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肠道菌群及其代谢物在放射性肠炎中的研究进展

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摘　要

放射性肠炎是盆腔放疗后的一种常见并发症，严重影响患者的生活质量。近年来，众多研究已经证实肠道菌群失调在放射性肠炎发生发展中起着重要作用。通过调节肠道菌群来治疗放射性肠炎的研究也较多，如补充益生元或益生菌、使用抗生素减少病原菌、肠道菌群移植等。此外，研究还发现，菌群代谢物作为菌群与宿主的纽带影响着放射性肠炎的发生发展，这些代谢物包括短链脂肪酸、胆汁酸以及色氨酸代谢物等。下面将以肠道菌群及其代谢物在放射性肠炎中的研究进展进行综述。

关键词

放射性肠炎，肠道菌群，肠道菌群代谢物，短链脂肪酸，胆汁酸

Research Progress of Intestinal Flora and Their Metabolites in Radiation Enteritis

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Abstract

Radiation enteritis is a common complication after pelvic radiotherapy, which seriously affects the quality of life of patients. In recent years, many studies have confirmed that intestinal flora imbal-

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ance plays an essential role in the occurrence and development of radiation enteritis. There are also many studies on treating radiation enteritis by regulating intestinal flora, such as supplementing prebiotics or probiotics, using antibiotics to reduce pathogens, and transplanting intestinal flora. In addition, the study also found that bacterial community metabolites, including short-chain fatty acids, bile acids, and tryptophan metabolites, as a link between the bacterial community and the host, affect the occurrence and development of radiation enteritis. The research progress of intestinal flora and their metabolites in radiation enteritis will be reviewed below.

Keywords

Radiation Enteritis, Intestinal Flora, Intestinal Flora Metabolites, Short-Chain Fatty Acids, Bile Acid

1. 放射性肠炎

随着盆腔放射技术的发展和应用，有 35%~61%的盆腔恶性肿瘤患者接受过盆腔放疗[1]。有 81%的盆腔放疗患者出现了肠道症状，超过 50%的患者认为这些肠道症状影响了他们的生活质量[2]。甚至有13.2%的严重晚期肠道并发症患者需要手术来干预处理[3]。由于随访时间等因素的限制，盆腔放疗后发生影响生活质量的胃肠道症状要比一般报道所认为的还要多[4] [5]。放射性肠炎又称放射性肠损伤，根据病程可将放射性肠炎分为急性放射性肠炎和慢性放射性肠炎。急性放射性肠炎的病程局限于三个月内，而慢性放射性肠炎可由急性放射性肠炎演变而来或在三个月后新发。放射性肠炎的主要表现包括便血、腹泻、腹痛、里急后重、肛门坠胀感等。晚期严重并发症包括肠道狭窄、梗阻、穿孔、难治性出血、瘘管形成和肛门失禁等[6]。放射性肠炎发病机制尚未完全阐明，研究主要集中在肠上皮、血管内皮细胞损伤、肠道干细胞的凋亡与再生、肠道菌群失调等方面。尽管已有一定的研究进展，但目前仍缺乏有效的预防或治疗策略[7] [8] [9] [10] [11]。

2. 肠道微生物群

据研究估算，与人体共存的细菌数量约为 10^{13}~10^{14} 个，接近于人体细胞的数量[12]，菌种则超过800 种[13]。这些细菌主要分布在胃肠道、皮肤、唾液、口腔黏膜和结膜等。其中肠道菌群含量最多，高达 8×10^{13} 个[12]。人体肠道菌群主要由厚壁菌门、拟杆菌门和放线菌门、变形菌门和梭杆菌门组成[14]。高物种多样性、高微生物基因丰度和稳定的微生物核心功能是健康微生物群的标志[15]。肠道菌群及其代谢物在保护宿主免受病原体入侵、调节宿主代谢、免疫和神经系统的发育和稳态等多种生理功能中发挥作用[16]。肠道菌群也已被证实在多种疾病中发挥重要作用，这些疾病包括炎症性肠病、结直肠癌、艰难梭菌感染、乳糜泻、糖尿病、冠心病等[16] [17]。

3. 肠道菌群与放射性肠炎

3.1. 菌群失调影响着放射性肠炎的发生发展

研究发现，相比于常规饲养小鼠，无菌小鼠辐射后的肠道损伤更轻，这说明肠道菌群在肠道辐射损伤中发挥重要作用[18]。许多研究显示，放射性肠炎患者的肠道菌群发生了失调[19] [20] [21]。肠道菌群

失调削弱了肠道上皮屏障功能，进一步加重和促进肠炎的发生[22]。粪便 16S rRNA 测序结果显示，放射性肠炎患者粪便菌群 α 多样性显著降低，β 多样性显著增高。在门水平，放射性肠炎患者粪便中变形菌门丰度较高，而拟杆菌门和厚壁菌门的丰度较低。在属水平，放射性肠炎患者粪便中沙雷氏菌属、拟杆菌属和普雷沃氏菌属最为丰富，而拟杆菌属显著降低。与非放射性肠炎患者相比，放射性肠炎患者中肠杆菌科、叶杆菌科和拜叶林克氏菌科增加，拟杆菌科和瘤胃球菌科下降[19]。肠道菌群组成的特异性变化可能激活粘膜免疫系统，导致慢性炎症和黏膜损伤的发展[23]。相似的研究结果显示，辐射后变形杆菌的丰度显著增加。而疣微菌门的丰度从放疗后的 2.9%下降到 0.0006% [24]。既往研究发现，变形杆菌在健康小鼠中较低[25]。而疣微菌门可能具有潜在的抗炎特性[26]。

3.2. 恢复肠道菌群可以改善放射性肠炎

许多研究发现，恢复肠道菌群可以改善放射性肠炎。补充益生元可以改善肠道菌群的失调并减轻放射性肠炎[27] [28]。在饮食调节方面，30%的热量限制饮食预处理可以通过改变小鼠肠道菌群来减轻小鼠的放射性肠损伤[29]。益生菌在防辐射方面的研究成果颇丰，补充鼠李糖乳杆菌能够显著减轻小鼠受到的放射损伤。此外，还观察到了与抗炎相关的微生物，如叶啉单胞菌科、产酸拟杆菌以及瘤胃球菌属的优势。而促炎微生物普雷沃氏菌属的数量减少。相比之下，仅接受放射治疗的患者中，普雷沃氏菌属数量增加，拟杆菌属数量减少[30]。一项随机对照试验结果显示，相较于使用 4%福尔马林灌肠，采用结肠冲洗结合口服抗生素治疗出血性放射性直肠炎表现出了更优的疗效[31]。值得注意的是，不同的抗生素会对微生物群和代谢组造成不同的影响[32]。采用抗生素鸡尾酒预处理放射小鼠，可以改善肠道菌群失调，并通过减少炎症和预防肠道纤维化来减轻肠道损伤[24]。在小鼠的“脏笼”共享实验中，首先对小鼠进行照射并筛选出幸存者。将无菌小鼠分别放入由幸存小鼠和对照组小鼠使用过的脏笼中。结果显示，相比于对照组，放置在幸存小鼠脏笼中的无菌小鼠存活率明显提高，肠道损伤更轻。进一步的幸存小鼠粪便移植试验，也获得了类似的结果，其中接受幸存小鼠粪便的无菌小鼠展现出明显的抗辐射效果[33]。临床研究也同样证实了粪菌移植对于缓解放射性肠炎患者的便血、腹痛、腹泻等症状具有积极效果，并且这些患者的肠道菌群在粪菌移植后发生了明显的改变[34] [35] [36]。移植后的患者菌群构成与供体菌群构成相似[36]。

4. 肠道微生物代谢物

肠道微生物组中的基因数量是人类基因组的近千倍，包含高达 2200 万个基因，相比之下，人类基因组中只有 2.3 万个基因[37]。这种丰富多样的微生物基因组引入了众多非宿主编码的酶蛋白[38]。作为宿主代谢功能的一个重要补充，这些微生物的酶蛋白能代谢宿主无法消化的饮食成分[39]。据估计，超过一半的粪便和尿液中的代谢物来源于肠道微生物群或者是经过肠道微生物群修饰[40]。这些肠道代谢物包括短链脂肪酸、色氨酸衍生物、次级胆汁酸、三甲胺-N-氧化物、支链氨基酸、多胺和维生素等[41]。这些代谢物可作为连接微生物与宿主之间的重要纽带，直接或间接的影响着宿主的健康状态。

5. 放射性肠炎中的菌群代谢物

5.1. 短链脂肪酸对放射性损伤具有防护作用

短链脂肪酸是由结肠细菌发酵膳食纤维和其他复杂碳水化合物产生的细菌代谢产物。包括甲酸、乙酸、丙酸、丁酸、异丁酸、戊酸和异戊酸等。除了为结肠上皮提供能量外，还具有抗炎、抗氧化、免疫调节、肠道神经系统调节以及抗肿瘤等多种生物活性[42]。放射治疗后，菌群发生了失调，多种短链脂肪酸水平发生改变[33] [43]。其中，丁酸盐可以通过激活 G 蛋白偶联受体(GPCR)以及维持受辐照动物的肠

道细菌组成，来减轻放射性肠道损伤[44]。丙酸盐可以改善肠道炎症[45] [46]。Guo 等[33]研究发现，相比于乙酸盐和丁酸盐，丙酸盐处理的放射小鼠存活率更高，损伤更轻。此外，许多短链脂肪酸可以抑制组蛋白去乙酰化酶(HDAC)的活性，抑制 HDAC 的活性，可以减轻肠道炎症，维持肠道免疫稳态[47] [48]。戊酸盐也具有显著的 HDAC 抑制作用[49]。Li 等[43]研究发现，与丁酸相比，戊酸具有更显著的辐射防护作用。进一步的研究发现，KRT1 基因可能在戊酸介导的辐射防护中发挥重要作用。尽管关于哪种短链脂肪酸在放射保护作用中更强仍存在不同观点，但普遍认为短链脂肪酸对放射损伤具有防护作用。

5.2. 胆汁酸及其相关信号通路为放射性肠炎提供了更多潜在靶点

胆汁酸在肝细胞内合成，合成的初级胆汁酸在肠道内被细菌转化为次级胆汁酸。菌群失调会导致胆汁酸的代谢紊乱，并影响宿主的健康[50]。胆汁酸可以激活不同的胆汁酸受体，包括法尼酯 X 受体(FXR)、G 蛋白偶联受体-1 (TGR5/GPBAR1)、孕激素 X 受体(PXR)和维生素 D 受体(VDR)，并对宿主的代谢和免疫功能产生深远的影响[51]。研究显示，经过放射后的小鼠粪便中次级胆汁酸水平降低，其中石胆酸的减少最为显著。然而，当补充石胆酸后，可以通过激活与胆汁酸相关的 TGR5 信号通路，而减轻放射性损伤[52]。植物乳杆菌能通过激活肠上皮中的 FXR-FGF15 信号通路促进 DNA 损伤修复，减轻辐射损伤。当给予 FXR 的激活剂后显着减轻了辐射诱导的肠道损伤。而补充 FXR 抑制剂，则消除了乳杆菌介导的对放射小鼠回肠的保护作用[53]。此外，研究还发现二甲双胍可以通过激活 FXR 信号来减轻放射性肠损伤，而这种保护作用是依赖于二甲双胍提高乳酸杆菌丰度来实现的[54]。另有研究显示，VDR 可以通过 Pmaip1 介导的途径抑制肠道干细胞凋亡，从而减轻放射性肠道损伤[55]。还有一项研究发现，VDR 还可以靶向 HIF/PDK1 途径来缓解放射性肠损伤[56]。由此可见，胆汁酸及其相关信号通路为放射性损伤防护提供了更多可能的潜在靶点。

5.3. 色氨酸代谢物及其他菌群相关物质

研究显示，在放射后幸存的小鼠粪便中，色氨酸途径代谢物吲哚 3-甲醛和犬尿酸的浓度分别是对照组的 5 倍和 8 倍。更为重要的是，补充这些代谢物可以有效地提供辐射保护作用[33]。由色氨酸脱氨生成的吲哚丙酸，可以通过孕烷 X 受体(PXR)/酰基辅酶 A 结合蛋白(ACBP)介导的信号通路发挥肠道辐射防护作用[57]。肠道菌群参与了多种维生素代谢，研究发现，B 族维生素代谢物吡哆胺在防止辐射诱导的细胞凋亡方面比氨磷汀更有效[58]。此外，细菌自身分泌的物质 p40 也被发现能减轻肠道炎症[59]。除了菌群与代谢物间的相互作用，不同代谢物也通过相互作用影响疾病发生和发展。例如，丁酸盐可调节胆汁酸代谢预防艰难梭菌感染[60]。这些发现提供了深入理解，但仍需更多研究揭示未知机制。

6. 结语与展望

放射性肠炎与菌群失调之间的关系已被广泛关注，但具体的机制仍然不清楚。当前，大部分关于放射性肠炎的研究都集中在急性放射损伤模型上，但慢性损伤与急性损伤在病理改变和机制上存在差异。通过补充益生元、益生菌、抗生素以及菌群移植等方法改善放射性肠炎的效果已经初步显现。然而，益生菌研究中的菌株、剂量、持续时间等不一致性，以及菌群定植和安全性问题，仍需深入探究。未来，益生菌与其他治疗手段的联合应用，以及基于个体微生物组的个性化治疗方案，可能成为放射性肠炎治疗的新方向[61]。在最近的一项研究中，一种基于“盾牌”武装的益生元可以增强大肠杆菌的胃肠道抗应激能力和肠道定植效果。结果显示，给药后 16 小时，“盾牌”武装的大肠杆菌的肠道保留率高达 47.54% ± 6.06%，而裸大肠杆菌在给药后 8 小时就几乎被完全排出[62]。在未来，创新的肠道靶向药物递送系统包括水凝胶、微球和纳米颗粒，将更进一步有助于治疗效果的提升[63]。菌群移植作为目前较前卫的菌群治疗方式，但

目前 FMT 治疗放射性肠炎的临床研究都是一些小样本的研究，且都未设置对照组[34] [35] [36]，这使得我们无法确切判断病情的改善是否真正来源于 FMT 的治疗效应，还是仅仅是自然恢复的结果。同时，FMT 并发症的出现、合适供体的选择等问题都有待进一步探讨。我们盼望有更多的相关研究能为此提供更强有力的支持，同时也期待能涌现更多的研究靶点，以深入揭示菌群调控的机制在放射性肠炎中的作用，为未来的治疗策略提供更全面的科学依据。

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