

NLRP3炎症小体在辐射损伤中的研究进展

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摘要

NLRP3是核苷酸结合寡聚结构域(NOD)样受体(NLR)的一员, 是由NOD、LRR和pyrin结构域组成的一种多蛋白复合物, 其导致caspase-1的自身蛋白水解激活, 随后引发促炎细胞因子IL-1 β 和IL-18释放, 导致细胞焦亡。放射疗法(RT)是恶性肿瘤的主要治疗方式之一, 但其引起的损伤极大影响着患者的预后, 极大限制RT的应用。因此探寻辐射损伤的有效防护及缓解方式迫在眉睫。有研究指出NLRP3炎症小体在辐射损伤中发挥着重要作用, 并已有大量研究探讨NLRP3在辐射所造成损伤产生的作用及其机制。本文将阐述NLRP3炎症小体对辐射引起多种损伤的影响及其激活机制, 以寻找预防或抵抗辐射损伤的潜在作用路径。

关键词

NLRP3, 炎症小体, 辐射, 辐射损伤, 研究进展

Research Progress of NLRP3 Inflammasome in Radiation Damage

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Abstract

NLRP3 is a member of nucleotide binding oligomeric domain (NOD)-like receptors (NLR), a multi-protein complex composed of NOD, LRR, and pyrin domains, which leads to autoproteolytic activation of caspase-1, followed by the release of pro-inflammatory cytokines IL-1 β and IL-18, leading to pyroptosis. Radiation therapy (RT) is one of the main treatment modalities for malignant tumors, but the damage caused by it greatly affects the prognosis of patients and greatly limits the use of RT. Therefore, it is urgent to explore effective protection and mitigation methods for radiation damage. Studies have pointed out that NLRP3 inflammasomes play an important role in radiation damage, and a large number of studies have explored the role and mechanism of NLRP3 in radiation-induced damage. This article will describe the effects of NLRP3 inflammasomes on various radiation-induced injuries and their activation mechanisms to find potential pathways to prevent or resist radiation damage.

Keywords

NLRP3, Inflammasomes, Radiation, Radiation Damage, Research Progress

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1. 引言

随着社会的发展,癌症的发病率逐年升高,放射疗法(Radio Therapy, RT)作为肿瘤等恶性复发性疾病的主要治疗方式[1][2],显著延长患者寿命的同时也无法避免地对正常生物组织的非特异性损伤,这是影响治疗的疗效和患者的生活质量的重要因素[3]。辐射损伤主要包括辐射致心血管损伤、认知障碍、辐射致肺损伤、辐射致肠损伤(RIIE)和辐射致其他系统变化。辐射损伤的发生机制涉及炎症,氧化应激, DNA 损伤,细胞凋亡以及多种细胞因子作用等。对正常组织损伤机制的评估表明,炎症反应在早期和晚期 IR 引起的损伤中起着重要作用[4]。

NOD 样受体 3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3)作为一类模式识别受体(PRR),可通过识别病原体相关分子模式(pathogen-related molecular patterns, PAMPs)和损伤相关分子模式(Damage-related molecular patterns, DAMPs),与中间接头蛋白结合,激活转录因子,参与组织的急性炎症反应。辐射作为一种外源性为先信号分子可以激活 NLRP3 炎症小体,一旦被激活,其可以触发 caspase-1 依赖的 gasderminD (GSDMD)介导的细胞焦亡,释放促炎因子 IL-1 β 和 IL-18,促使辐射周围组织发生炎症性损伤。

对于 RT 引起的损伤,目前还缺乏十分有效的治疗方法。在这篇文章中,回顾了 NLRP3 炎症小体在辐射损伤中的作用及激活机制,以探索可能的辐射损伤治疗策略。

2. NLRP3 概述

炎症是由先天免疫系统产生的一系列保护性反应,通过消除病原体和恢复细胞有机体的稳态来使宿主受益[5]。炎症小体是炎症发生发展的关键因素,其是存在于细胞质中的炎症信号复合物,内含表达模式识别受体(PRR),包括黑色素瘤 2 (AIM2)样受体(ALRs)、核苷酸结合寡聚结构域(NOD)样受体(NOD-like

receptor, NLR)和 Pyrin 中缺失的受体,可以在感受到病原体相关分子模式(PAMP)和损伤相关分子模式(DAMP)后导致炎症小体的激活[6] [7]。目前被人们发现的炎症小体均含有 1 个蛋白酶(Caspase)、ASC 蛋白(apoptosis-associated speck-like protein containing CARD)和一种 HIN200 或者 NLR 家族蛋白[8]。NLRP3 作为 NLR 家族的一员,由氨基末端 pyrin 结构域(PYD)、中心 NACHT 域和羧基末端富含亮氨酸重复序列(LRR)结构域组成[9]。经刺激后, NLRP3 会暴露其 pyrin 结构域,该结构域与 ASC 结合,ASC 通过 CARD-CARD 相互作用募集效应分子 pro-caspase-1, 形成一个大蛋白复合体——NLRP3 炎症小体[10]。NLRP3 炎症小体的激活导致 caspase-1 的自切割和激活,一方面 caspase-1 的激活作用于 GSDMD, 随后在细胞膜上形成孔状结构,过度的孔隙形成可破坏细胞结构而引起 Pyroptosis (一种炎症形式的细胞程序性死亡)[11], 另一方面 caspase-1 将 IL-1 β 和 IL-18 转化为它们的成熟形式分泌到细胞外,从而激活炎症反应[12] [13]。

3. 辐射与 NLRP3 炎症小体激活

研究者们发现 NLRP3 炎症小体在辐射损伤中起着重要作用,辐射诱导的组织损伤导致了系统免疫反应和免疫细胞中的 NLRP3 炎症小体激活[14], 炎症小体的激活是一个两步的“启动和激活”过程,启动的特征是上调炎症小体核心成分的表达和诱导翻译后修饰(PTMs) [12], 如宿主体内的微生物分子脂多糖(LPS)或细胞因子 TNF- α 可以作为“启动信号”激活核因子(NF- κ B), 并上调 NLRP3 和 Pro-IL-1 β 的表达。启动后 NLRP3 可以被多种外源性和内源性刺激激活[15]。

Liu 等[16]研究表明,辐射可诱导小鼠骨髓巨噬细胞产生 NLRP3 炎症小体。Wu 等[17]在感染烟曲霉的辐射小鼠的支气管上皮细胞中发现 NLRP3 的上调和 NLRP3-ASC 炎症体的激活,表明 NLRP3 炎症小体在辐射介导的肺上皮细胞屏障发生的焦亡诱导损伤中发挥关键作用。同时在体内,为了确定 NLRP3 在辐射诱导的 BMDM 焦亡中的作用,实验者从 NLRP3 敲除小鼠中分离出 NLRP3 敲除骨髓来源巨噬细胞(bone marrow-derived macrophages, BMDM), 培养后暴露于 10 Gy 辐射中发现,敲除 NLRP3 可将 10 Gy 诱导的细胞死亡从 25.98%恢复到 5.45%。流式显示的辐射诱导细胞焦亡比例也从 31.47%显著降低到 16.83%。在 WB 实验中表明,暴露于 10Gy 的正常 BMDM 中比敲除 NLRP3 炎症小体的 BMDM 中 Caspase-1 表达升高,同时还发现敲除 NLRP3 抑制辐射诱导的 IL-1 β 产生[16]。这一实验表明敲除 NLRP3 可以显著降低辐射引起的细胞凋亡比例,同时减少细胞焦亡的发生。实际 NLRP3 激活的上游信号通常是相互关联和重叠的,包括离子内化和外排、溶酶体破坏、线粒体疾病、代谢功能障碍和鞘脂代谢改变等[18]。NLRP3 炎症小体激活的分子机制尚未完全阐明,但近几年研究表明,辐射损伤中辐射导致的线粒体功能障碍与 NLRP3 炎症体的激活关系最为密切[12], 下面将对几种 NLRP3 炎症小体的几种激活机制进行详细介绍。

线粒体功能障碍与 NLRP3 激活

NLRP3 炎症小体的激活方式多种多样,具体机制可能与细胞类型、压力类型和应激大小有关[19]。线粒体功能障碍可能被认为是 NLRP3 炎症小体不同激活模式的中心环节[20], 可导致线粒体内膜电位的改变、ROS 的产生、钙内流、mtDNA 的释放等不同情况的发生[21] [22]。多项研究报道辐射可导致线粒体损伤,这与细胞凋亡、Ca²⁺稳态、氧化还原调节以及 ATP 合成密切相关[23], 辐射诱导线粒体功能障碍,导致线粒体膜电位和复合体相关亚基的表达量下降,产生 mtROS 释放, mtDNA 转位到细胞质,激活 caspase-1, 诱导 IL-1 β 产生[24], 同时激活了 TGF- β 1 的表达[25]; 在直接或间接 IR 对生精细胞损伤的观察中发现线粒体超微结构的严重损伤, IR 诱导氧化损伤和炎症因子的释放导致线粒体结构受损及代谢紊乱[26]; α 2-巨球蛋白通过减轻线粒体功能障碍改善辐射诱导的成纤维细胞损伤[27]。同时,线粒体膜电位的丧失以及线粒体膜通透性转换孔结构的形成介导了细胞凋亡的过程[28]。线粒体功能障碍过度产生的

mtROS、mtDNA 的过胞质易位或通过诱导 α -微管蛋白乙酰化将线粒体重新定位到 NLRP3 附近,是 NLRP3 炎性体复合物激活的关键因素[29]。事实上,外部 NLRP3 激活剂诱导 caspase-1 和 NLRP3 非依赖性线粒体损伤会导致或直接激活 NLRP3 炎性体的分子释放,包括 mROS、线粒体 DNA (mtDNA)和心磷脂[30] [31]。辐射旁观者效应(RIBE)导致炎症反应的相关研究表明,线粒体功能障碍及过度产生 ROS 和 mtDNA 在其中占有重要的地位。Zhou 等[32]发现在辐射导致线粒体功能失调的过程中 ROS 的产生会触发 NLRP3 炎性体的激活。上述研究揭示了线粒体损伤和感知释放的 mtDNA 在 NLRP3 炎症小体激活中的重要性 [33] [34]。

综上所述,辐射导致线粒体功能障碍在 NLRP3 炎症小体激活中占据重要地位,但具体机制仍需探索研究。

1) mtDNA 与 NLRP3 炎症小体激活

线粒体 DNA (mtDNA)是唯一的非核基因组,与核 DNA (nDNA)相比,mtDNA 由于靠近线粒体活性氧(mtROS),且缺乏修复机制,因此更不稳定,更容易受到氧化应激的影响[35]。越来越多的证据表明,当 mtDNA 泄漏到细胞质中时,它会成为炎症的重要驱动因素[21] [36]。mtDNA 是一种线粒体危险相关分子模式(mtDAMPs),可以与各种模式识别受体(PRRs)结合,激活先天免疫系统。研究结果表明,线粒体功能障碍导致 mtDNA 泄漏,会导致 NLRP3 炎症小体的激活[37]。2011 年, Nakahira 等[34]首次提出 mtDNA 参与 NLRP3 炎症小体的激活。在 LPS 或 ATP 的作用下,功能障碍的线粒体导致 ROS 过度产生,并促进线粒体通透性过渡通道(mPTP)形成,从而促进 mtDNA 向细胞质的转移。之后在对顺铂的研究中发现,顺铂诱导线粒体功能障碍,导致 mtDNA 泄漏到细胞质中激活 cGAS-STING 信号传导,导致 NLRP3 炎症小体的激活[38];李宁等[39]发现细胞质中 mtDNA 的水平可以通过 LPS 处理而升高,进而引起 cGAS 的上调和 STING 的激活;显著促进 mtDNA 转染后 NLRP3 介导的细胞焦亡;在 PINK1 缺陷小鼠中发现 mtDNA 释放导致 NLRP3 炎症小体活化[40]。多项研究报导,辐射诱导线粒体功能障碍导致 mtDNA 泄漏到细胞质中与 NLRP3 炎症小体结合,引起 NLRP3 炎症小体激活[41];同时在对重复照射 EA-R 细胞的研究中发现,线粒体功能障碍导致 TDP-43 以线粒体膜电位依赖性方式易位至线粒体,从而进一步促进 mtDNA 进入细胞质。细胞质中的 mtDNA 不断刺激 DNA 感受器 cGAS,进而激活 cGAS-STING-NF- κ B 信号,增加 NLRP3 的表达[38] [42] [43]。杨艳敏等[44]用萆芩宁和胡椒碱对非酒精性脂肪性肝病大鼠进行干预,发现大鼠肝脏与肌肉 mtDNA 拷贝数增加,改善 IR 导致的线粒体损伤,提示从线粒体损伤以及 mtDNA 入手,减少 NLRP3 炎症小体激活从而改善辐射损伤可能是可行的研究方向。

2) ROS 和 NLRP3 炎症小体激活

ROS 是辐射引起的生物系统损害的主要介质之一,辐射后产生过量 ROS 会导致氧化应激并扰乱细胞内的氧化还原平衡[45]。辐射暴露后 ROS 的持续形成可能是 T 淋巴细胞和其他细胞放射敏感性的来源[46],线粒体功能障碍可导致 ROS 的释放,进而损害线粒体及其 mtDNA,从而增强相关的炎症反应。多个实验表明,许多触发因子对 NLRP3 炎症小体的激活都依赖于 ROS 的产生[47] [48] [49]。丁艳平等[50]在辐射导致的小鼠肝损伤模型发现,辐射导致的线粒体损伤释放 ROS,进而激活 NLRP3 炎症小体通路,使得炎性细胞因子在体内聚集,引起肝功能损伤。Li 等[51]在实验中发现,与对照 THP-1 细胞组相比,低剂量辐射处理的 THP-1 细胞组 ROS 产生显著增加。NLRP3 的激活增加了 IL-1 β 和 IL-18 的产生,而 ROS 特异性抑制剂治疗则降低了这些细胞因子的产生。这些结果表明 ROS 介导低剂量辐射诱导的 NLRP3 炎性体激活。基于这些发现,有实验者[52]测试 ROS 或组织蛋白酶 B 抑制的效果,发现它们都完全减弱了 NLRP3 的表达,同时线粒体 ROS 的特异性抑制被证明可以防止 NLRP3 炎性体的激活[53]。

3) Ca^{2+} 信号传导和 NLRP3 炎性体激活

Ca^{2+} 稳态在 NLRP3 的激活中起着重要作用, 作为 NLRP3 激活的重要上游信号[54], Ca^{2+} 信号传导可以控制不同的细胞过程, 包括细胞转录、分化、迁移、增殖、细胞代谢和细胞死亡等[55]。过往研究表明, 辐射细胞内细胞内钙的升高可导致线粒体中 Ca^{2+} 过载, 导致线粒体功能受损, 产生 mtROS, 释放 mtDNA, 心磷脂从内膜向外膜转移, 从而激活 NLRP3 炎性小体[56] [57]。除此之外, Lee 等[54]提出的一种可能性是, Ca^{2+} 可以促进 NLRP3 和适配器 ASC (包含 CARD 的凋亡相关斑点样蛋白) 的相互作用从而激活, 尽管尚不清楚其作用靶点。Murakami 等[58]的研究表明, Ca^{2+} 信号传导对线粒体起关键的促进作用, 阻断 Ca^{2+} 通道可以抑制 NLRP3 炎症小体激活; 同时通过阻断 NLRP3 激活剂诱导的 Ca^{2+} 流动, 观察到 mtROS 和 mtDNA 的释放也受到抑制, 这说明 Ca^{2+} 是造成线粒体损伤和 NLRP3 炎症小体激活的一个原因[59]。在细胞中, Ca^{2+} 的作用取决于其位置和浓度。 Ca^{2+} 水平的短暂升高会导致生理变化, 而 Ca^{2+} 水平的持续升高会对细胞产生一些负面影响, 许多疾病的病因都与 Ca^{2+} 通量的缺陷相关[60]。辐射可以通过下调内质网 Ca^{2+} -ATP 酶的表达来阻断 Ca^{2+} 的流动, 从而经 NLRP3 炎性体的激活导致辐射损伤[61]。 Ca^{2+} 作为上游 NLRP3 信号在辐射损伤中的作用仍有待进一步研究。

4. 辐射损伤

4.1. 放射性肺损伤

RT 被认为是肺癌包括小细胞肺癌(SCLC)和非小细胞肺癌(NSCLC)的标准治疗方案。然而, 30% 或更多接受放疗的肺部恶性肿瘤患者和约 10%~15% 的其他胸部恶性肿瘤患者发生临床显著肺损伤[62] [63]。辐射引起的肺损伤包括肺炎和肺纤维化。辐射诱发的肺炎是导致发病率和死亡率增加的原因[64]。研究表明, NLRP3 炎性小体在哮喘、特发性肺病、放射性肺炎等多种炎性疾病的发生发展中起关键作用[65] [66]。NLRP3 介导的细胞焦亡参与了辐射和免疫损伤的修复[16]。Wu 等[17]研究发现, 辐射通过 NLRP3 介导的细胞焦亡导致肺上皮细胞屏障的破坏, 进而增加对烟曲霉的易感性并加速肺损伤。李晓宇等[67]实验表明, 低剂量辐射激活 NLRP3 炎性体并增加 IL-1 β 和 IL-18 的分泌。低剂量照射时这些变化会在肺组织中引起超敏反应, 并在用外源性试剂(例如 LPS)刺激后加剧肺炎症状。

4.2. 辐射导致的肠损伤

小肠对辐射高度敏感。放射诱发的肠损伤(RII)是腹部和盆腔肿瘤治疗中最常见和最严重的并发症。导致黏膜屏障破坏、电解质紊乱、细菌感染、败血症等并发症, 严重影响患者治疗, 降低患者生活质量[68] [69], 目前尚无有效干预措施。辐射诱发的肠病其病理生理过程非常复杂。辐射诱发的急性肠损伤是由炎症引起的隐窝上皮细胞凋亡引起的, 导致绒毛上皮细胞的替代不足和持续的黏膜屏障断裂[70]。虽然肠道辐射损伤通常取决于肠隐窝细胞死亡的程度, 但辐射也会引起细胞功能改变和免疫系统激活, 导致黏膜破裂[71]。辐射诱导的线粒体呼吸链复合物抑制以及随后由线粒体功能障碍引起的一系列反应也有助于肠上皮细胞的凋亡[72]。

据报道 NLRP3 炎症小体介导的细胞焦亡与加剧辐射引起的肠道损伤和心血管损伤有关[73] [74]。Ala 等[75]通过实验证明, 在辐射诱导的肠损伤小鼠模型和细胞培养模型中 NLRP3、caspase-1 和 IL-1 β 被激活。并发现西格列汀通过抑制 NLRP3 炎性体激活来减轻辐射引起的肠道损伤并减少下游促炎细胞因子的分泌。Hu 等[76]研究表明, 罗格列酮治疗可显著改善黏膜绒毛和隐窝的结构损伤以及放射后炎症细胞浸润。其主要机制为通过抑制巨噬细胞中 NLRP3 炎性体和 TNF- α 的表达来减轻辐射引起的肠损伤中的炎症。Sun 等[77]证实白藜芦醇通过抑制小鼠 NLRP-3 炎症小体来对抗辐射诱导的炎症性肠病, 并支持 Sirt1

作为肠道辐射保护的潜在生物标志物和治疗靶点。综上所述, NLRP3 作为 RIII 防治的重要靶点, 已渐渐被大家所重视。

4.3. 放射性心血管损伤

癌症患者的慢性健康问题包括心血管疾病(CVD), 这是该人群发病和死亡的主要原因。心血管疾病风险增加与胸部照射之间存在显著相关性, 这会导致癌症幸存者出现短期和长期心血管并发症[78]。虽然急性心包炎可由高剂量辐射引起, 但辐射诱发的心脏损伤可能需要数十年才能出现症状[79]。常见的心血管疾病包括加速动脉粥样硬化、心肌重塑、纤维化和心脏瓣膜损伤。最近的流行病学、临床和临床前研究表明, 电离辐射会导致心血管损伤, 炎症变化以及活性氧(ROS)的产生似乎是早期辐射诱导的心脏组织损伤的主要原因。另一方面, 这种持续存在的炎症和氧化应激状态会导致组织的持续受损[80] [81]。

研究发现 NF- κ B 激活是辐射诱导的心脏效应的早期反应。核因子- κ B (NF- κ B) 是一种多亚基转录因子, 可调节多个基因的表达并参与免疫应答、炎症应答和细胞凋亡等各种生物学过程[82]。NF- κ B 激活是诱导 NLRP3 表达起始信号。越来越多的证据表明 NLRP3 炎症小体与辐射导致的心血管疾病有关。最近的研究表明, 在 C57BL/6 小鼠进行胸部照射后 NLRP3 炎症小体被激活[83]。THP-1 单核细胞的照射导致类似的炎症小体活化, 导致白细胞介素-1 β (IL-1 β) 和 IL-18 的表达增加[73]。这一点尤其重要, 因为 IL-1 β 分泌被认为参与辐射诱导的 CVD 的发展。在直接照射 2 周后给予 IL-1 β 受体阻滞剂可改善辐射诱导的小鼠炎症介质的持续表达[84]。

4.4. 放射性认知障碍

放射性认知障碍是放疗后的严重并发症, 其特征是神经炎症, 这与其进展密切相关[85]。NLRP3 炎症小体与创伤性脑损伤诱导的神经炎症的发生和进展以及神经退行性疾病的生长有关[86] [87]。此外, NLRP3 炎症小体存在于小胶质细胞中, 并在神经炎症过程中发挥作用[88]。Liu 等[89]研究发现阿魏酸可以增强受照射小鼠的学习记忆能力, 改善海马组织的病理变化。靶向 NLRP3 炎症小体的阿魏酸对辐射诱发的神经损伤具有神经保护作用。抑制 NLRP3 炎症小体活性可能是放射认知障碍的一种可能的治疗方法。

5. 小结与展望

NLRP3 炎症小体作为炎症反应中最重要的关键因子之一, 在辐射损伤的防治方面具有重要意义, 过去几年, NLRP3 炎症小体的激活机制及其分子机制的研究都取得了巨大进展, 线粒体被认为是其中的关键点, 这与线粒体功能障碍以及炎症的反应密切相关。由于线粒体功能障碍释放的各种线粒体成分或产物引起的炎症反应失调已被证明会导致许多人类疾病, 从过度炎症驱动的疾病到低效炎症反应导致的疾病[90]。在辐射诱导的炎症反应中也不例外, 辐射诱导的线粒体功能障碍被发现是诱导 NLRP3 炎症小体激活的关键机制, 而近几年的研究中虽然详细揭示了 NLRP3 对 IL-1 β 和 IL-18 的影响机制, 并证明当前 IL-1 β 和 IL-18 受体拮抗剂治疗可作为临床潜在治疗方案[91], 但很少关注到线粒体靶向药物调节炎症的可能性, 日后针对线粒体功能障碍以及 mtDNA, mtROS 相关的靶向药物可能是临床治疗的新方向, 同时中药对于 NLRP3 炎症小体所致相关疾病的治疗也是未来研究的大方向。尽管目前研究表明 NLRP3 炎症小体是辐射损伤防治的关键靶点, 但 NLRP3 炎症小体在肿瘤中的作用仍未完全阐明, 需要进行更多的研究以阐明 NLRP3 炎症小体的激活及分子机制以及辐射损伤中基于抗 NLRP3 治疗策略的优势和副作用。

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