutrition, EEN)治疗是一种直接输送营养物质至肠道从而改善活动性IBD的特殊饮食疗法. 因EEN存在促黏膜愈合效果好、副作用少和复发率低的优点, 目前已成为儿童CD患者的一线治疗手段[61]. 此外, 研究显示EEN对缓解成人活动性CD也有疗效且无明显的副作用[62]. 其治疗机制可能与调节肠道微生物群以及下调促炎细胞因子恢复黏膜损伤有关[63], 但目前尚无直接证据. 同时, Alghamdi等人[64]发现, 单一的ENN并不能引起肠道微生物的显著变化, 因此EEN是否通过微生物介导黏膜修复需要进一步确认. 尽管目前对EEN疗法研究尚不充足, 但现有数据表明未来EEN应用前景广阔. 补充肠道生长因子是黏膜愈合的有效手段之一. 皮下生长激素、表皮生长因子、粒细胞集落刺激因子等在促进IBD患者的黏膜愈合中效果显著[60]. 伴随着医学再生时代的到来, 依靠不同来源的间充质干细胞刺激肠上皮细胞增殖分化和调节免疫来促黏膜修复的间充质干细胞移植法也展现出广阔的前景[65]. 多能干细胞来源的间充质干细胞通过刺激肠上皮细胞增殖和增加胰岛素样生长因子的分泌, 可增加$Lgr5^{+}$肠干细胞的数量[66]. 人胚胎干细胞来源的间充质干细胞可有效抑制结肠中Th1增殖[67], 而多能干细胞来源间充质干细胞则直接抑制Th2分化[68]. 类器官培养与干细胞移植原理相似, 研究证明, 器官来源的肠道干细胞移植到受损结肠具有诱导组织再生的可能性[69]. 将体外培养类器官结肠移植到$Rag2^{-/-}DSS^{-}$结肠炎模型后, 供体细胞能够再生肠隐窝结构, 重塑肠上皮细胞屏障[69]. 间充质干细胞移植法成为一种恢复肠黏膜损伤治疗IBD的有前景的治疗方法, 再生医学在IBD中的应用仍值得进一步探究.

(2) 恢复氧化还原平衡. 结肠黏膜中蓄积的ROS引起的氧化还原不平衡是IBD患者的病理特征之一, 其严重影响肠道稳态, 导致持续的肠道炎症. 在正常生理状态下, 机体氧化还原反应处于动态平衡状态, 抗氧化系统可清除体内过多的ROS, 因此恢复氧化还原平衡有望成为IBD的新治疗策略(表1). 该策略通过增

表 1 恢复氧化还原平衡的策略

Table 1 Strategies for restoring redox balance

策略	手段	机制	文献
增加ROS清除	上调内源性酶	上调体内抗氧化酶HO-1, NQO1的表达	[70]
		上调SOD与GPx的活性	[71]
		上调CAT, SOD, GPx的活性	[72]
	补充非酶抗氧化剂	直接补充抗氧化剂如GSH, Trx-1	[73]
		间接从植物源性食物中补充抗氧化活性物质	[74]
		补充抗氧化剂核黄素	[78]
减少ROS产生	抑制线粒体ROS产生	MitoQ靶向抑制线粒体ROS产生	[80]
	抑制氧化酶催化反应	通过DPI抑制NOX活性	[81]
		通过别嘌醇抑制XO活性	[83]

加ROS的清除和减少ROS的产生达到恢复氧化还原平衡的目的. ROS的清除主要依赖于内源性酶和非酶抗氧化剂组成的抗氧化系统. 首先, 上调内源性酶的表达或活性可以增加ROS清除. 据报道, Nrf2-ARE通路的激活可提高抗氧化基因的表达, 进一步增加体内血红素氧合酶1(heme oxygenase-1, HO-1)、NAD(P)H醌脱氢酶1(NAD(P)H dehydrogenase quinone 1, NQO1)等内源性抗氧化酶的累积, 从而保护结肠炎小鼠的结肠细胞[70]. 研究表明, 通过补充精氨酸和GSH能够使超氧化物歧化酶(superoxide dismutase, SOD)与GPx的活性提高, 增加自由基的清除, 从而缓解DSS诱导的小鼠结肠炎模型体内氧化应激造成的损伤[71]. 另一项研究表明, 益生菌配伍沙棘在DSS诱导的小鼠结肠炎模型体内通过增强过氧化氢酶(catalase, CAT), SOD, GPx活性清除ROS以恢复氧化还原平衡[72]. 其次, 补充非酶抗氧化剂也是增加ROS清除的有效措施. 已有科学家证明, 直接补充抗氧化剂如GSH、硫氧还蛋白(thioredoxin, Trx-1)可直接与ROS相互作用, 清除ROS从而恢复氧化还原平衡[73]. 此外, 间接从植物源性食物中获取的具有抗氧化活性的生物活性化合物(如氨基酸)也有助于ROS的清除[74]. 部分氨基酸可通过自身结构特异性与自由基结合从而清除自由基, 如精氨酸[75]. 某些氨基酸也可通过增加抗氧化剂GSH的储备来缓解肠道氧化应激, 如L-谷氨酰胺[76]和甘氨酸[77]. 抗氧化剂作为辅助性治疗药物也具有较好的疗效, 一项关于CD患者的前瞻性临床研究表明, 除标准的药物治疗外, 补充抗氧化剂核黄素可改善全身氧化还原状态[78].

在炎症部位, ROS还可通过调控炎性因子加速其自身的产生, 加重肠道组织损伤[79], 因此减少ROS的产生也是一种重要手段. 特异性的ROS生成抑制剂通过抑制ROS的主要来源途径(线粒体中的氧化磷酸化过程及相关氧化酶催化反应)可有效减少ROS的产生. MitoQ是新发现的一种靶向线粒体的ROS生成抑制剂. 在人类IBD中, 多药耐药蛋白-1(multi-drug resistant associate protein 1, MDR1)基因与线粒体ROS清除所需的*SOD2*基因表达呈负相关, 研究表明MitoQ可显著降低线粒体ROS水平, 抑制NLRP3活性从而减缓MDR1缺陷小鼠和DSS诱导的结肠炎小鼠的慢性结肠炎的发展[80], 抑制IBD患者体内的ROS生成酶的功能也可有效阻断ROS的产生. 研究表明, NADPH氧化酶(NADPH oxidases, NOX)抑制剂二苯基氯化碘盐(diphenyleneiodonium, DPI)可以抑制ROS的产生从而减少与胃肠道炎症相关的氧化应激[81]. 而黄嘌呤氧化酶(xanthine oxidase, XO)抑制剂别嘌醇也被证实在治疗IBD方面明显优于免疫抑制剂[82], 并且与硫嘌呤联合使用后可以明显降低IBD患者体内XO活性, 以达到治疗的目的[83]. 恢复氧化还原平衡策略中药物的研究进展仍然落后于机制研究, 抗氧化应激药物的临床转化从实验室研究向临床是一个重要研究方向.

3.2 IBD创新药物研究进展

尽管传统药物和现有治疗方法很多, 但许多患者对药物不耐受或治疗无反应. IBD等慢性炎症性疾病的治疗需要具有新作用机制、给药方便和安全性高的药物(表2).

表 2　IBD新药研究进展

Table 2　Advance of emerging drug for IBD

类型	药物	药物类型	IBD类型	文献
生物制剂	Adalimumab	TNF-α阻滞剂	IIIb(UC)	[89]
	Abilumab	整合素(α4β7)拮抗剂	Ⅱb(CD), Ⅱb(UC)	[90,91]
	AJM300	整合素(α4)抑制剂	Ⅲ(UC)	[92]
	PF-00547659	抗MAdCAM抗体	Ⅱ(UC)	[84]
	Olamkicept	sIL-6R/IL-5复合物抑制剂	Ⅱ(UC)	[93]
	Brazikumab	抗IL-23抗体	Ⅱ(CD)	[102]
	Ustekinumab	抗IL-12/23-p40抗体	Ⅲ(UC)	[85]
	Guselkumab	IL-23p19抗体	Ⅱ-GALAXI-1(CD)	[86]
	Risankizumab	IL-23p19抗体	Ⅲ-FORTIFY(CD)	[87]
小分子药	Ozanimod	S1PR1/5受体调节剂	Ⅲ(CD), Ⅲ(UC)	[96]
	Etrasimod	S1PR1/4/5受体调节剂	Ⅲ(UC)	[97]
	Upadacitinib	JAK1抑制剂	IIIb(UC)	[89]
	Apremilast	PDE4抑制剂	Ⅱ(UC)	[99]

生物制剂能选择性地干预在IBD发病机制中发挥关键作用的特异性分子，如抗TNF-α抗体、抗整合素抗体[84]、抗白介素(interleukin，IL)类抗体[85~87]. 抗TNF-α单克隆抗体通过阻断TNF-α作用通路而发挥全身抗炎作用, 有较长且较好的临床使用基础, 尽管有出现免疫原性及失效快等问题，抗TNF-α单克隆抗体仍然是急性重症患者的首选药物[88]，包括英夫利西单抗(infliximab)、阿达木单抗(adalimumab)[89]、赛妥珠单抗(certolizumab)和戈利木单抗(golimumab)等. 抗整合素类抗体可以干扰白细胞向炎症部位的黏附、迁移, 起效慢但有稳定持久的缓解维持效果. 例如, 特异性阻断α4β7的Abilumab[90,91]和阻断α4β1，α4β7的AJM300[92]. 此外，抗IL-6R抗体Olamkicept[93]、抗IL-12/23抗体Brazikumab与Ustekinumab[94]等也为IBD临床治疗提供了一定帮助.

新型小分子药物主要包括抑制淋巴细胞迁移的S1P受体调节剂、抑制STAT通路的JAK抑制剂以及其他小分子药物. S1P受体调节剂已在临床证明对IBD患者的治疗安全有效[95]，如用于治疗中度至重度活动性UC的Ozanimod[96]和Etrasimod[97]. JAK是参与IBD发病机制中STAT通路中的重要分子, Upadacitinib作为一种选择性的口服JAK抑制剂, 在3期诱导试验中对中度至重度UC的诱导和维持治疗效果优于安慰剂[98]. 其他小分子制剂，如口服磷酸二酯酶(phosphodiesterase 4, PDE4)抑制剂Apremilast，对活动性UC患者的疗效在一项2期双盲实验中得到了验证[99].

此外，针对传统治疗药物以及新兴治疗药物普遍存在的稳定性欠佳、靶向性不强以及药物不良反应较大等不足, 药物的改造工作在持续地同步展开. 现有研究通过改善药物稳定性[100]、靶向递送药物至病理部位[101]设计了一系列药物递送系统以延长药物滞留时间, 提高生物利用度及最大程度减少潜在不良反应. 但治疗的有效性却还有待增强，安全高效的潜在药物的探索工作仍在进行. 中草药是中华文明的瑰宝，蕴含许多有益于IBD治疗的药物，其中小檗碱[102]等活性成分治疗IBD的机制被大量研究，或许从中草药中获取灵感有助于突破现有用药的局限性.

4　结论与展望

基于遗传背景, 探索我国IBD易感基因谱, 阐明基因与环境、微生物之间的内在联系可能成为我国IBD治疗的重要转折点. 针对IBD发生发展关键环节, 一方面通过加速ROS清除、减少ROS产生等手段来恢复IBD患者肠道氧化还原平衡，不仅有效减少肠上皮细胞异常死亡，而且有利于重塑肠上皮细胞屏障；另一方面肠道菌群疗法和非免疫疗法，从减缓IBD患者肠黏膜损伤着手，避免因使用免疫抑制药物而带来的潜

在感染风险. 虽然中草药中的有效成分如小檗碱对于IBD的治疗具有很好的疗效, 但生物利用度低、溶解性差等缺陷有待优化. 探索新治疗策略与研发创新药物以及利用药物递送系统有望为IBD的治疗带来新的曙光. 此外, 越来越多证据表明, 免疫检查点与肠黏膜免疫稳态联系密切, 如唾液酸结合免疫球蛋白样凝集素[103]. 通过靶向各免疫检查点来调节肠道免疫微环境, 或许有助于重塑肠黏膜免疫稳态. 目前IBD治疗的创新药物并未达到理想的特异性与安全性, 在分子或细胞水平进一步了解关键病理过程, 将有助于研发兼具特异性与安全性的治疗药物, 为每位患者和疾病的每个阶段带来更具体的治疗方法.

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IBD: essential links of pathogenesis and drugs for intervention

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The incidence of inflammatory bowel disease (IBD) has increased significantly in recent years but the efficient treatment strategies are still lacking. Generally, IBD results from the complicated interactions among interference of environmental factors, genetic susceptibility, and abnormal intestinal microorganism. Considering the complex pathogenesis, it will be a significant process to identify the key development stage of IBD for the purpose of breaking the bottleneck of clinic drug treatment. For this purpose, this review makes a detailed summarization on the effect of various factors on the disease occurrence with an emphasis on several key issues including the damage of the intestinal epithelial cell barrier caused by the oxidative stress-mediated abnormal death of intestinal cells, the impairment of the innate immune barrier induced by the dysregulation of the intestinal immune microenvironment. At the same time, this review explored new therapeutic strategies capable of targeting the key processes mentioned above, which will be useful for clinical drug intervention via advanced drug delivery systems.

IBD, risk factor, key process, new strategy, drug for intervention

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