[DOI]10.12016/j.issn.2096-1456.202550349

·综述·

头颈肿瘤放疗后口腔微生态失调及其干预策略的研究进展

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【摘要】 放射治疗（放疗）是头颈肿瘤的重要治疗手段之一，但在其杀伤肿瘤的同时会显著影响口腔微生态稳态，与放射性口腔黏膜炎等多种并发症密切相关。随着放疗剂量的累积与时间的延长，口腔菌群中链球菌属等的丰富度和多样性呈现下降趋势；但放疗同时会选择性地促进变形菌门、拟杆菌门等菌群的增殖，这些门类中富含多种条件致病菌。放疗通过激活核因子κB（NF-κB）通路诱发慢性炎症与氧化应激，损伤上皮屏障并抑制局部免疫，引起唾液腺等器官损伤，还可通过口腔-肠道轴引发全身性疾病，构成一个多层级、相互关联的致病网络。在干预方面，通过使用益生菌、益生元等口腔微生态调控措施，对放射性口腔黏膜炎等副反应显示出良好疗效。以唾液为载体的口腔菌群移植技术正逐渐兴起，并有望成为重建口腔微生态平衡的核心策略之一。现有干预手段为临床实践提供了初步路径，但该领域仍面临若干关键的科学问题：口腔微生态与全身性疾病的关联仍停留在相关性表面，缺乏因果性论证；口腔菌群移植的供体筛选标准、移植方案及长期安全性等关键参数尚未明确。因此，未来的研究应致力于开展大规模的临床试验，确立口腔微生态干预措施的标准化流程与安全性评价体系，探讨益生菌、益生元与菌群移植等联合治疗策略，推动个体化精准调控的发展，从而更有效地应对放疗所致口腔微生态失调，改善头颈肿瘤患者的治疗效果与生活质量。

【关键词】 头颈肿瘤；放射治疗；放射性口腔黏膜病；口腔微生态；菌群失调；益生菌；益生元；菌群移植；口腔菌群；精准调控
【中图分类号】 R78　**【文献标志码】** A　**【文章编号】** 2096-1456（2026）04-0385-10
【引用著录格式】 刘雪，李雨霏，杨薪瑶，等. 头颈肿瘤放疗后口腔微生态失调及其干预策略的研究进展[J]. 口腔疾病防治, 2026, 34(4): 385-394. doi:10.12016/j.issn.2096-1456.202550349.

微信公众号

Research progress on oral microecological imbalance and intervention strategies after radiotherapy for head and neck tumors

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【Abstract】 Radiotherapy is a crucial treatment modality for head and neck tumors. However, while effectively killing tumor cells, it significantly disrupts the homeostasis of the oral microecology, which is closely associated with various complications such as radiation-induced oral mucositis. Literature review indicates that as radiotherapy doses accumulate and treatment durations extend, the richness and diversity of the oral microbiota show a declining trend, with the genus *Streptococcus* decreasing most markedly. In contrast, radiotherapy selectively promotes the proliferation of bacte-

【收稿日期】 2025-08-11；**【修回日期】** 2025-11-11
【基金项目】 国家自然科学基金项目（82071104）；上海市重中之重研究中心（2022ZZ01017）；上海市“科技创新行动计划”长三角科技创新共同体领域项目（21002411300）；中国医学科学院医学与健康科技创新工程项目（2019-I2M-5-037）
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rial phyla such as Proteobacteria and Bacteroidetes, which are rich in opportunistic pathogens. Mechanistically, radiotherapy activates the nuclear factor-kappa B pathway, triggering chronic inflammation and oxidative stress, damaging the epithelial barrier, suppressing local immunity, and causing damage to organs such as the salivary glands. It can also induce systemic diseases via the oral-gut axis, forming a multi-level, interconnected pathogenic network. In terms of interventions, treatment strategies including probiotics and prebiotics have shown promising efficacy against side effects such as radiation-induced oral mucositis. Saliva-based oral microbiota transplantation is an emerging strategy that is expected to become widely utilized for restoring oral microecological balance. Existing interventions provide preliminary pathways for clinical practice, but this field still faces several key scientific questions. The association between oral microecology and systemic diseases remains largely correlative, lacking causal evidence. Furthermore, critical parameters for oral microbiota transplantation, such as donor screening criteria, transplantation protocols, and long-term safety, are not yet well-defined. Therefore, future research should focus on conducting large-scale clinical trials to establish standardized protocols and safety evaluation systems for oral microecological interventions, and explore combined treatment therapies such as probiotics, prebiotics, and microbiota transplantation to advance the development of personalized precision modulation. These will enable more effective management of radiotherapy-induced oral microecological dysbiosis and improve treatment outcomes and quality of life for patients with head and neck tumors.

【Key words】 head and neck tumor; radiotherapy; radiation-induced oral mucosal disease; oral microecological; microecology imbalance; probiotics; prebiotics; microbiota transplantation; oral microbiota; precision modulation

J Prev Treat Stomatol Dis, 2026, 34(4): 385-394.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from the National Natural Science Foundation of China (No. 82071104); Shanghai's Top Priority Research Center (No. 2022ZZ01017); the Yangtze River Delta Science and Technology Innovation Community Project of the "Science and Technology Innovation Action Plan" in Shanghai (No. 21002411300); Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (No. 2019-I2M-5-037).

头颈部恶性肿瘤是全球第6大常见的恶性肿瘤[1]，放射治疗（放疗）作为头颈部恶性肿瘤的主要治疗手段之一[2]，在治疗过程中常导致口腔微生态失调，同时与黏膜炎、味觉障碍、龋齿等多种副反应密切相关[3]。高通量测序技术的发展，使得从微生物层面深入分析接受放疗的头颈部肿瘤患者口腔菌群的变化特征及机制成为可能[4]。健康人群的口腔微生物群处于平衡状态，可以产生丰富的生物活性代谢物，对于维护黏膜完整性和调节免疫系统至关重要[5]。在头颈肿瘤患者放射治疗中，随着放疗剂量的累积与时间的延长，口腔菌群的丰富度和多样性发生变化，微生态稳定性显著降低[6]。本文总结头颈肿瘤放疗患者口腔微生态的变化与机制，探讨放疗患者口腔微生态的调控策略，为改善患者的治疗耐受性与长期生活质量提供理论依据。

1　放疗导致口腔微生态失衡

1.1　放疗致口腔菌群变化特征

口腔微生物群是人体内仅次于肠道菌群的第二大微生物群落，包含超过1 000种不同的微生物；在口腔内的不同生态位点，如牙齿、牙龈和舌头等，定植着具有部位特异性的菌群，形成独特的微生物“指纹”[7-8]。研究进一步表明，健康人群的唾液微生物组成与口腔疾病患者之间存在显著差异，不仅体现在物种结构上，也反映于功能基因及代谢途径的层面[9]。放疗可导致口腔菌群结构失调[10]，Gao等[11]研究显示，放疗后的龈下菌斑微生物组群的多样性和丰富度与放疗前相比均降低，其中链球菌属的减少最为显著。与此相反，放疗会选择性地促进变形菌门、拟杆菌门等菌群的增殖，这些门类中富含多种条件致病菌[12]，重塑口腔微生物群落结构[13]。Hou等[14]研究显示，在门水平上，变形菌门和螺旋体门的总体相对丰度呈现明显上升趋势，而梭杆菌门水平呈下降趋势；在属水平上，假单胞菌属、密螺旋体属、颗粒链菌属等与放射剂量呈显著正相关；普雷沃菌属、梭杆菌属、毛螺旋菌属、弯曲杆菌属、消化链球菌属和阿托波菌属等与放射剂量呈显著负相关（表1）。

表1　与放疗剂量显著相关的口腔微生物分类单元

Table 1　Oral microbial taxa showing a significant correlation with radiation doses

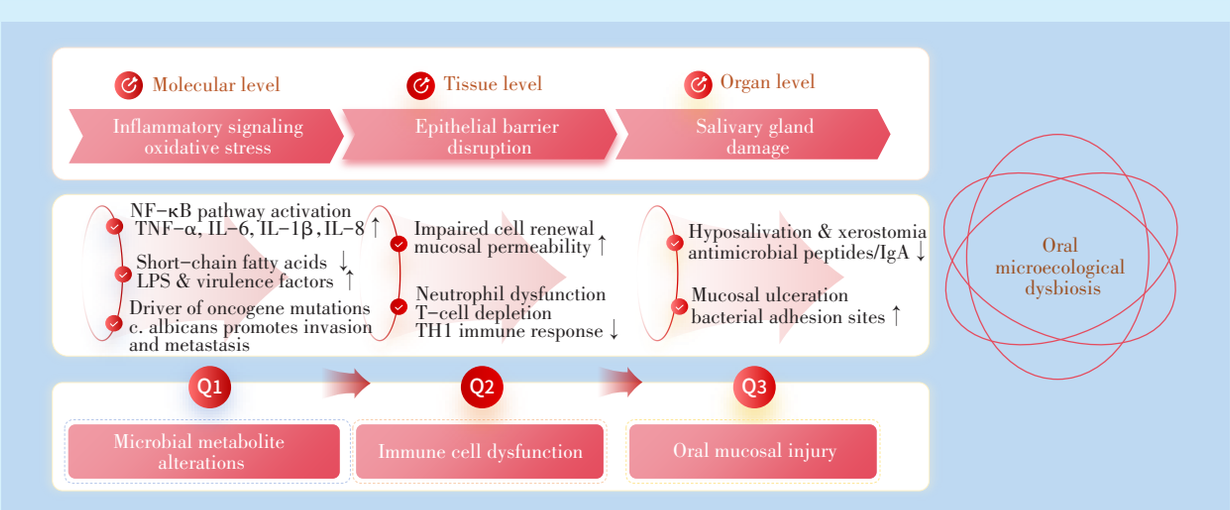
Microbial taxa	Specific species	Correlation trend
Gate level	*Proteobacteria*	Positive correlation
	Spirochaetes	Positive correlation
	Fusobacteria	Negative correlation
Genus level	*Pseudomonas*	Positive correlation
	Treponema	Positive correlation
	Granulicatella	Positive correlation
	Capnocytophaga	Positive correlation
	Prevotella	Negative correlation
	Fusobacterium	Negative correlation
	Leptotrichia	Negative correlation
	Campylobacter	Negative correlation
	Helicobacter	Negative correlation
	Peptostreptococcus	Negative correlation
	Atopobium	Negative correlation

1.2　放疗后条件致病菌的定植与感染

放疗不仅破坏口腔菌群平衡，同时削弱了正常菌群对外来病原体的拮抗作用，并改变了真菌群落的组成，导致致病菌在口腔内定植和繁殖加剧。Maurya等[15]发现放疗后大肠杆菌数量增多；Kumpitsch等[16]研究显示，放射治疗后嗜血杆菌属（*Haemophilus*）、韦荣球菌属（*Veillonella*）、颗粒链菌属（*Granulicatella*）的相对丰富度在放疗后增加，甚至检测出肠球菌（*Enterococcus*）和不动杆菌（*Acinetobacter*）等原不属于口腔的条件致病菌[17]。这些微生物原本在健康口腔中含量极低或被抑制，但放疗可能破坏局部免疫屏障，使其转变为致病菌，增加感染风险[18]。在真菌方面，Al-Manei等[19]的回顾性研究揭示了放疗过程中真菌的动态变化，首次检测到非白色念珠菌物种、茄镰刀菌和杰丁念珠菌，其真菌多样性及多物种共存现象也更显著。白色念珠菌与光滑念珠菌等主要病原体在放疗等驱动下形成了更为复杂的生态网络。监测放疗患者口腔菌群动态变化、了解放疗后口腔菌群失调的机制对预防继发感染具有重要意义。

2　放疗后口腔菌群失调的机制

放射治疗通过激活核因子κB（nuclear factor-kappa B，NF-κB）通路等引发慢性炎症与基因毒性，损伤上皮屏障并抑制局部免疫，最终导致唾液腺等器官的损伤，甚至引发全身性疾病，各层级病理变化相互关联（图1）。



This schematic illustrates the multi-level pathogenic mechanism driven by oral microecological dysbiosis as the core factor. Dysregulation at the molecular level (e.g., inflammatory signaling and oxidative stress, microbial metabolite alterations) initiates pathologies at the tissue level (e.g., epithelial barrier disruption and immune cell dysfunction). These changes progressively evolve into clinical manifestations such as salivary gland damage and oral mucosal injury. The interactions across these levels form a self-reinforcing cycle that continuously exacerbates oral microecological dysbiosis. LPS: lipopolysaccharide; NF-kB: nuclear factor-kappa B; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; IL-1β: interleukin-1 beta; IL-8: interleukin-8; IgA: immunoglobulin A; TH1: T helper 1 (cells)

Figure 1　Mechanisms of radiotherapy-induced oral microecological dysbiosis in patients with head and neck tumor

图1　头颈肿瘤患者放射治疗所致口腔微生态失调的机制

2.1　炎症信号通路激活与氧化应激

口腔微生态失调与慢性炎症[20]、基因毒素释放[21]、致癌物的产生或抗癌化合物合成的抑制有关[22]。放射线辐射引起的微生态失调将正常共生的普雷沃氏菌转化为机会性病原体，促使其产生黏附素、蛋白酶、溶血素、脂多糖和细胞外多糖[23]等毒力因子。脂多糖通过持续激活NF-κB等炎症信号通路，导致促炎细胞因子，如白细胞介素-1β（interleukin-1β，IL-1β）、白细胞介素6（interleukin-6，IL-6）和白细胞介素8（interleukin-8，IL-8）的异常大量分泌。这些细胞因子不仅是急性期反应的核心介质，其过度产生与局部及全身的氧化应激水平升高密切相关[24]。普雷沃氏菌、梭杆菌、牙龈卟啉单胞菌等病原体在NF-κB通路的激活具有协同作用，共同加剧炎症反应[25-26]。临床研究证实，癌组织中IL-6的高水平与患者不良预后以及远处转移显著相关[27]。IL-1β、IL-6和肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）可用作相关炎症的重要生物标志物[28]。

放疗所致口腔微生态失调的另一个关键因素在于，白色念珠菌等具备直接的基因毒性，能够将酒精代谢为强效致癌物乙醛，并抑制包括铁载体组非核糖体肽在内的具有抗癌活性的天然化合物的合成[22]。特定微生物的丰度与关键的致癌基因突变事件直接关联，放线菌门中的富集与抑癌基因TP53（tumor protein p53，TP53）突变有关，而厚壁菌门的大量存在与原钙黏蛋白1（FAT Atypical cadherin 1，FAT1）、轴抑制蛋白1（Axin 1，AXIN1）等通路基因的反复突变有关[21]。此外，白色念珠菌可通过增加基质金属蛋白酶的合成[29]，以促进组织侵袭、激活促肿瘤信号通路以及上调与转移事件相关的基因[30]，促进肿瘤的发生发展。

2.2　上皮屏障破坏、局部免疫细胞功能障碍

微生物群落和宿主免疫反应造成的破坏也会导致细胞因子分泌异常[31]。口腔黏膜对射线具有较高的敏感性[32]。放射线干扰口腔黏膜上皮细胞的正常更新，破坏黏膜的机械保护屏障[33]，导致黏膜损伤、糜烂甚至坏死，为口腔内细菌及代谢产物更易侵入深层组织提供了病理通道[34]。口腔中机会性病原体如牙龈卟啉单胞菌[35]，可刺激髓源性树突状抑制细胞的产生，从而抑制关键的抗肿瘤$CD8^+$T细胞功能，还可以诱导基质金属蛋白酶-9的过表达，并干扰p53等抑癌基因功能[36]，直接参与肿瘤的恶性进展[37]。

放疗产生的电离辐射会破坏黏膜表面特异性抗体屏障，具体表现为吞噬细胞、T淋巴细胞数量及功能下降，并导致特异与非特异性体液免疫因子的缺乏[38]。此外，由白细胞介素-2（interleukin-2，IL-2）、干扰素-γ（interferon-gamma，IFN-γ）和TNF-α等驱动的TH1细胞免疫反应也受到削弱，TH1反应通常与改善的临床结果相关[39]，这也促使上述细胞因子被作为癌症治疗方法进行深入研究[40]。白细胞介素-10（interleukin-10，IL-10）具有免疫抑制作用[41]，可阻止TH1细胞因子的产生，在口腔鳞状细胞癌中通常升高[42]。肿瘤基质中的中性粒细胞浸润程度与较高的中性粒细胞-淋巴细胞比率均与头颈肿瘤患者较差的总体生存率相关[43]。

2.3　唾液腺功能障碍与全身性疾病

唾液腺主要包括腮腺、颌下腺和舌下腺[44]，位于面部外侧和下颌区域，在维持口腔健康方面起着至关重要的作用[45]。在放射治疗过程中腺体通常会暴露于辐射野内，其浆液细胞具有较高的放射敏感性，放疗后会立即死亡，伴随着炎性细胞浸润至唾液腺组织[46]，放疗后，唾液腺组织常出现腺实质萎缩、间质纤维化等病变[47]。在动脉粥样硬化斑块中检测到福赛坦氏菌、放线菌和牙龈卟啉单胞菌等多种牙周病原体[48]。此外，口腔链球菌也被发现是引发细菌性心内膜炎的重要致病因子[49]。在因果关系论证中，动物模型研究提供了更为深入的机制性证据[50]，在非酒精性脂肪性肝病的小鼠模型中，无需胆碱缺乏或其他饮食、基因修饰的协同作用，单独感染II型牙龈卟啉单胞菌可增加疾病进展，口腔病原体可能是驱动疾病发展的独立致病因子[51-52]。

除心血管与代谢疾病外，牙龈卟啉单胞菌、齿垢密螺旋体、福赛坦氏菌等口腔致病菌的富集与糖尿病[53]、阿尔茨海默病[54]、肠癌[55]、胃癌[56]、胰腺癌[57]、脂肪肝疾病[58]等全身性疾病的发病率或预后存在关联。其中，在阿尔兹海默症患者脑组织中检测到牙龈卟啉单胞菌及其毒性代谢产物牙龈蛋白酶，提示了其潜在的直接神经毒性作用[59]，这也为口腔生态失调影响帕金森病等神经系统疾病的发病机制提供了合理的推测依据[60]。口腔–肠道轴是解释这些远程效应的重要通路，在健康状态下，口腔细菌在肠道中的定植能力很差[61-62]。但在肠道屏障功能受损或微生态失衡等病理状态下，口腔病原体则可在肠道中异常定植与扩增[63]。例如，在炎症性肠病、肝硬化患者[64]的肠道菌群

中，均观察到口腔来源微生物的丰度增加[65]。然而，目前大多数研究仍处于发现相关性阶段，其确切的因果关系和机制尚需要更多实验性研究证实[66]。

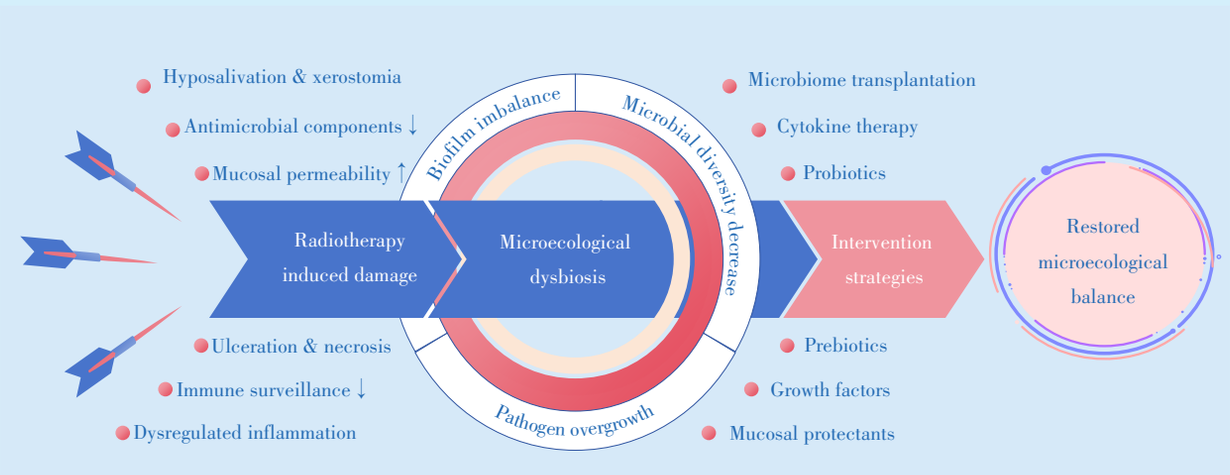
3　口腔微生态调控的干预措施

口腔微生态学说强调微生物群落的整体性和动态平衡[67]，口腔微生物群落的组成和功能在健康和疾病状态下存在显著差异[68]，通过益生菌、益生元、天然药物及菌群移植等方式维护口腔微生态平衡，已成为口腔疾病防治的新方向（图2）。

3.1　益生菌

益生菌是通过抑制或减少病原微生物来治疗疾病、改善健康的活微生物[69]。益生菌可在口腔黏膜定植或通过调节免疫抑制致病菌过度生长，减轻局部炎症反应，促进黏膜修复[70]，成为口腔疾病防治技术研究的新兴领域[71]。口腔唾液中的黏蛋白覆盖于上皮组织表面形成薄膜[72]，有助于唾液链球菌、短乳杆菌CD2和罗伊氏乳杆菌等黏附定植。Peng等[73]纳入160例接受放疗的头颈部恶性肿瘤患者的研究中，患者被随机分为口服唾液链球菌K12（*Streptococcus salivarius* K12，*Ss*K12）组与安慰剂组，*Ss*K12组每日口服3次*Ss*K12（1×10^9 CFU/次）。结果显示，*Ss*K12能显著改善放射性口腔黏膜炎的各项指标，包括降低发生率、缩短发作时间并减轻严重程度。高通量测序分析结果显示安慰剂组厚壁菌门的相对丰度呈下降趋势，放疗结束时链球菌属的相对丰度显著降低，而*Ss*K12组在放疗期间保持相对稳定。相反，安慰剂组在放疗结束时月形单胞菌属和不动杆菌属的相对丰度增加，而在*Ss*K12组中显著降低，进一步验证了口腔微生物群变化与黏膜炎的相关性。Galofré等[74]开展了1项三盲、随机对照试验，试验组每日口服1次罗伊氏乳杆菌（1×10^8 CFU/次），连续30 d，并与安慰剂组进行对比，同时对全口进行机械清创，发现黏膜炎种植体中牙龈卟啉单胞菌的细菌载量显著降低，能够减轻黏膜炎的严重程度。同时Feng等[75]研究发现，含漱或口服特定益生菌制剂可显著降低口腔黏膜炎的严重程度和发生率，改善患者进食疼痛和生活质量。

短乳杆菌CD2是相关研究中涉及最广泛的益生菌。其活性制剂含有不少于2×10^9 CFU的活菌，并主要通过降低精氨酸的生物利用度来发挥其抗炎特性[76]。此外，乳杆菌和拟杆菌属可触发树突状细胞产生Ⅰ型干扰素[77]，增强抗肿瘤$CD8^+$T细胞的交叉启动，对免疫刺激作用产生影响[78]。双歧杆菌、BIFICO益生菌组合（长双歧杆菌、嗜酸乳杆菌、乳酸球菌）可以通过口腔-肠道微生物轴定植于胃肠道，影响肠道微生物群，提高头颈部肿瘤患者的免疫反应，同时肠道微生物群也可能通过微生物轴影响口腔微生态。Xia等[79]对接受同步放化疗的鼻咽癌患者予以含双歧杆菌为主的益生菌



This figure illustrates the cascade of oral pathological consequences resulting from radiotherapy (e.g., hyposalivation, impaired mucosal barrier, decreased immune surveillance, and dysregulated inflammation) and the corresponding potential intervention strategies (e.g., microbiome transplantation, cytokine therapy, and probiotics) aiming to restore a balanced microecology

Figure 2　Pathological progression and intervention strategies for radiotherapy-induced damage in patients with head and neck tumor

图2　头颈肿瘤患者放射治疗性损伤的病理演变与干预策略

组合（1×10^9 CFU植物乳杆菌MH-301+ 1×10^9 CFU动物牙孢杆菌LPL-RH+1×10^9 CFU鼠李糖乳杆菌LGG-18+1×10^9 CFU嗜酸乳杆菌），每日2次，每次1粒），可显著降低患者黏膜炎的严重程度，并缓解T淋巴细胞数量的下降，进一步通过小鼠实验证实，此益生菌干预对肠道微生物群具有改善作用，这与Guo等[80]对双歧杆菌的研究结论一致。Jiang等[81]在接受同步放化疗的鼻咽癌患者的研究中发现，放化疗全程口服BIFICO益生菌，2次/ d、每次服用3粒，可以显著降低口腔黏膜炎的发病率，减轻其严重程度。

3.2　益生元

益生元是能够选择性促进口腔内有益菌生长，抑制有害菌活动的化合物，有助于维持口腔微生态的平衡[82]，常用于自身有益菌数量尚可，但需要进一步促进其生长或防御菌群失调的患者。Morsy等[83]通过局部使用Omega-3纳米乳胶对口腔微生物组的影响，发现厚壁菌门/拟杆菌门比例显著降低，且Omega-3组黏膜炎分级均显著低于常规治疗组。医护人员应全面评估放疗导致的口干[84]、味觉障碍[85]、黏膜炎[86]、疼痛[87]等副反应程度，结合患者的生物标志物[88]、免疫参数[89]、饮食[90]等，选择合适的益生菌、益生元等调控口腔微生态[91]，预防感染，提供个性化的干预措施，增强患者战胜疾病的信心。

3.3　口腔菌群移植的探索

口腔菌群移植是指将健康供体的口腔微生物群落移植到患者口腔，以恢复微生态平衡的创新疗法[92]。近年来，随着菌群移植技术的迅速发展，肠道菌群移植已被大量研究证实可安全有效地用于治疗复发性难辨梭状芽孢杆菌感染[93]与炎症性肠病[94]等多种消化道疾病，并逐渐成为治疗儿童孤独症[95]、尿路感染[96]等疾病的潜在策略。然而，与相对封闭的肠道环境不同，口腔作为一个直接与外界相通的开放环境[97]，其菌群易受饮食、呼吸及口腔卫生习惯等因素影响，导致口腔菌群移植的临床研究较肠道菌群移植滞后。Xiao等[98]将健康小鼠的口腔微生物移植到放射性口腔黏膜炎模型小鼠（每日1次，每次5×10^6 CFU/150 uL，连续10 d），高通量测序显示，口腔菌群移植显著提高了受体小鼠菌群的α多样性，逆转了放疗引起的乳杆菌属丰度的升高，恢复了口腔微生态多样性，同时口腔菌群移植减少了受体小鼠的体重下降、脱发和黏膜炎等症状。Goloshchapov等[99]报道了1例6月龄神经母细胞瘤患儿的临床案例，该患儿在化疗期间每天接受其健康母亲的13.5 mL唾液进行口腔菌群移植，最终仅出现1级黏膜炎。进一步分析显示，患者口腔中葡萄球菌与黄色单胞菌等病原菌的相对丰度降低，而链球菌等相对丰度增加。研究指出，口腔唾液的中性pH环境及其所含的免疫球蛋白有助于维持菌群稳态[100]，以唾液为载体的口腔菌群移植有望成为防治口腔微生态失调的潜在核心策略。

4　小　结

放疗在有效杀伤头颈肿瘤的同时，会破坏患者的口腔微生态平衡，损伤口腔黏膜、唾液腺等，甚至可能通过口腔-肠道轴等途径影响全身系统性疾病的发生与发展。目前益生菌、益生元、菌群移植等多种口腔微生态的调控策略已被证实能够竞争性抑制致病菌、有效稳定口腔微生态，未来可进一步探索联合疗法，优化靶向调控策略。同时，必须高度重视安全性问题，系统评估潜在机会致病菌的传播风险、对宿主免疫系统的远期影响，以及对口腔乃至远端器官微生态平衡的干扰。在技术层面，基于基因组学、微生物组学及蛋白质组学等多组学数据，筛选并验证可用于临床诊断的口腔微生态失调关键生物标志物；进而开发便捷、高效的微生态诊断试剂盒，为口腔疾病的早期预警、疗效动态监测及益生菌等干预措施的精准实施提供实用工具，为构建口腔与全身系统性疾病的双向、协同调控体系奠定基础，最终推动基于微生态的个体化健康管理模式的建立。

【Author contributions】 Liu X wrote the article. Li YF, Yang XY, Li H, Zhang AL, Cui L, Huang ZW collected the references, revised the article. Hou LL conceptualized the article, guided and critically reviewed the article structures. All authors read and approved the final manuscript.

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