

化疗所致肠黏膜炎的病理机制和治疗策略研究进展^Δ

晏晓晨*, 王宗奎, 叶生亮*(中国医学科学院输血研究所, 成都 610052)

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摘要 肠黏膜炎是恶性肿瘤化疗引起的常见并发症之一,严重影响化疗效果并降低患者的生存质量。本文系统综述了化疗所致肠黏膜炎的病理机制,涵盖肠道氧化性、炎症性、细胞凋亡性损伤以及肠道屏障受损和肠道菌群失调等多个方面。同时,本文对当前肠黏膜炎的治疗策略进展进行了全面总结,包括化学药物及复合材料、天然药物、中药复方、生长因子、血液制品干预以及粪菌移植等。未来可加强多学科交叉创新,结合动物模型和大样本临床试验,开发高效低毒的治疗药物以平衡化疗的毒性与抗肿瘤疗效。

关键词 肠黏膜炎;化疗;病理机制;治疗策略;研究进展

Research progress on the pathological mechanisms and therapeutic strategies of chemotherapy-induced intestinal mucositis

YAN Xiaochen, WANG Zongkui, YE Shengliang (Institute of Blood Transfusion, Chinese Academy of Medical Sciences, Chengdu 610052, China)

ABSTRACT Intestinal mucositis is a common complication induced by chemotherapy in malignant tumors, which severely compromises the efficacy of chemotherapy and reduces patients' quality of life. This article systematically reviews the pathological mechanisms underlying chemotherapy-induced intestinal mucositis, encompassing oxidative damage, inflammatory injury, apoptotic damage, disruption of the intestinal barrier, and intestinal dysbiosis. Additionally, it provides a comprehensive summary of current therapeutic strategies for intestinal mucositis, including chemical agents and composite materials, natural products, compound prescription of traditional Chinese medicine, growth factors, blood products, and fecal microbiota transplantation. Future efforts should strengthen multidisciplinary cross-innovation, integrating animal models and large-scale clinical trials to develop highly effective and low-toxicity therapeutic drugs that balance chemotherapy toxicity and antitumor efficacy.

KEYWORDS intestinal mucositis; chemotherapy; pathological mechanisms; therapeutic strategies; research progress

恶性肿瘤在全世界范围内呈现出较高的发病率与死亡率,严重威胁人类健康。目前,化疗仍是恶性肿瘤系统性治疗的核心手段之一,常见化疗药物包括蒽环类、铂类、紫杉烷类化合物以及抗代谢药等^[1]。然而,化疗药物因缺乏靶向性,常引发骨髓抑制、神经毒性及胃肠道黏膜损伤等毒性反应,其中化疗所致肠黏膜炎是最严重的并发症之一,主要临床表现为重度腹泻、腹痛、消化道出血及营养吸收障碍等,且约30%~40%的患者因肠黏膜炎导致化疗效果不佳,甚至增加感染性休克的风险^[2-3]。由于化疗所致肠黏膜炎的普遍性和挑战性,近年来受到业界较大关注,化疗所致肠黏膜炎的病理机制与治疗策略研究也取得了重要进展,其研究成果对提高肿瘤患者生活质量和改善肿瘤患者的预后具有重要的

临床应用价值和社会效益。本文就化疗所致肠黏膜炎的病理机制和治疗策略的相关研究进展进行综述,以期临床防治化疗所致肠黏膜炎提供参考。

1 化疗所致肠黏膜炎的病理机制

蒽环类化合物多柔比星、铂类化合物顺铂、抗代谢药5-氟尿嘧啶(5-fluorouracil, 5-FU)等化疗药物主要通过抑制DNA合成,诱导细胞凋亡,从而对肿瘤细胞产生杀伤作用;然而肠隐窝干细胞因高度增殖特性,在化疗过程中特别容易发生DNA损伤,最终诱发黏膜炎,主要表现为隐窝结构破坏、绒毛萎缩、组织更新能力下降以及肠道吸收与屏障功能障碍等^[4-5]。基于此,笔者对化疗所致肠黏膜炎的病理机制进行归纳总结,具体如下。

1.1 肠道氧化性损伤

活性氧(reactive oxygen species, ROS)作为机体正常代谢的有氧产物,在生理状态下可清除微生物和肿瘤细胞,但化疗药物引发的氧化-抗氧化失衡会导致氧化应激,并通过DNA损伤和细胞死亡机制加重肠黏膜炎^[6]。多柔比星可通过促进ROS产生,破坏人肠道类器官中的呼吸链复合物I,导致线粒体功能障碍,激活p53,进而引发肠道炎症^[7]。伊立替康以ROS依赖性方式

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* 第一作者 硕士研究生。研究方向:血浆蛋白质在化疗损伤中的应用。E-mail: sxsyanxiaochen@student.pumc.edu.cn

通信作者 副研究员,硕士生导师。研究方向:血浆蛋白质的开发与应用。E-mail: shengliang.ye@ibt.pumc.edu.cn

上调白细胞介素 1β (interleukin- 1β , IL- 1β)表达,诱导炎症细胞浸润并导致小鼠回肠组织损伤^[9]。5-FU可通过激活S100钙结合蛋白B/晚期糖基化终末产物受体/核因子 κ B(nuclear factor- κ B, NF- κ B)信号通路,抑制核转录因子红系2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)/血红素加氧酶1(heme oxygenase-1, HO-1)信号通路,促进炎症小体活化,从而引发小鼠肠绒毛萎缩和肠神经元死亡^[9-10]。顺铂可通过抑制磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, PKB, 也称Akt)/Nrf2信号通路和Wnt家族成员3A/ β -联蛋白(Wnt3A/ β -catenin)信号通路,加剧氧化损伤并抑制大鼠肠隐窝干细胞增殖^[11]。环磷酰胺则可通过抑制Nrf2抗氧化途径,并激活NF- κ B/丝裂原激活的蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路,从而导致小鼠肠黏膜损伤^[12]。

1.2 肠道炎症性损伤

炎症反应在维持生理稳态中具有清除病原体 and 促进组织修复的作用,但过度激活的炎症反应会导致病理性损伤。Toll样受体(Toll-like receptor, TLR)作为关键模式识别受体,可通过激活NF- κ B、PI3K/Akt/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)等信号通路调控炎症因子表达,在化疗药物诱导的肠黏膜炎中发挥核心作用^[13]。伊立替康可通过激活TLR4/NF- κ B信号通路,诱导小鼠出现胃肠道功能障碍^[14]。多柔比星可通过调控TLR2/TLR9信号通路,诱导小鼠肠黏膜炎的发生^[15]。5-FU可通过激活TLR/髓样分化因子88/NF- κ B/MAPK信号通路上调肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)、IL- 1β 、IL-6等促炎因子表达,从而加重小鼠肠黏膜炎^[16]。顺铂则可通过上调IL-6、TNF- α 及单核细胞趋化蛋白1(monocyte chemoattractant protein-1, MCP-1)表达,导致小肠绒毛损伤,加重小鼠肠黏膜炎^[17]。

1.3 肠道细胞凋亡性损伤

在生理状态下,肠上皮细胞凋亡主要发生于绒毛尖端和隐窝顶部的成熟分化细胞,而隐窝基底部的干细胞群凋亡程度较低,其凋亡过程与细胞更新速率相关^[18]。顺铂可显著升高小鼠绒毛和隐窝区域肠上皮细胞的凋亡率,可通过调节蛋白激酶R样内质网激酶/真核翻译起始因子2/激活转录因子4内质网应激信号通路,激活p38 MAPK/p53信号通路,抑制抗凋亡蛋白B细胞淋巴瘤2(B-cell lymphoma-2, Bcl-2)表达,上调促凋亡蛋白Bcl-2相关X蛋白(Bcl-2-associated X protein, Bax)表达,从而导致肠黏膜炎的发生^[19-20]。此外,5-FU可通过p53/p53上调凋亡调控因子途径诱导细胞凋亡,同时引发炎症反应,加重小鼠肠黏膜炎^[21]。环磷酰胺可升高Bax/Bcl-2比值,降低肠黏膜炎小鼠CD4⁺T和CD8⁺T细胞水平,增加凋亡细胞数量^[22]。

1.4 肠道屏障受损

肠黏膜功能屏障由肠黏膜基底膜、上皮细胞层及黏液层构成,肠干细胞通过调控上皮细胞增殖与死亡平衡,以及紧密连接蛋白表达和黏液屏障稳定性来维持肠道上皮屏障的完整性^[23]。肠道干细胞依赖Wnt/ β -catenin信号通路实现上皮再生,而顺铂能通过抑制Wnt/ β -catenin信号通路影响大鼠肠道干细胞及肠上皮细胞增殖^[11];环磷酰胺和伊立替康均可降低小鼠肠道组织中紧密连接蛋白表达,导致肠屏障功能受损^[22,24];5-FU则可通过激活环磷酸腺苷/蛋白激酶A/环磷酸腺苷反应元件结合蛋白信号通路,损伤大鼠肠黏膜屏障^[25]。

1.5 肠道菌群失调

肠道菌群作为维持肠道稳态的核心微生态系统,其平衡易被化疗药物扰乱,从而破坏肠道黏膜屏障的完整性,使肠黏膜更容易受到炎症介质的损害,形成恶性循环^[26]。伊立替康可通过促进细菌 β -葡萄糖醛酸酶的过表达引发肠黏膜炎,导致结肠癌患者肠道中韦荣氏球菌属、梭菌属和普雷沃氏菌属等致病菌的相对丰度升高^[27]。还有研究发现,采用FOLFOX方案(5-FU、甲酰四氢叶酸和奥沙利铂)治疗会破坏厚壁菌门和拟杆菌门菌群的组成,导致结直肠癌小鼠发生肠黏膜炎^[28]。环磷酰胺可降低小鼠肠道中益生菌双歧杆菌的相对丰度并升高致病菌拟杆菌的相对丰度,从而加剧肠道菌群紊乱,进而导致肠黏膜炎^[29]。多柔比星则可通过降低大鼠肠道菌群的物种多样性,抑制有益微生物的繁殖,加剧肠黏膜炎^[30]。

2 化疗所致肠黏膜炎的治疗策略

2.1 化学药物及复合材料干预

氨磷汀作为半胱氨酸衍生物硫代磷酸盐,对大剂量甲氨蝶呤诱导的小鼠肠黏膜炎具有改善作用,可通过抑制细胞凋亡并促进隐窝-绒毛结构恢复实现黏膜修复^[31]。组蛋白去乙酰化酶抑制剂-氮杂酪氨酸-苯丁酸异羟肟酸化合物可通过调节MAPK/胞外信号调节激酶信号通路,抑制MCP-1、TNF- α 和IL-6等炎症因子表达,缓解顺铂导致的小鼠肠黏膜炎^[17]。富勒烯作为纳米复合材料,可降低氧化应激水平,减少IL- 1β 释放及中性粒细胞、嗜酸性粒细胞浸润,从而减轻伊立替康化疗导致的小鼠肠黏膜炎^[19]。

2.2 天然药物干预

黄芪多糖是一种从黄芪中分离出来的天然药物,因具有抗氧化、抗炎和免疫调节特性,能够维持人体肠道屏障的完整性,已成为学界关注的热点。研究证实,黄芪多糖可通过降低F4/80标志物和分化簇11b表达,调节肠道免疫微环境,从而缓解5-FU化疗导致的小鼠肠黏膜炎^[32]。金雀异黄酮诱导红曲菌分泌的胞外多糖可升高小鼠结肠中细胞因子水平,并激活PI3K/Akt/MAPK/NF- κ B信号通路,增强免疫调节功能,进而减轻肠黏膜炎^[22]。姜黄素可通过抑制NF- κ B活化、减轻氧化

应激及内质网应激等多重机制,改善伊立替康诱导的小鼠肠黏膜炎^[33]。百里酞可通过调控NF- κ B/缺氧诱导因子1(hypoxia-inducible factor 1, HIF-1)信号通路发挥抗氧化与抗炎作用,从而有效减轻5-FU诱导的小鼠肠黏膜炎^[34]。

2.3 中药复方干预

中药复方通过多成分、多靶点作用机制在防治化疗所致肠黏膜炎中展现出潜力。健脾养胃汤由黄芪、生白术、蚌壳、姜半夏、神曲、麦芽、茯苓组成,其中黄芪作为核心组成,可通过靶向抑制NF- κ B信号通路,显著降低炎症因子(如TNF- α 、IL-6)的表达水平;姜半夏则可通过抑制细胞凋亡相关蛋白表达,促进肠道上皮细胞的增殖与修复;该复方制剂在实验研究中对5-FU诱导的大鼠肠黏膜炎具有显著的改善作用^[35]。疏补温肾固肠方对伊立替康诱导的小鼠延迟性腹泻具有显著改善作用,其作用机制可能与抑制TLR4/NF- κ B信号通路激活、改善肠黏膜屏障功能、减轻肠黏膜炎有关^[41]。胃肠安丸可通过促进肠黏膜修复和肠上皮细胞增殖,改善肠黏膜炎,从而恢复5-FU诱导的肠梗阻患者的肠道功能损伤^[36]。

2.4 粪菌移植干预

粪菌移植(fecal microbiota transplantation, FMT)是一种将健康人粪便中的功能菌群移植到患者肠道内,以重建患者肠道微生物群的方法^[37]。一些临床试验已将FMT应用于溃疡性结肠炎患者和肠易激综合征患者,取得了不错的疗效^[38]。研究发现,对FOLFOX方案诱导的结直肠癌小鼠进行FMT后,小鼠杯状细胞数量增加、连接蛋白表达增多、凋亡细胞数量减少、肠道微生物群结构恢复,肠黏膜炎明显改善^[39]。

2.5 生长因子干预

生长因子作为促进细胞生长和修复的蛋白,可通过2种主要策略应对肠黏膜炎:一是通过阻滞肠道干细胞的细胞周期以降低化疗诱导的凋亡敏感性,从而保护干细胞;二是通过有丝分裂生长因子促进损伤后的肠上皮细胞增殖、分化及迁移,加速损伤后修复^[5]。口服表皮生长因子可通过刺激肠上皮细胞水解酶活性恢复,改善甲氨蝶呤诱导的大鼠肠黏膜炎^[40]。角质细胞生长因子可通过调控肠上皮细胞的有丝分裂和分化,缓解化疗与放疗联合作用引起的小肠绒毛萎缩,从而减轻小鼠肠黏膜炎^[41]。此外,转化生长因子 β 、胰岛素样生长因子、粒细胞-巨噬细胞集落刺激因子以及胰高血糖素样肽2等也被证实可以促进化疗损伤后肠道的更新修复,缓解肠黏膜炎^[5]。尽管生长因子的应用前景广阔,但其安全性需谨慎评估,例如在化疗期间同时给予胰岛素样生长因子可能加剧甲氨蝶呤诱导的肠毒性^[42]。

2.6 血液制品干预

血液制品主要指以健康人血液为原料,采用生物化学工艺或分离纯化技术制备的生物活性制剂,包括人血白蛋白、静脉注射免疫球蛋白(intravenous immunoglobulin, IVIg)、富血小板血浆及凝血因子等。白蛋白作

为血浆中含量最丰富的蛋白,具有优异的药物载体特性,能够从血液循环中渗出并富集于炎症部位。研究表明,以变性的人血白蛋白装载亚硒酸盐制成的复合纳米颗粒可显著降低顺铂诱导的小鼠肠道氧化应激,改善肠道通透性并缓解胃动力障碍,减轻肠黏膜炎^[43]。IVIg是从健康人血浆中提取的以免疫球蛋白G为主要成分的生物制品,具有抗氧化、抗炎和调节免疫等多重作用,已被广泛应用于恶性肿瘤、自身免疫性疾病及免疫缺陷疾病的治疗。研究发现,在奥沙利铂诱导的小鼠结肠损伤模型中,IVIg可通过增加杯状细胞数量和降低炎症因子水平,从而改善肠黏膜炎^[44]。IVIg还可通过抑制脾酪氨酸激酶/PI3K/Akt信号通路和铁死亡,减轻肠道上皮屏障损伤,进而改善多柔比星诱导的小鼠肠黏膜炎^[45]。

2.7 辅助治疗干预

在化疗所致肠黏膜炎的辅助治疗中,氨基酸与维生素的应用较为广泛,其中谷氨酰胺可通过改善肠黏膜炎、恢复氮平衡及调节免疫发挥作用^[46];维生素D、E可通过其在肠道内的抗炎和调节免疫特性,显著改善胃肠道黏膜炎^[47]。辅酶Q10和维生素C可通过调节肠道微生物来缓解多柔比星引起的大鼠肠黏膜炎^[48]。此外,益生菌也是保护化疗所致肠黏膜炎的有效辅助制剂,如乳酸菌可通过抗氧化、抑制致病菌定植、增强肠道上皮屏障等机制保护肠道;双歧杆菌可通过增强肠道上皮屏障、调节免疫和平衡肠道菌群等机制改善肠道环境;布拉氏酵母菌可通过抑制炎症因子水平,修复肠漏并平衡肠道菌群;益生菌混合物(含短双歧杆菌、嗜酸乳杆菌、干酪乳杆菌和嗜热链球菌)可通过抗炎作用改善大鼠肠道菌群失调^[46,49]。此外,口服长双歧杆菌可促进肠黏膜炎小鼠肠液中分泌型免疫球蛋白A的分泌,从而减轻炎症,逆转伊立替康诱导的肠黏膜炎^[50]。

3 总结与展望

化疗所致肠黏膜炎往往导致患者治疗中断和生活质量下降,已成为恶性肿瘤治疗的主要障碍。本文系统地综述了化疗所致肠黏膜炎的病理机制:化疗药物可通过诱导过量ROS产生,破坏氧化-抗氧化平衡,诱发氧化应激,从而引起肠道氧化性损伤;可通过促进炎症因子的释放,激活炎症反应,从而引起肠道炎症性损伤;可通过促进肠上皮细胞凋亡,引发肠道细胞凋亡性损伤;还可通过破坏肠道屏障,促进肠道菌群失调,进一步加剧感染,形成持续性肠黏膜炎的恶性循环。

化疗所致肠黏膜炎的发生机制复杂,其防治仍面临许多挑战。现有化学和天然药物在治疗化疗所致肠黏膜炎方面仍存在副作用及疗效限制,中医药防治机制也需深入解析,FMT及血液制品干预虽在治疗中表现出潜力,但仍需通过大规模临床研究验证其安全性和有效性。未来需加强多学科交叉创新,结合动物模型和大样本临床试验,开发高效低毒的治疗药物以平衡化疗的毒性与抗肿瘤疗效。

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