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述评 EDITORIAL

基于铁死亡探讨防治溃疡性结肠炎的机制

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Mechanism of prevention and treatment of ulcerative colitis from the perspective of iron death

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease, the etiology and pathogenesis of which have not been fully clarified. As society develops and stress increases, the number of patients with UC continues to increase, especially in Asia. The risk of colorectal cancer is greatly increased in patients with UC compared to healthy individuals. Although the exact pathogenesis of the disease is currently unknown, studies have shown that it is closely related to a variety of factors, including the immune system, the environment, intestinal microecological balance, and genetics. Ferroptosis associated damage occurs in patients with UC and in models of UC, and is effectively alleviated with the use of ferroptosis inhibitors. Ferroptosis is a new form of regulatory cell death caused by iron overaccumulation and lipid peroxidation and is characterised by iron deposition, abnormal lipid peroxidation, and abnormal amino acid metabolism. This article reviews the three main features of ferroptosis to explore the mechanisms and strategies for the prevention and treatment of UC based on iron death.

Key Words: Ferroptosis; Ulcerative colitis; Cell death

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摘要

溃疡性结肠炎(ulcerative colitis, UC)是一种慢性炎症性肠道疾病, 其病因和发病机制尚未完全明确. 随着社会

的发展和压力的增加, UC患者数量持续增加, 尤其是在亚洲, 且与健康个体相比, UC患者患结直肠癌的风险大大增加. 虽然目前其具体发病机制尚不清楚, 但研究表明与免疫系统、环境、肠道微生态平衡、遗传等多种因素密切相关. UC患者体内与UC模型会发生铁死亡损伤, 且在运用铁死亡抑制剂后可有效缓解症状. 铁死亡是一种新形式的调节性细胞死亡, 是由铁过度积累和脂质过氧化引起的, 其特征是铁沉积、脂质过氧化异常和氨基酸代谢异常. 本文就铁死亡的三大特征探讨基于铁死亡防治UC的机制及治疗策略作一综述.

关键词: 铁死亡; 溃疡性结肠炎; 细胞死亡

核心提要: 铁死亡是一种新型程序性细胞死亡方式, 其最显著的特征是铁沉积、脂质过氧化和氨基酸代谢, 三大特征均与溃疡性结肠炎(ulcerative colitis, UC)的发生发展密切相关, 极有可能为UC的治疗提供更多的方向.

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0 引言

溃疡性结肠炎(ulcerative colitis, UC)是一种以反复发生的结肠黏膜慢性炎症和溃疡为特征的疾病, 其特征临床表现为排便次数增多并伴有黏液脓血便. UC病变部位大多侵犯至结直肠黏膜和黏膜下层[1]. 到2023年, 全球UC的患病率估计将达到500万例, 并且全球范围内的发病率正在增加[2-4]. 目前的药物治疗主要目的集中于诱导缓解, 包括5-氨基水杨酸药物和糖皮质激素、生物制剂等. 尽管药物选择性不断增多, 但仍有20%的患者需要接受直肠结肠切除术来治疗UC[5]. 因此UC的防治仍值得进一步探究.

越来越多的研究证据表明, 细胞死亡将成为UC的关键治疗靶点. 细胞死亡是哺乳动物的发育、内环境稳态的维持以及疾病发生的重要环节之一, 其途径包括凋亡、自噬、细胞焦亡、铁死亡等. 铁死亡最早于2012年由美国科学家Brent R. Stockwell及其团队首次提出和描述, 是一种由不受限制的脂质过氧化和随后的膜损伤引起的铁依赖性调节细胞死亡形式[6]. 在此, 我们进一步讨论了铁死亡在UC发病过程中的重要性, 并为UC的药理学靶点提供了新的视角和潜力.

1 铁死亡的定义及特征

铁死亡是一种新型程序性细胞死亡方式, 其本质是铁离子依赖的脂质过氧化产物超量蓄积引起的以线粒体改变为主的氧化损伤, 在细胞形态结构、生物学及遗传学表现上均不同于其他类型的细胞死亡[6]. 从形态上看, 铁死亡的特点是线粒体体积变小、线粒体嵴减少或消失、双层膜密度增加, 但细胞膜保持完整, 染色质和细胞核大小正常[6-8]. 从机制上讲, 铁死亡主要通过内外两条途径发生. 内在途径主要通过阻断细胞内抗氧化酶的表达或活性, 如谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPX4)[7,9,10]. 外在途径主要通过抑制胱氨酸/谷氨酸反向转运体(cystine/glutamate antiporter, System Xc^-)[11,12]或激活转铁蛋白(transferrin, TF)、转铁蛋白受体蛋白1(transferrin Receptor 1, TFR1). 铁死亡的特征是铁沉积、脂质过氧化和氨基酸代谢.

2 铁死亡特征与UC

2.1 铁沉积与UC 铁死亡的一个核心特征是其对细胞内铁的依赖性. 正常情况下, 细胞需要铁元素来执行一系列生物学功能, 包括DNA合成、维生素和氨基酸代谢等[13,14]. 铁代谢是一个动态过程, 涉及铁的吸收、储存、利用和流出等多个步骤, TF、TFR1起关键作用[15]. 血清铁主要通过肠道吸收和TF的调控来维持稳定. 在细胞外, 铁通常以稳定的Fe^{3+}形式储存和运输, 进入细胞后则被还原金属酶还原为Fe^{2+}[16]. TFR1通过识别TF与血清中Fe^{3+}的结合并形成络合物. 铁蛋白(ferritin , Ferr)是一种重要的胞质铁储存蛋白, 可螯合过量的游离铁, 具有抗铁死亡的作用[17,18]. 当细胞膜上的TFR1表达增加、Ferr及TF的表达减少时, 过量的游离Fe^{2+}聚集在细胞质中失去平衡, 就会引发铁死亡. 研究表明, 过量的Fe^{2+}可通过芬顿反应引起细胞脂质过氧化代谢, 产生大量羟自由基和活性氧(reactive oxygen species, ROS)引起铁死亡, 对DNA、蛋白质和膜脂造成有害的氧化损伤[19-21], 这可能是结肠炎的致病因素.

缺铁性贫血是UC常见的并发症之一. 在UC中, 缺铁的最常见原因是肠粘膜炎症加剧, 胃肠道失血和吸收不良导致铁流失增加. 铁调素是一种在肝脏中产生的肽激素, 在调节铁稳态方面发挥着关键作用. 铁转运蛋白(ferroportin, FPN)能将铁转运到储存铁的细胞之外, 大量表达于肠细胞、巨噬细胞和肝细胞中, 而铁调素是其直接抑制剂[22]. 当FPN受抑制时, 铁输出受到抑制, 肠道吸收的铁难以转运到循环中, 其他细胞释放铁的过程也受到抑制, 从而导致血清中铁含量降低[23]. 一些临床研究已经观察到, 在UC患者的肠道组织中, 存在异常的

铁积聚[24]. 还一些研究还发现, 与铁代谢和铁调控相关的基因在UC患者中可能表现出异常, 导致铁在肠道内的不平衡, 从而促进铁死亡的发生. 遗传性血色素沉着病是一种基因突变导致的铁过载疾病, 其特征是近端肠道中铁吸收增加. 血色病Hfe$^{-/-}$小鼠的结肠组织中丙二醛(malondialdehyde, MDA)升高, 表现出更严重的疾病症状, 且更容易发生实验性结肠炎[25-27]. 实验发现, 铁死亡的特异性抑制剂铁他汀-1(ferrostatin-1, Fer-1)、铁死亡抑制剂利普司他丁-1(liproxstatin-1, Lip-1)、铁螯合剂去铁酮(deferiprone, DFP)和抗氧化剂丁基羟基茴香醚, 均可改善葡聚糖硫酸钠盐(dextran sulfate sodium salt, DSS)诱导的结肠炎[24,28]. 这可能是一种有前途的UC治疗策略.

2.2 脂质代谢异常与UC 细胞膜的脂质双层结构直接决定生物膜的特性, 对于维持膜功能的完整性至关重要[29]. 脂质过氧化是铁死亡执行过程的中心环节, 作用位点为细胞膜与细胞器膜膜磷脂上的脂质, 主要为易受氧化的多不饱和脂肪酸, 造成质膜完整性的破坏[30,31]. 多不饱和脂肪酸(polyunsaturated fatty acid, PUFA)是细胞膜的关键成分, 在细胞中具有多种功能, 作为细胞膜的结构“构件”、能量供应者, 甚至作为信号分子, 优先被活性自由基氧化. PUFAs, 特别是花生四烯酸和肾上腺酸极易被过氧化[32,33]. 酰基辅酶A合成酶长链家族成员4(acyl-CoA synthetase long-chain family member 4, ACSL4)催化游离AA/ARA到CoA的生化反应, 形成AA/ARA-CoA衍生物, 然后激活其酯化为磷脂. 溶血磷脂酰胆碱酰转移酶3(recombinant lysophosphatidylcholine acyltransferase 3, LPCAT3)催化AA/AdA-CoA和膜PE的生物合成, 形成AA/AdA-PE. 最后, 脂氧合酶(lipoxygenase, LOXs)将AA-PE和AdA-PE氧化为铁死亡信号(PE-AA-OH和PE-AdA-OOH)[34-36]. 在UC患者的结肠黏膜中PUFAs的磷脂(PUFA-PLs)显著升高[37]. ACSL4在UC患者的回肠和结肠以及DSS诱导的UC小鼠中显著上调, 促进铁死亡[28]. 此外, ACSL4-siRNA Caco2细胞可免受缺氧/复氧诱导的脂质过氧化和细胞死亡[38]. 调查显示, 人群中炎症性肠病(inflammatory bowel disease, IBD)发病率的增加与富含PUFA的西方饮食有关[39]. 实验表明[40], 喂食小鼠富含PUFA的西式饮食加速了肠上皮细胞中中性粒细胞和单核细胞的局部浸润. 因此, 低脂饮食可能是UC患者抑制铁死亡反应的安全且有益的策略.

2.3 氨基酸代谢异常与UC System Xc$^-$-GSH-GPX4轴对铁死亡的抑制作用已被广泛接受. 铁死亡的表现之一是GPX4的失活和谷胱甘肽(glutathione, r-glutamyl cysteingl +glycine, GSH)的消耗, 这是修复脂质氢过氧化物引起的细胞膜损伤和清除ROS的最重要的抗氧化途径[41]. System Xc$^-$由两个蛋白质亚基SLC7A11和SLC3A2组成, 是一种氨基酸转运蛋白[42,43]. 胱氨酸通过System Xc$^-$从细胞外空间转运到细胞内, 随后通过硫氧还蛋白还原酶1转化为半胱氨酸(cysteine, Cys). GSH通常被称为人体的主要抗氧化剂. GSH是GPX4的重要辅助因子, 可促进GPX4将有毒的磷脂氢过氧化物还原为无毒的磷脂醇, 充当中枢铁死亡抑制剂[10,44]. 当细胞内System Xc$^-$活性降低时, Cys含量减少、GSH消耗和GPX4活性降低, 导致脂质过氧化引起的铁死亡. 同时, CoQ氧化还原酶铁死亡抑制蛋白1(ferroptosis suppressor protein 1, FSP1)与GPX4并行抑制铁死亡. FSP1可将细胞膜上的泛醌还原为泛醇, 并作为自由基捕获抗氧化剂, 防止细胞膜上的脂质过氧化[9,45,46]. 这两者都作为抗氧化剂来抑制脂质过氧化. 研究发现, 与健康对照相比, UC患者中GPX4的基因和蛋白表达均降低[47]. 在DSS诱导的UC模型中, GPX4表达显着降低, ACSL4表达升高, 结肠组织中铁丰度和脂质过氧化水平增加, 线粒体受损[48]. 研究发现, 富含PUFA的饮食会使IEC特异性Gpx4$^{+/-}$小鼠诱发局灶性肠炎. 更引人注目的是, 与野生型同窝小鼠相比, IEC Gpx4$^{+/-}$小鼠更易患有DSS诱导的实验性结肠炎[39].

ALOX催化脂质氢过氧化物的产生并驱动铁死亡[49]. 已有研究表明[50,51], 在IBD患者和UC小鼠模型中, ALOX5和ALOX15的表达水平均显著上调. 而ALOX15$^{-/-}$可减轻DSS诱导的UC小鼠的疾病症状, 抑制脂质过氧化代谢物的产生. 相反, ALOX15基因过表达小鼠更易患有DSS 诱导的实验性结肠炎[52]. 磷脂酰乙醇胺结合蛋白1(recombinant phosphatidylethanolamine binding protein 1, PEBP1)是ALOX15的主要调节分子, 与IBD严重程度呈正相关. Lin等[53]发现, PEBP1缺乏可保护小鼠免受DSS或TNBS诱导的实验性结肠炎, 并加速损伤粘膜的恢复. 这些研究表明ALOX在UC的发病中起关键作用.

还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate hydride, NADPH)是烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADP)的还原形式, 是所有生物体中必需的电子供体. NADPH的产生主要依赖于磷酸戊糖途径[54]. 许多铁死亡调节剂, 例如GPX4、AIFM2、NOX和POR, 使用NADP/NADPH系统来调节电子转移[55,56], 较高水平的NADPH或较低的NADP/NADPH 比率可促进对铁死亡的抵抗[57].

3 铁死亡的调控与UC中的应用

目前, 铁死亡的调控主要依靠其诱导剂和抑制剂. 铁死亡诱导剂具有不同的作用机制. Erastin及其类似物、柳氮磺吡啶、索拉非尼可抑制System Xc$^-$的功能, 而RSL3、1,2-二氧戊环、茄碱则抑制GPX4活性. 丁硫氨

酸亚磺酰亚胺消耗细胞内GSH. 铁霉素、蒿甲醚、硫酸亚铁铵和氯化亚铁会促进活铁超负荷. 铁死亡的抑制剂分为两类, 一类抑制铁的积累, 如DFO、甲磺酸去铁胺、2,2'-吡啶. 另一类抑制脂质过氧化, 如铁他汀-1(ferrostatin-1, Fer-1)、利普司他丁-1(liproxstatin-1, Lip-1)、维生素E等. 柳氮磺吡啶属于传统的氨基水杨酸制剂, 口服后能够在UC患者的肠道菌群中作用, 代谢后可生成5-ASA和磺胺吡啶, 抑制前列腺素合成、释放, 抵抗肠黏膜脂肪酸氧化, 降低肠道通透性, 进而达到减少炎性浸润的目的, 但是用药以后不良反应发生率相对较高, 对患者的整体生活质量产生一定的影响,不能用于维持治疗[58]. Fer-1、Lip-1是铁死亡特异性抑制剂, 目前较多运用于UC铁死亡相关实验研究中. 其余大多数化合物在UC中的作用靶点和潜在应用仍有待深入了解.

除了小分子抑制剂外, 一部分中药单体、单药、复方也展现出对铁死亡的抑制作用, 以治疗UC. 核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)是一种转录因子, 在抗氧化过程中发挥着关键作用[59]. 当胞内抗氧化剂被ROS耗尽时, Nrf2易位到细胞核, 驱动血红素氧合酶1(heme oxygenase-1, HO-1)转录[60]. Chen等[28]研究发现, 阻断Nrf2/HO-1信号通路可抑制铁死亡并有效改善DSS诱导的UC. Chen等[61]研究结果确定了黄芪多糖通过抑制NRF2/HO-1通路在实验性结肠炎小鼠模型和人Caco-2细胞中达到预防铁死亡的新作用. 仙茅苷是仙茅中的天然成分, Wang等[62]发现仙茅苷可以增加IEC-6细胞的硒敏感性并促进GPX4转录水平, 可通过诱导GPX4来预防UC中的铁死亡. 姜烯酮A是一种生姜提取物, Zhu等[63]研究表明, 姜烯酮A可以减轻DSS诱导的结肠炎小鼠中的铁死亡, 其保护作用与激活Nrf2-Gpx4信号通路有关. 原儿茶酸(protocatechuic acid, PCA)是一种常见的天然小分子酚酸化合物, 并且是很多中药(如丹参、芙蓉等)中的有效活性成分. Yang等[64]发现PCA可通过调节肠道菌群和铁死亡来预防UC. Yokote等[65]研究发现青黛治疗后增加了UC患者粘膜中的抗氧化基因, 结肠组织中还原型谷胱甘肽、CYP1A1和GPX4的蛋白表达增加. 探索发现青黛的主要成分靛玉红和靛蓝也具有抑制铁死亡的作用. 葛根芩连汤是UC的经典方剂, Wang等[66]发现葛根芩连汤可显著改善铁死亡标志物(铁负荷、MDA、GSH和线粒体形态)的水平以及铁死亡相关蛋白(GPX4、SLC7A11和ACSL4)的表达. 葛根芩连汤可以通过抑制铁死亡来防止结肠损伤和肠上皮屏障功能障碍. Hu等[67]发现芍药甘草汤可通过下调结肠组织中的铁死亡来预防UC.

4 结论

近年来, 作为一种全新的调节性细胞死亡方式, 铁死亡在多个领域取得了广泛的进展, 研究证实铁死亡在多种人类疾病的发生或进展中具有病理学意义, 如多种肿瘤、神经退行性变、急性肾损伤、缺血/再灌注损伤、炎症性疾病等. UC是一种慢性非特异性的肠道炎症, 主要累及结肠和直肠, 多呈反复发作, 临床表现为腹痛、腹泻、里急后重、黏液脓血便等. 铁死亡的主要特征已在UC患者和动物模型的结肠组织中广泛观察到. 铁死亡在UC的发病机制和进展中起着重要作用. UC通常伴随着肠道内的炎症和溃疡. 肠道上皮细胞的受损可能干扰正常的铁吸收和利用. 反复的肠道炎症导致释放多种炎症介质, 这些介质可能干扰铁代谢和调控. UC患者可能经历反复的肠道出血, 这可能会导致铁的丧失, 慢性失血可能导致铁缺乏性贫血, 进一步影响铁代谢和利用. 铁死亡通常涉及氧化应激反应, 这可能加剧UC的炎症和肠道损伤. 脂质过氧化物的生成也会损害肠道黏膜的完整性, 进一步加剧UC的病理生理过程. 本文通过深入研究铁代谢、脂质过氧化等方面的机制, 认识到铁死亡与UC关系密切, 更好地理解了UC的发病机制, 为这一疾病的治疗手段提供了新的线索. 但铁死亡可能只是UC病理生理复杂性的一部分, 仍然需要进一步的研究来确认这一关联, 以及铁死亡在该疾病的确切作用机制, 为UC治疗的新靶点提供更有力的支持.

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• 消息 •

《世界华人消化杂志》正文要求

本刊讯 本刊正文标题层次为 0引言; 1 材料和方法, 1.1 材料, 1.2 方法; 2 结果; 3 讨论; 4 参考文献. 序号一律左顶格写, 后空1格写标题; 2级标题后空1格接正文. 以下逐条陈述: (1)引言 应包括该研究的目的和该研究与其他相关研究的关系. (2)材料和方法 应尽量简短, 但应让其他有经验的研究者能够重复该实验. 对新的方法应该详细描述, 以前发表过的方法引用参考文献即可, 有关文献中或试剂手册中的方法的改进仅描述改进之处即可. (3)结果 实验结果应合理采用图表和文字表示, 在结果中应避免讨论. (4)讨论 要简明, 应集中对所得的结果做出解释而不是重复叙述, 也不应是大量文献的回顾. 图表的数量要精选. 表应有表序和表题, 并有足够具有自明性的信息, 使读者不查阅正文即可理解该表的内容. 表内每一栏均应有表头, 表内非公知通用缩写应在表注中说明, 表格一律使用三线表(不用竖线), 在正文中该出现的地方应注出. 图应有图序、图题和图注, 以使其容易被读者理解, 所有的图应在正文中该出现的地方注出. 同一个主题内容的彩色图、黑白图、线条图, 统一用一个注解分别叙述. 如: 图1 萎缩性胃炎治疗前后病理变化. A: …; B: …; C: …; D: …; E: …; F: …; G: …. 曲线图可按●、○、■、□、▲、△顺序使用标准的符号. 统计学显著性用: $^{a}P<0.05$, $^{b}P<0.01$($P>0.05$不注). 如同一表中另有一套P值, 则$^{e}P<0.05$, $^{d}P<0.01$; 第3套为$^{e}P<0.05$, $^{f}P<0.01$. P值后注明何种检验及其具体数字, 如$P<0.01$, $t = 4.56$ *vs* 对照组等, 注在表的左下方. 表内采用阿拉伯数字, 共同的计量单位符号应注在表的右上方, 表内个位数、小数点、±、-应上下对齐. “空白”表示无此项或未测, “-”代表阴性未发现, 不能用同左、同上等. 表图勿与正文内容重复. 表图的标目尽量用t/min, c/(mol/L), p/kPa, V/mL, t/℃表达. 黑白图请附黑白照片, 并拷入光盘内; 彩色图请提供冲洗的彩色照片, 请不要提供计算机打印的照片. 彩色图片大小7.5 cm×4.5 cm, 必须使用双面胶条黏贴在正文内, 不能使用浆糊黏贴. (5)志谢 后加冒号, 排在讨论后及参考文献前, 左齐.

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