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放射性肠炎的发生机制及治疗的研究进展

解璇莹*，王海云，程永波#

新疆医科大学第一附属医院消化病一科，新疆 乌鲁木齐

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摘　要

随着新辅助治疗越来越多地运用于癌症患者的治疗中，放射性肠炎的发病率逐年增高，患者生活质量明显降低，放射性肠炎的发生机制与治疗的研究也是近年来的关注热点，本文旨在通过对放射性肠炎发生机制及治疗等相关研究现状进行综述，对放射性肠炎的预防与临床治疗提供新思路。

关键词

放射性肠炎，发生机制，治疗

Progress in the Pathogenesis and Treatment of Radiation Enteritis

Xuanying Xie*, Haiyun Wang, Yongbo Cheng#

Department I of Gastroenterology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi Xinjiang

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Abstract

With the increasing application of neoadjuvant therapy in the treatment of cancer patients, the incidence of radiation enteritis is increasing year by year, and the quality of life of patients is significantly reduced. The research on the pathogenesis and treatment of radiation enteritis is also a hot topic in recent years. This paper aims to review the current research status of the pathogenesis and treatment of radiation enteritis. It provides a new idea for the prevention and clinical treatment of radiation enteritis.

*第一作者。
#通讯作者。

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Keywords

Radiation Enteritis, Pathogenesis, Treatment

1. 引言

放射治疗作为临床恶性肿瘤治疗的一线治疗方法，对多种恶性肿瘤具有很好的治疗效果，是目前应用于宫颈癌、直肠癌、膀胱癌、前列腺癌和睾丸癌等恶性肿瘤的重要治疗方式之一[1]，在癌症治疗过程中，约有 50%~70%的癌症患者接受放疗[2]。伴随着术前术后放疗的广泛应用，放射治疗通过高能射线产生的电离辐射诱导癌细胞 DNA 损伤和死亡的同时，不可避免的使照射野范围内的组织或器官发生放射反应或放射损伤[3] [4]。并可能产生急性或慢性的毒副作用[5]。放射治疗损伤的发生或早或晚，甚至在治疗结束后仍有可能发生，损伤发生在胃肠道中时，病变可累及所有节段，形成放射性肠炎[2]。

放射性肠炎便是指盆腔恶性肿瘤患者放疗引起的肠道辐射损伤[6] [7]。按病程看，临床上公认的放射性肠炎有两种不同类型：急性放射性肠炎，在放疗后 6 周内发病，通常在 3 月内恢复正常；慢性放射性肠炎，在放疗后 8~12 月才出现临床症状，甚至可在放疗结束后的数年至数十年出现[8]。慢性放射性肠炎患者主要表现为出血性腹泻和结肠炎症反应，而急性放射性肠炎患者大部分为非出血性腹泻[9]。按患者临床表现来看，放射性直肠损伤可分类为毛细血管扩张型、溃疡型、狭窄型及混合型：毛细血管扩张型主要表现为便血；溃疡型则主要伴有直肠症状，包括肛门膨胀肛门疼痛、大便增多、急便、粘液性大便、下急和大便失禁；狭窄型，根据狭窄程度不同，可表现为下腹痛、排便困难、排便减少、粪便变稀、小肠梗阻等症状；混合型，症状复杂多样[10]。仅 2015 年中国骨盆恶性肿瘤新发病例数就超过 50 万例；75%的盆腔放疗患者发生急性放射性直肠损伤，5%~20%的患者发生慢性放射性直肠损伤[11]。但据 Gami B 等人研究报道[12]，81%接受盆腔放疗的患者出现胃肠道症状，只有 55%的患者向医生寻求帮助，放射性肠炎发病率可能被严重低估了。随着新辅助放化疗技术应用于临床，癌症存活患者的数量增加，辐射引起的腹盆腔疾病的发病率也更是随之增加，如今放射性肠炎的研究引起了越来越多学者的重视，对于其原理机制及治疗方式更是研究的热点。

2. 放射性肠炎的发生机制

2.1. 辐射损伤的机制

大量研究表明，辐射损伤主要有两个机制：直接 DNA 损伤和活性氧(ROS)的产生[13]。辐射一方面可直接诱导 DNA 断裂，导致细胞的癌变或凋亡等损[14] [15]，另一方面引发水的辐射分解产生活性氧并引发随后的氧化应激，间接损伤 DNA、脂质、蛋白质等分子的损伤[16] [17]。辐射引起的 DNA 损伤的主要类型为单链断裂(SSBs)和双链断裂(DSBs)、糖和碱基修饰以及 DNA-蛋白质交联[18]。当 DNA 受到辐射损伤时将有多种细胞改变被引发，如 DNA 修复、细胞周期延迟或阻滞、细胞凋亡[19]。运动失调性毛细血管扩张症突变蛋白(ataxia telangiectasia mumted, ATM)及 Rad3 相关蛋白(ATR)是参与 DNA 损伤监测，细胞周期延迟或阻滞及 DNA 修复的重要蛋白。当 DNA 受损发生时，由 Mrell、Rad50 和 Nbsl 组成的 MRN 复合体感应到其发生，ATM 则立即被激活，激活后的 ATM 可将抑癌蛋白 P53、DNA 修复蛋白 Nibrin

(NBS1)与检查点激酶 2 (CHK2)等参与细胞周期调控及 DNA 修复等活动的多种下游靶蛋白磷酸化，直接导致细胞周期阻滞、DNA 修复或凋亡[20]。ATR 与 ATM 有相似的作用，但 ATM 主要在 DNA 双链断裂发生时优先被激活，而 ATR 则在单链 DNA 断裂时被激活[21]。同时抑癌蛋白 P53 也同样参与调控，当 DNA 受到辐射损伤时，P53 与 mdm2 的结合减少，浓度升高，其可激活 DNA 修复蛋白同时促进诱导细胞周期停滞的基因的转录，而当 DNA 损伤程度超过自体可修复限度，P53 亦可以启动细胞凋亡[22]，引发组织的损伤与坏死。

另一方面，大量实验数据均表明，辐射可导致机体内水分子电离产生大量的活性氧(ROS) [23]，打破机体氧化与抗氧化平衡，导致氧化应激[24] [25]。机体处于氧化应激状态下，多不饱和脂肪酸发生脂质过氧化反应，导致胞膜损伤、细胞结构破坏、酶活性降低[26] [27]。受伤的细胞释放化学诱导因子，引发非特异性炎症[28] [29]。同时 ROS 能引发细胞中的 DNA、蛋白质等生物大分子的损伤，如 ROS 与 DNA 作用形成加合物，其在 DNA 复制时可引发碱基错配从而引起 DNA 的点突变[30]。而与此同时 DNA 损伤又可以提升细胞内 ROS 水平[31]，辐射损伤的两种机制之间也存在着相互影响作用[32]。

2.2. 肠道损伤的发生

辐射损伤发生后，通过直接损伤 DNA 与产生活性氧发生氧化应激反应，大量细胞凋亡组织坏死，肠道黏膜遭到严重损伤，而细胞膜遭到大量破坏，激活 NF-κB 等多种转录因子，NF-KB 可诱导多种与炎症相关的因子与酶激增，如肿瘤坏死因子-α (TNF-α)、白介素-6 (IL-6)、白介素-1β (IL-1β)、粘附因子、趋化因子、环氧合酶-2 (COX-2)等。另一方面，TNF-α 在其作用下产生，又会激活更多的 NF-κB，加重炎症反应的发生[33]。血管内皮细胞在辐射的作用下亦发生凋亡及上述炎症反应，后期肠道黏膜下血管内皮细胞肿胀、增生、纤维化，形成闭塞性血管炎，肠道组织缺血缺氧加剧，导致肠纤维化、肠腔狭窄等肠道组织变化，严重可致肠坏死、肠瘘、肠穿孔和肠梗阻[34] [35]。

3. 放射性肠炎的治疗

3.1. 细菌治疗

细菌及其衍生物用于治疗放射性肠炎为当下研究的热点问题，大量研究显示，肠道菌群调节治疗不仅可以起到抗氧化、抗炎等作用，减轻肠道受到的辐射损伤，同时一些细菌及其衍生物可以增强放疗治疗的效果。在放疗的同时行相关细菌协同治疗可起到一举多得的效果。

当患者接受放射治疗后，肠道菌群发生改变，Wang 等[36]研究证明，放疗后患者肠道菌群的多样性明显降低。辐射损伤发生后，肠道的蠕动减低导致机会致病菌的行动阻滞，增加其定植的机会，导致肠道致病菌的大量繁殖，肠道菌群失调加剧[37]。Chen 等[38]研究证明，益生菌能促进肠道中 IgG、IgA、IgM 等免疫球蛋白的生成,还刺激分泌性 IgA 的产生，免疫球蛋白的增多可以调节免疫功能，增强机体免疫力，改善肠道营养吸收利用，间接降低肠道内相关炎症因子水平[39]。大量实验证明通过肠道定植、抗炎作用、抗氧化能力和微生物群调节，益生菌如嗜酸乳杆菌、乳杆菌、双歧杆菌和嗜热链球菌等可以治疗胃肠道损伤[40] [41] [42]。而益生菌中乳酸菌的研究最为深入，Yan 等的研究表明，乳酸菌分泌的 p40、p75 等蛋白可调节细胞因子、保护肠上皮细胞间紧密连接，同时还可以抑制 p38 丝裂原活化蛋白激酶(MAPK)，激活 COX-2 通路，从而发挥抗凋亡和抗炎作用[43]。Sharma 等研究证明，短乳杆菌 CD2 制成的含片使用后可以降低炎症细胞因子的表达，明显降低头颈癌患者放疗后口腔黏膜炎的发生率[44]。

同时，细菌治疗与放射治疗相结合的，还有增强放疗效果的作用，如李斯特菌就已被证明可作为载体将放射性核素传递至肿瘤部位，提高治疗的效率，减少对机体正常组织的伤害。Quispe-Tintaya 等人[45]和 Chandra 等人[46]就将减毒李斯特菌放射性同位素 188 铼(188Re)偶联治疗胰腺癌，李斯特菌可产生 IL-6

等信号分子，这些信号分子被肿瘤细胞选择性地吸引，可运载放射性同位素至肿瘤细胞；同时李斯特菌自身就可以通过产生 ROS 引起 DNA 损伤起到破坏肿瘤细胞的作用，其与 188 Re 诱导的电离辐射结合，可在不伤害周围正常组织的情况下特异性地抗肿瘤治疗，并增强其治疗效果。

3.2. 其他治疗

目前临床上对放射性肠炎的治疗有内镜下止血、高压氧治疗、肠外营养干预、保留灌肠及外科手术等措施。口服及灌肠药物常选用谷氨酰胺、康复新液、糖皮质激素、硫糖铝、美沙拉嗪，中药制剂等药物，修复、保护肠黏膜，减轻炎症反应。最新研究表明 γ-氨基丁酸[47]、依达拉奉[48]等药物对于肠道放射性肠炎也有治疗作用，可减轻肠道氧化应激。

Liang 等经荟萃分析后发现治疗放射性肠炎的多种口服药物中，中药汤剂的治疗效果最好[49]。黄连、黄芪、甘草和白头翁是放射性肠炎中医治疗中常用的草药，Hou 等研究[50]明确黄芪多糖通过调控有丝分裂原激活蛋白激酶(AMPK)/核因子(NK)-κB)炎症信号通路的表达，减轻肠道炎症反应，对放射性肠炎有确切的治疗作用。临床经验表明，中医治疗对于放射性肠炎患者相关腹泻、腹痛，消化道出血等临床症状效果明显，但中草药成分复杂，相关临床实验研究数据较少，治疗机制研究不清，希望后续可加强相关研究。

纳米技术也运用于放射损伤的防护与治疗中，纳米辐射防护药物也为放射性肠炎的预防与治疗提供了更多的可能[51]，如 Zhuo 等人[52]研究用水凝胶负载两种纳米颗粒：多巴胺纳米颗粒(PDA-NPs)和间充质干细胞分泌的细胞外小囊泡(MSC-sEV)，这种多功能水凝胶对 ROS 具有清除作用，可显著降低辐射造成的炎症及氧化损伤。

4. 总结与展望

随着放射治疗在肿瘤治疗中的应用日益增多，放射性肠炎患病率迅速升高，放射损伤引发的肠道出血、肠梗阻、肠瘘等并发症时常迁延不愈，复发难治，严重影响患者的生活质量。故我们还需更加深入地研究放射性肠炎病理机制，以期获得更多预防及治疗方法的启示。放疗后血管损伤相关研究已有很多，淋巴管与血管结构相似，多与血管伴行，但关于辐射后淋巴管损伤相关研究较少，辐射后淋巴管是否发生损伤，损伤为何种表现，有待我们进一步研究。中药及微生物治疗法是目前放射性肠炎治疗方法研究的热点，大量研究表明，一系列中医药治疗可能减轻结直肠组织纤维化、黏膜损伤及炎症反应。微生物及其衍生物对于减轻放疗损伤、增强放疗效率的作用也得到了大量的研究证实，这些无不说明中药及微生物治疗对于放射性肠炎治疗的无限潜力。

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