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· 评述与综述 ·

IL-22在放射性肠损伤中的研究进展

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摘要: 放射性肠损伤(radiation-induced intestinal injury, RII)是盆腹腔肿瘤患者放射治疗后常见的严重并发症, 其核心病理机制涉及肠隐窝Lgr5⁺干细胞耗竭、肠黏膜屏障破坏、肠道菌群失调及炎症级联反应等。白介素22(interleukin-22, IL-22)因介导免疫细胞与上皮细胞间的精密通讯而受到广泛关注。本文从放射性肠损伤的发病机制出发, 系统综述IL-22在RII中的治疗潜力, 旨在为RII的临床防治提供新方向。未来研究应聚焦于IL-22递送系统优化、生物标志物筛选及菌群-免疫联合治疗策略, 从而为RII的临床应用转化提供新思路。

关键词: 放射性肠损伤; IL-22; 肠道稳态

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Research progress of IL-22 in radiation-induced intestinal injury

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Abstract: Radiation-induced intestinal injury (RII) is a prevalent and devastating complication in patients with pelvic and abdominal tumors following radiotherapy. The pathological hallmark of RII involves the depletion of Lgr5⁺ intestinal stem cells (ISCs), disruption of the intestinal mucosal barrier, gut microbiota dysbiosis, and uncontrolled inflammatory cascades, which not only severely impair patients' quality of life but also limit the efficacy of radiotherapy. Interleukin-22 (IL-22), a member of the IL-10 cytokine family, has emerged as a promising candidate due to its unique epithelia-targeting protective properties, which is distinct from most other cytokines. This review aims to systematically synthesize the biological characteristics of IL-22, its multifaceted roles and underlying mechanisms in RII, and to discuss the challenges and prospects of its clinical translation, providing a comprehensive foundation for future research and therapeutic development. IL-22 serves as a critical bridge connecting immune regulation and epithelial repair, holding great promise for the treatment of RII. Through mechanism-driven innovations in delivery systems, biomarker-guided precision medicine, and synergistic combination therapies, the protective effects of IL-22 can be maximized while mitigating potential risks, paving the way for its successful clinical translation to improve the outcomes of patients with RII. In the context of RII, IL-22 exerts multiple protective effects through distinct mechanisms. Firstly, it serves as a core protector of Lgr5⁺ ISCs, the cornerstone of intestinal epithelial homeostasis and regeneration. Secondly, IL-22 plays a pivotal role in repairing radiation-damaged intestinal mucosal barriers. It promotes the secretion of mucins from goblet cells to reinforce the mucus layer, upregulates the expression of tight junction proteins (ZO-1 and Occludin) to reduce intestinal permeability. Thirdly, IL-22 inhibits inflammatory response in RII while its long-term or excessive activation may increase the risk of malignant cancer. Fourthly, IL-22 engages in bidirectional crosstalk with the gut microbiota. Despite its significant therapeutic potential, the clinical translation of IL-22 for RII faces several challenges: the administration of IL-22 may cause off-target effects and systemic inflammation; sustained activation of the STAT3 pathway may promote the proliferation of residual tumor cells; the complex

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crosstalk between IL-22 and other immune factors in the radiotherapy microenvironment remains unclear. To address these issues, future research should focus on: developing targeted delivery systems to achieve site-specific enrichment of IL-22; establishing a biomarker system integrating multi-omics data to predict treatment response and guide personalized medicine; and exploring microbiota-immune combination strategies to synergistically enhance endogenous IL-22 function. Additionally, rigorous safety evaluations in tumor models are essential to define the safe window of IL-22 application and avoid potential carcinogenic risks.

Key words: radiation-induced intestinal injury; interleukin-22; gut homeostasis

恶性肿瘤的发病率和死亡率在全球范围内持续攀升,已成为威胁公众健康的重大公共卫生问题^[1]。盆腹腔恶性肿瘤(如宫颈癌、前列腺癌、直肠癌)患者数量庞大,约占肿瘤患者总数的50%。放疗是其核心治疗手段之一,约超过60%的患者需接受放射治疗^[2]。然而,由于肠上皮细胞具有高度增殖活性,对电离辐射极其敏感,盆腹腔放疗不可避免地会损伤邻近的健康肠道组织,进而诱发放射性肠损伤(radiation-induced intestinal injury, RII)^[3]。

放射性肠损伤可分为急性放射性肠损伤(acute radiation-induced intestinal injury, ARII)和慢性放射性肠损伤(chronic radiation-induced intestinal injury, CRII)。ARII通常发生于放疗后3个月内,60%~90%的患者表现为腹泻、腹痛、血便和里急后重等症^[4];CRII则常出现于放疗后3个月至数年,以反复腹泻、便血、肠道狭窄及梗阻为主要特征,在接受盆腹腔放疗的患者中尤为普遍^[5]。放射性肠损伤的病理特点是电离辐射直接损伤肠隐窝干细胞,破坏其自我更新与分化能力,导致肠上皮再生障碍、屏障功能丧失、肠道菌群失衡与易位,进而触发强烈的炎症级联反应和组织纤维化进程。这些病理变化不仅严重影响患者的生活质量,也限制放疗的整体效果。目前,临床上针对放射性肠损伤缺乏特效疗法,主要为对症支持治疗(如止泻、止痛、营养支持)和抗炎药物(如5-氨基水杨酸)应用,但整体疗效仍然有限^[6]。因此,深入探索放射性肠损伤的发病机制并发展新型有效的防治策略,对于改善患者预后和生活质量具有迫切的临床需求和重要的科学价值。

值得关注的是,与大多数细胞因子不同,白细胞介素-22(interleukin-22, IL-22)展现出独特的上皮细胞靶向性保护功能。IL-22能够促进肠道干细胞增殖、刺激杯状细胞分泌黏蛋白、诱导潘氏细胞及肠上皮细胞产生抗菌肽,在溃疡性结肠炎、感染性肠炎及胰腺炎等多种组织损伤和炎症性疾病模型中均表现出显著的修复和保护作用^[7-9]。基于IL-22在肠道损

伤修复中的关键地位及在多种疾病模型中的保护效果,其在放射性肠损伤防治领域正迅速成为一个备受瞩目的新兴治疗靶点。本文对IL-22在放射性肠损伤中的治疗潜力进行综述,旨在为放射性肠损伤的治疗及临床应用提供新的策略。

1 IL-22的生物学特性及信号调控

1.1 IL-22的来源与受体分布

IL-22是一种由146个氨基酸组成的糖蛋白,是IL-10细胞因子家族的重要成员,最早于2000年在小鼠经IL-9刺激的T细胞系中被鉴定^[10]。IL-22主要由多种活化的淋巴细胞产生,包括适应性免疫系统的Th1、Th17、Th22、CD8⁺ T细胞、 $\gamma\delta$ T细胞,以及固有免疫系统的固有淋巴细胞(innate lymphoid cells, ILCs)。在ILCs中,3型固有淋巴样细胞(group 3 innate lymphoid cells, ILC3),特别是淋巴组织诱导细胞(lymphoid tissue inducer, LTI)和NKp46⁺ ILC3s亚群,是肠道等黏膜屏障组织中IL-22最关键的来源,它们的分化和功能依赖于维甲酸相关孤儿受体 γ t(retinoic acid-related orphan receptor gamma t, ROR γ t)^[11]。某些髓系细胞(如巨噬细胞、中性粒细胞)在特定条件下也能产生IL-22,但贡献相对有限。

IL-22的生物学功能依赖于与细胞表面受体复合物的结合,该复合物由IL-22R1和IL-10R2两个亚基组成^[12]。IL-10R2广泛表达于多种细胞类型(包括免疫细胞和部分非免疫细胞),而IL-22R1的表达则具有显著的组织特异性,主要局限于上皮细胞(如肠上皮细胞、肝细胞、角质形成细胞、呼吸道上皮细胞等)和部分基质细胞^[13]。这种独特的受体分布模式是IL-22发挥其高度上皮细胞靶向性生物学效应的结构基础^[14]。

1.2 IL-22信号通路调控

IL-22与由IL-10R2和IL-22R1两条受体链构成的复合物结合后^[15],可促使Janus激酶1(Janus kinase 1, JAK1)及酪氨酸激酶2(tyrosine kinase 2, TYK2)

被激活,随后诱导信号转导与转录激活因子3(signal transducer and activator of transcription 3, STAT3)上酪氨酸残基的磷酸化反应。经磷酸化的STAT3形成二聚体并进入细胞核,调控一系列下游靶基因的表达,如Reg3g、S100A8和MUC2等。除了经典的STAT3信号通路外,IL-22还能够刺激MAPK和PI3K/AKT等多种信号转导途径^[16]。需要强调的是,IL-22的持续激活具有促进肿瘤发生的风险,因此IL-22信号的强度和持续时间必须受到严格调控^[17]。其负调控机制主要包括细胞因子信号转导抑制蛋白3(suppressor of cytokine signaling 3, SOCS3)的反馈抑制作用以及IL-22结合蛋白(IL-22 binding protein, IL-22BP)的竞争性拮抗。IL-22BP主要由树突状细胞分泌,在肠道炎症区域表达上调,可高亲和力结合IL-22,阻断其与受体IL-22R1的结合,从而抑

制STAT3磷酸化及下游靶基因的表达,防止黏膜过度修复导致的病理损伤^[18]。

2 IL-22在放射性肠损伤中的作用及机制

IL-22在多种疾病的治疗过程中展现出潜在应用价值。IL-22通过促进隐窝干细胞的增殖与分化平衡、提升肠道黏膜屏障的完整性、减轻肠道炎症、调节菌群生态失衡,修复辐射带来的一系列损伤(图1)。但相关研究不尽相同,有些则表明IL-22会通过抑制某些通路来促进炎症以及肿瘤的发生^[19]。因此,系统探讨IL-22在放射性肠损伤过程中的调控作用及潜在机制,对放射性肠损伤的修复具有重要的意义。

2.1 IL-22在肠道干细胞(ISC)中的作用

肠干细胞(intestinal stem cell, ISC)在维持肠道上皮稳态和再生中扮演核心角色,其通过不对称分裂

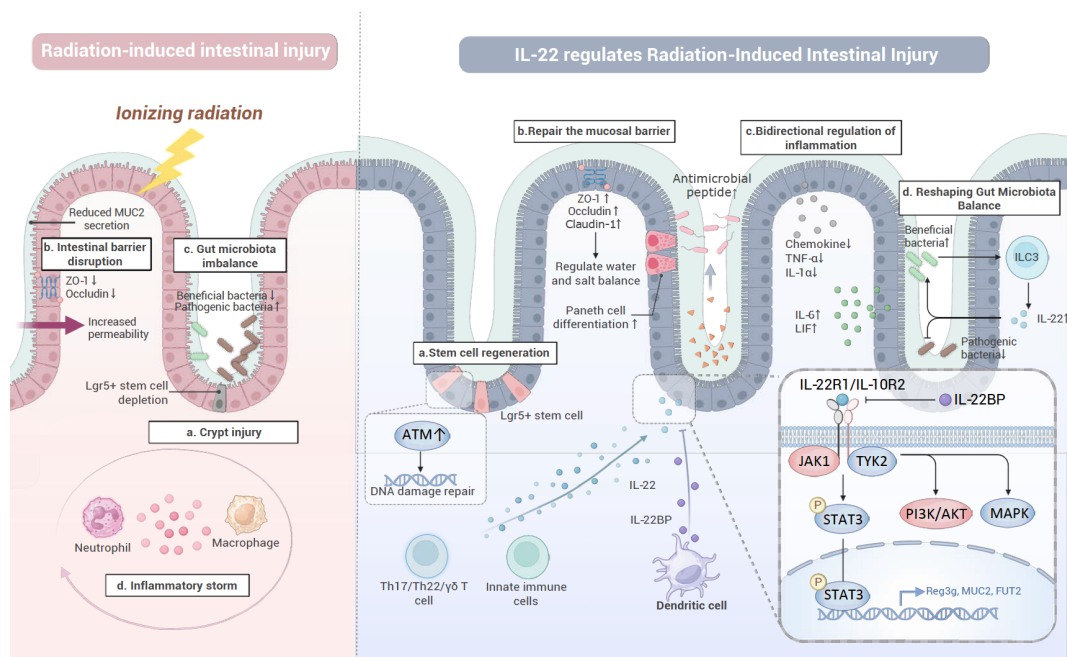


图1 IL-22在放射性肠损伤中的多靶点保护作用及调控网络示意图

IL-22主要由ILCs、T辅助细胞(Th17、Th22)及 $\gamma\delta$ T细胞等免疫细胞分泌,其生物学功能依赖于与靶细胞表面的IL-22受体(IL-22R1/IL-10R2异二聚体)结合后启动下游信号通路。值得注意的是,IL-22的活性受树突状细胞来源的IL-22BP的精准调控。IL-22通过以下四大途径发挥维持肠道稳态的保护作用:(a)肠干细胞再生;(b)修复肠道屏障;(c)调控炎症微环境;(d)调节菌群平衡。

Figure 1 Schematic diagram of the multi-target protective effects and molecular regulatory network of IL-22 in radiation-induced intestinal injury

IL-22 is mainly secreted by immune cells such as innate lymphoid cells (ILCs), helper T cells (Th17, Th22) and $\gamma\delta$ T cells. Its biological functions rely on binding to the IL-22 receptor (IL-22R1/IL-10R2 heterodimer) on the surface of target cells to activate downstream signaling pathways. Notably, the activity of IL-22 is precisely regulated by dendritic cell-derived IL-22 binding protein (IL-22BP). IL-22 exerts protective effects in maintaining intestinal homeostasis through the following four pathways: (a) intestinal stem cell regeneration; (b) intestinal barrier repair; (c) regulation of the inflammatory microenvironment; (d) regulation of gut microbiota balance.

实现自我更新,并分化为多种肠上皮细胞(intestinal epithelial cell, IEC),是肠上皮损伤修复的关键来源。电离辐射会显著减少ISC的数量,破坏隐窝结构,是放射性肠损伤的关键病理基础之一^[20]。

IL-22是促进辐射后ISC存活、增殖及肠上皮再生的核心保护因子。Lindemans等^[21]研究表明,辐射损伤后,IL-22能够直接作用于Lgr5⁺ ISC,通过激活STAT3信号通路,显著增强肠道类器官的生长、出芽及ISC增殖,并证明这一再生过程不依赖于潘氏细胞的支持。Tang等^[22]进一步报道,口服白蜡树苷可通过上调IL-22水平,恢复13 Gy全腹照射后小鼠肠道隐窝中Lgr5⁺ ISC的数量,增加隐窝中Ki67阳性细胞、潘氏细胞及杯状细胞数量,并降低辐射诱导的体外培养的人肠上皮细胞系和小鼠小肠类器官的凋亡,促进肠上皮再生。

Wang等^[23]利用单细胞RNA测序分析发现,化学性交感神经失神经支配后会导致肠上皮IL-22信号减弱,阻碍辐射后肠上皮再生;而外源性补充重组IL-22-Fc融合蛋白可有效逆转这一缺陷。更重要的是,使用IL-22中和抗体(α IL-22)处理会抑制辐射后肠上皮中IL-22下游靶基因(如Reg3b、Reg3g)的表达,并显著减少再生隐窝的数量,直接证实了IL-22在放射性肠损伤后ISC保护和上皮修复中的不可或缺性。Hou等^[24]发现,乳酸菌可刺激固有层淋巴细胞(lamina propria lymphocyte, LPL)分泌IL-22,进而激活STAT3信号通路,加速ISC再生,保护肠黏膜屏障的完整性。IL-22亦是ISC应对基因毒性压力(如辐射)的关键调控因子,其通过STAT3调控共济失调毛细血管扩张突变(ataxia telangiectasia mutated, ATM)表达,启动DNA损伤应答(DNA-damage response, DDR),促进DNA修复或清除严重受损细胞。缺乏IL-22会导致ISC的DDR功能缺陷、突变积累,显著增加远期结肠癌风险^[25]。

值得注意的是,IL-22对ISC的作用存在一定复杂性。有研究显示,在稳态或特定损伤模型中,IL-22虽能驱动转运扩增细胞(transit-amplifying cells, TACs)增殖以支持上皮再生和类器官生长,但可能通过抑制Wnt和Notch信号通路,削弱Lgr5⁺ ISC自身的存活能力^[26]。这与上述在放射性损伤模型中观察到的IL-22对Lgr5⁺ ISC的显著保护作用形成对比,提示IL-22的功能可能受到微环境与损伤类型的精细调控。

综上所述,IL-22通过激活STAT3信号通路和调控DNA损伤反应等关键机制,发挥对Lgr5⁺ ISC的核心保护作用,促进其存活、增殖和分化,驱动肠上皮再生。多种干预策略(如药物诱导、益生菌、直接补充等)通过提升IL-22水平展现出辐射防护潜力。然而,IL-22对ISC(尤其是Lgr5⁺ ISC)的直接作用在不同生理病理背景下可能存在差异,其细胞靶向性和调控网络仍需深入研究。

2.2 IL-22在肠黏膜屏障中的作用

肠黏膜屏障是机体抵御肠道内致病微生物及有害物质入侵的关键防线,其功能完整性依赖于物理、化学、免疫及生物屏障的协同作用。电离辐射可严重破坏肠道上皮稳态,损害上述屏障功能,进而引发菌群易位及系统性炎症反应。IL-22在辐射所致肠黏膜屏障损伤的修复过程中发挥核心作用。

杯状细胞分泌的黏液层构成抵御微生物入侵的首道物理屏障。辐射可导致杯状细胞数量减少和黏液分泌不足,从而削弱该屏障功能。IL-22通过激活STAT3信号通路,直接诱导肠上皮细胞表达MUC2等黏蛋白^[27],促进黏液合成与分泌。在葡聚糖硫酸钠(dextran sulfate sodium, DSS)诱导的结肠炎模型中,香菇多糖可通过激活Dectin-1-ILC3通路促进IL-22分泌,而IL-22能上调杯状细胞黏蛋白及岩藻糖基转移酶的表达,同时增强抗菌肽生成,从而修复受损黏液层并强化其抗菌性能^[28],提示IL-22在放射性肠损伤中对于黏液屏障的维持与修复具有关键作用。

肠道上皮细胞间的紧密连接严格控制细胞旁通透性,是防止微生物和抗原经细胞旁途径入侵的核心物理结构。辐射可破坏紧密连接蛋白的表达与分布,显著增加肠道通透性。Liu等^[29]在放射性肠损伤模型中发现,口服魔芋葡甘露聚糖(konjac glucomannan, KGM)可通过提升肠道IL-22水平,有效缓解辐射引起的肠道通透性损伤,并增强屏障完整性。此外,IL-22对紧密连接蛋白具有多效调控作用。Wang等^[30]在溃疡性结肠炎(ulcerative colitis, UC)模型中的研究表明,IL-22可增加结肠组织中杯状细胞的数量,并促进紧密连接蛋白(如ZO-1、Occludin、Claudin1)的表达,从而修复屏障结构并减少细菌感染。值得注意的是,IL-22对特定Claudin蛋白的作用具有复杂性。在IL-22的作用下,Claudin-2的表达水平上调,导致肠道通透性增加,进而促进肠道内病原体的清除,但同时也可能诱发腹泻等肠道

功能紊乱相关症状^[31]。然而,其在放射性损伤背景下对屏障功能的整体影响需结合其他紧密连接蛋白的变化进行综合评估。

潘氏细胞及肠上皮细胞分泌的抗菌肽构成重要的化学屏障,可直接抑制或清除微生物。IL-22是诱导包括潘氏细胞在内的肠上皮细胞表达多种抗菌肽的关键细胞因子^[32]。它不仅能促进潘氏细胞分化,还可广泛增强抗菌肽的合成,通过直接杀菌及抑制细菌黏附与入侵来强化化学屏障功能,从而有效抑制辐射后的菌群易位。研究显示CCR6⁺ ILC3通过分泌IL-22调控肠道及肝脏中抗菌肽的表达,在术后感染中有效抑制细菌扩散^[33]。更为直接的是,He等^[34]利用人源小肠类器官模型进一步证实,IL-22处理可显著提升潘氏细胞数量及其标志性抗菌蛋白溶菌酶的表达,凸显了IL-22在调控潘氏细胞功能中的重要作用。

综上所述,IL-22通过促进黏液分泌、调控紧密连接蛋白表达及增强抗菌肽生成等多重机制,协同维护并修复辐射损伤后的肠黏膜屏障功能。这些作用共同奠定了IL-22在放射性肠损伤中宿主防御与组织修复的核心地位,也为靶向IL-22信号通路以增强屏障功能、防治放射性肠损伤提供了重要的策略方向。

2.3 IL-22在肠道炎症中的作用

在放射性肠损伤中,辐射暴露触发强烈的、不受控制的炎症级联反应,是组织损伤的核心病理基础之一。在盆腹腔肿瘤患者放射治疗诱发的急性肠损伤中,促炎基因表达诱导炎症级联反应,驱动炎症介质和促炎细胞因子释放。IL-22在调节放射性肠损伤相关炎症中发挥关键作用。口服罗伊氏乳杆菌可通过持续递送IL-22,显著降低肠道及血浆中促炎因子(如TNF- α 、IL-1 α)的水平,同时上调具有组织保护和抗炎潜能的因子(如IL-6、LIF)的表达,从而有效缓解辐射诱导的肠道炎症^[35]。

Li等^[36]研究发现,黄芩素可通过激活ILC3中的芳香烃受体(aryl hydrocarbon receptor, AhR)/IL-22通路增强肠上皮屏障功能,从而缓解肠道炎症。此外,Th17细胞来源的IL-22能够通过STAT3-C/EBP β 信号轴,直接抑制肠上皮细胞表达关键趋化因子,进而减少中性粒细胞和巨噬细胞等炎性细胞向肠组织的聚集,有助于维持肠道免疫稳态并控制炎症进程^[37]。这些机制在结肠炎等多种肠道炎症模型中

得到进一步验证,并揭示了IL-22发挥抗炎保护作用的多途径调控通路。

IL-22信号通路并非始终发挥保护作用。长期或过度激活IL-22信号,尤其在慢性炎症背景下,可能通过持续刺激上皮细胞增殖并抑制凋亡,增加恶性转化风险。在结肠炎相关癌症模型中,IL-22与抑瘤素M(oncostatin M, OSM)形成的信号轴(IL-22-OSM轴)可维持STAT3通路持续活化,进而促进肿瘤细胞增殖、存活及血管生成。Cineus等^[17]发现,在溃疡性结肠炎患者中,肠道组织内IL-22与OSM受体表达呈高度同步性,且与患者进展为结直肠癌的风险呈正相关。这些发现提示,在放射性肠损伤的慢性期或持续性炎症状态下,需警惕长期IL-22过度激活可能带来的潜在致癌风险。

综上所述,IL-22通过精密调控免疫细胞浸润、炎症因子网络及上皮细胞增殖,在放射性肠损伤相关炎症的发生、发展与转归中扮演核心角色。其既可通过抑制趋化因子释放、增强屏障功能及诱导保护性因子等途径发挥抗炎与组织保护作用,也存在长期过度激活促进上皮细胞增殖并增加癌变风险的潜在弊端。深入理解IL-22在放射性肠损伤不同阶段及微环境条件下的作用机制与动态平衡,对于开发靶向IL-22通路的干预策略,从而安全有效地防治放射性肠损伤及相关炎症并发症具有重要指导意义。

2.4 IL-22与肠道微生物的相互作用

放射性肠损伤还会引发显著的肠道菌群失调,其特征表现为有益共生菌丰度降低、微生物多样性下降以及潜在致病菌相对增多。在正常情况下,肠道微生物菌落构成一个复杂的生态系统,包含双歧杆菌、乳杆菌和拟杆菌等多种共生菌,在维持肠道稳态、代谢调节及免疫功能中发挥关键作用。辐射暴露可破坏这一生态平衡,导致有益菌数量减少,而部分条件致病菌(如肠杆菌科)或潜在致病菌(如致病性大肠杆菌谱系、沙门氏菌等)则可能过度增殖。这种菌群失衡将进一步加剧辐射诱导的肠道炎症,并阻碍组织修复进程。

肠道菌群可通过其代谢产物显著影响IL-22的分泌,而IL-22亦能反向调节菌群结构,形成双向互作网络,这在放射性肠损伤中尤为重要。一方面,菌群代谢产物对IL-22的分泌具有调控作用。肠道共生菌代谢膳食色氨酸所产生的吲哚类化合物是AHR的内源性配体,AHR在ILC3等细胞上表达,其激活可直

接驱动IL-22的产生。在放射性肠损伤中,菌群失调导致这些有益的AHR配体水平下降,从而抑制ILC3分泌IL-22,削弱其介导的肠黏膜保护作用。Han等^[38]在辐射损伤模型中发现,补充热灭活双歧杆菌能够恢复肠道AHR活性,显著增强IL-22表达,进而促进组织修复。此外,共生菌(特别是毛螺菌科、瘤胃菌科等)通过发酵膳食纤维产生短链脂肪酸(short-chain fatty acids, SCFAs), SCFAs可通过激活G蛋白偶联受体(G protein-coupled receptors, GPCRs)和抑制组蛋白去乙酰化酶(histone deacetylase, HDAC),促进固有层中CD4⁺ T细胞和ILC3分泌IL-22^[39]。辐射引起的菌群紊乱导致SCFAs产量减少,影响IL-22的正常分泌。Liu等^[40]在辐射诱导的肠道损伤小鼠模型中证实,口服益生元菊粉凝胶能够增加毛螺菌、阿克曼氏菌、布劳特氏菌的丰度,提升肠道丁酸等SCFAs的水平,进而促进IL-22表达,缓解肠道炎症并促进修复。

另一方面,IL-22不仅是菌群代谢的响应因子,也积极参与菌群组成的调控。Kamioka等^[41]研究表明,IL-22通过激活STAT3通路,上调岩藻糖转移酶2(fucosyltransferase 2, FUT2)表达,诱导肠上皮细胞发生岩藻糖基化,增强肠道对病原体的定植抗性。这些岩藻糖基化产物可作为专性厌氧共生菌(如拟杆菌)优先利用的营养源,促进其生长;同时抑制某些机会性病原体(如粪肠球菌)的过度增殖,从而维持菌群平衡,预防致命性感染并减轻炎症。这一机制提示,在放射性肠损伤中增强IL-22信号可能有助于塑造有利于宿主的菌群结构,进而促进黏膜修复和屏障功能恢复。

尽管AHR、SCFAs和岩藻糖基化等关键互作机制已被初步揭示,但IL-22-菌群轴在放射性损伤中的完整调控网络、时空动态变化及其对远期后遗症(如肠纤维化、癌变)的影响仍未完全阐明。未来研究需深入探索这一复杂互作网络,并开发基于调控IL-22-菌群轴的精准干预策略(如特定菌株、代谢产物、岩藻糖基化模拟物等),为放射性肠损伤的防治提供新靶点。

3 总结与展望

放射性肠损伤是肿瘤放疗后常见的严重并发症,现有治疗手段及效果有限,亟需发展新的治疗策略。IL-22作为一种具有多靶点调节功能的细胞因

子,可通过作用于肠上皮细胞、免疫细胞及肠道微生物,在维持黏膜屏障、调控炎症反应和促进组织修复中发挥关键作用,其在炎症性肠病、肠易激综合征及肠道感染等多种消化道疾病中已显示出良好的保护潜力^[42-44]。因此,系统阐释IL-22在放射性肠损伤中的作用机制并推进其临床转化,具有重要的科学意义。

在放射性肠损伤治疗中,IL-22具有促进隐窝干细胞再生、修复肠上皮屏障、双向调节炎症反应及重塑菌群稳态等多重保护作用。然而,其临床转化仍面临诸多问题与挑战:首先,全身性给予IL-22可能导致非靶器官暴露,引发系统性炎症等不良反应^[45];其次,STAT3通路的持续激活可能促进残留肿瘤细胞增殖,存在潜在的致癌风险^[46];此外,IL-22与其他免疫因子(如IL-17、TGF- β 等)在放疗微环境中的复交互作用尚不明确;最后,患者个体间对IL-22治疗的反应存在差异,也为其精准应用带来挑战。值得关注的是,Wang等^[47]的研究表明,基线血清IL-22水平或可作为预测患者放射敏感性的生物标志物,有助于在放疗前识别高风险人群。

针对上述挑战,未来研究重点应从以下方向展开。第一,开发靶向递送系统。为避免全身给药带来的风险,可设计结肠定位的纳米载体(如树枝状大孔介孔二氧化硅纳米颗粒)或工程菌(如表达IL-22的罗伊氏乳杆菌),实现IL-22在病灶部位的特异性富集,提高局部疗效并降低系统毒性^[45,48]。第二,建立生物标志物体系。整合基因组、蛋白质组及微生物组等多组学数据,筛选与治疗反应相关的预测标志物(如STAT3通路活化状态、基线IL-22水平或特定菌群特征),为个体化用药提供依据。第三,构建菌群-免疫联合干预策略。肠道菌群及其代谢产物(如短链脂肪酸)可调节IL-22的分泌,而IL-22亦能反馈影响菌群结构,形成双向调控网络^[39]。通过益生菌、益生元或菌群移植等方式调整微环境,可能协同增强内源性IL-22的功能,形成多途径整合的治疗策略。

此外,必须高度重视IL-22的潜在致癌风险及其与放疗微环境的交互作用。需在肿瘤模型中系统评估IL-22对残留癌细胞的潜在影响,明确其安全窗口,探索术后短期应用等策略以规避风险。同时,需深入研究IL-22与放疗微环境中其他关键免疫因子(如IL-17、TGF- β 、IFN- γ)的交互作用网络,以全面评

估联合治疗潜力。最后,需要建立更接近临床场景的动物模型来评估IL-22长期使用的安全性。通过上述机制驱动的创新递送系统设计和严谨的临床转化研究,平衡IL-22的保护效应与潜在风险,将有助于推动其成为放射性肠损伤治疗的安全有效靶点。

综上,IL-22是连接免疫调控与上皮修复的关键桥梁分子。通过靶向递送、生物标志物引导及菌群-免疫协同策略,有望将IL-22发展为放射性肠损伤的有效治疗手段,未来需持续推进机制研究向临床实践的转化。

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