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·牙周医学专栏　综述·

牙周炎与炎症性肠病的相关性研究进展

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【摘要】　牙周炎是由菌斑微生物引起的牙周支持组织慢性炎症性疾病，而炎症性肠病（inflammatory bowel disease，IBD）是以胃肠道损伤为特征的慢性炎症性疾病。研究发现，二者存在密切关联。肠道菌群在IBD发展过程中发挥重要作用。当肠道菌群出现紊乱时，会引发肠道屏障破坏，激发免疫炎症反应，影响IBD的疾病进程。牙周炎患者和健康个体的唾液菌群存在显著差异，牙周致病菌可随唾液进入肠道，通过影响肠道菌群组成、免疫反应、肠道代谢物生成、肠道屏障功能间的相互作用，参与IBD的发生发展。目前，针对肠道菌群的干预策略（如粪菌移植和益生菌补充）在牙周炎治疗中显示出潜在应用价值。这些方法可能通过调节菌群，对牙周炎和IBD发挥协同治疗作用。本文对牙周炎与炎症性肠病的相关性研究进展进行综述，以期为两种疾病的防治提供新思路。

【关键词】　牙周炎；　唾液菌群；　口-肠轴；　肠道菌群；　炎症性肠病；　溃疡性结肠炎；　克罗恩病；　益生菌
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Research progress on the association between periodontitis and inflammatory bowel disease

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【Abstract】　Periodontitis is a chronic inflammatory disease of the periodontal supporting tissues caused by plaque microorganisms, whereas inflammatory bowel disease (IBD) is a chronic inflammatory disease characterized by gastrointestinal tract damage. Studies have revealed a close association between periodontitis and IBD, and gut microbiota has been shown to play an important role in the development of IBD. When the gut microbiota is disturbed, it leads to intestinal barrier disruption, triggers immune-inflammatory responses, and influences IBD progression. There are significant differences between the salivary microbiota of periodontitis patients and healthy individuals, and periodontal pathogens can enter the intestinal tract with saliva and participate in the development of IBD by influencing the interactions between gut microbiota composition, immune responses, metabolite production, and intestinal barrier function. Current gut microbiota-targeted intervention strategies, such as fecal microbiota transplantation (FMT) and probiotic supplementation, have shown potential therapeutic value in the treatment of periodontitis. These approaches may exert synergistic effects on both periodontitis and IBD through microbiota modulation. This review summarizes research progress on the relationship between periodontitis and IBD to provide a foundation for the prevention and treatment of these two diseases.

【Key words】　periodontitis;　salivary microbiota;　oral-gut axis;　gut microbiota;　inflammatory bowel disease;　ulcerative colitis;　Crohn's disease;　probiotics
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牙周炎是由菌斑微生物引起的牙周支持组织的慢性炎症性疾病，发病率高，容易复发，主要表现为牙周支持组织炎症、牙槽骨吸收、牙齿松动及丧失[1]。近年来的研究表明，牙周炎与糖尿病[2]、心血管疾病[3]、类风湿性关节炎[4]以及炎症性肠病（inflammatory bowel disease，IBD）[5]等多种全身系统性疾病密切相关。

IBD是一种以慢性、复发性炎症反应和胃肠道损伤为特征的疾病，包括克罗恩病（Crohn's disease，CD）和溃疡性结肠炎（ulcerative colitis，UC）。在中国，IBD的发病率呈上升趋势，平均每10万人中就有10.04人患有IBD，严重影响患者生存质量[6-7]。大量研究表明IBD与牙周炎之间密切相关[8-9]。IBD患者牙周炎的患病率显著高于非IBD对照组[10]。一项病例对照研究结果显示，IBD患者牙周筛查评分≥5的比例较对照组显著上升[11]。另一项队列研究表明，牙周炎可能会增加CD和UC的发病风险[12]。笔者对牙周炎与炎症性肠病的相关性研究进展进行综述，以期提升对牙周炎影响全身系统性疾病的认识，并为牙周炎及IBD的防治提供新的策略和思路。

1　牙周炎导致肠道菌群紊乱的途径

“口-肠轴”是口腔与胃肠道联系的交互通道，其功能状态会影响胃肠道疾病的发生发展[13-14]。尽管传统观点认为胃酸和胆汁酸能清除口腔细菌，阻止其到达下消化道，但最新研究显示，部分口腔细菌，如以生物膜形式培养的牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P. gingivalis*），对酸性环境具有耐受性[15]。唾液腺切除后，小鼠肠道结构和肠道菌群发生显著改变，包括乳杆菌科丰度增加和消化链球菌科丰度改变，表明唾液菌群能影响肠道菌群[16]。给予无菌小鼠人类唾液细菌后，在小鼠肠道中检测出克雷伯菌等口腔细菌[17]。在口腔炎症环境下，克雷伯菌能通过调整细菌表面电荷、亲疏水性或形成特定的黏附结构等方式，促进其在肠道中的定植[18]。Schmidt等[19]、Abdelbary等[20]的工作揭示，约三分之一的肠道细菌菌株源自口腔，或是同一口腔菌株的特殊肠道亚型，且IBD与肠癌患者口腔和粪便间的微生物传播程度显著高于健康对照组。因此，大量口腔细菌通过“口-肠轴”进入肠道，改变肠道菌群，诱发炎症反应[21]。

牙周炎患者唾液中含有大量牙周致病菌，细菌总量和多样性显著高于健康个体[22-23]。与健康个体相比，牙周炎患者肠道菌群失调，表现为乳杆菌科、梭菌科和消化链球菌科等丰度增加[24]。牙周治疗则改善肠道菌群，进一步证实牙周炎对肠道菌群的负面影响[24-25]。本团队研究发现，唾液菌群在肠道中持续存在至少24 h，牙周炎患者粪便样本中唾液来源微生物数量增加，且牙周炎唾液灌胃后小鼠肠道菌群紊乱[23, 25]。上述研究表明，牙周致病菌可通过唾液进入胃肠道，影响肠道菌群。

2　牙周致病菌参与IBD的发生发展

肠道菌群是定植于肠道内的微生物群落的总称，肠道菌群紊乱不仅影响生理功能，还与多种疾病的发生存在密切关联，如IBD、糖尿病、阿尔茨海默病等[26]。IBD患者肠道菌群的α多样性显著低于非IBD对照组[27]。粪肠球菌作为菌群失调的重要组成部分，可加剧IL-10$^{-/-}$小鼠的结肠炎[28]。上述研究都表明肠道菌群在IBD发展进程中发挥关键作用。

口腔细菌通过肠道菌群参与IBD的发生发展。研究发现，IBD患者粪便样本中*P. gingivalis*与具核梭杆菌（*Fusobacterium nucleatum*，*F. nucleatum*）的相对丰度显著高于对照组[29]。这些口腔细菌在进入肠道后，直接影响肠道功能。*P. gingivalis*植入结肠炎小鼠直肠后，小鼠疾病活动指数、结肠上皮丢失和炎性细胞浸润显著增加[29]。*F. nucleatum*可加重肠道菌群紊乱，导致胆汁酸代谢失调和上皮损伤[30]。伴放线聚集杆菌感染后，小鼠肠道菌群紊乱，结肠中巨噬细胞、中性粒细胞和单核细胞数量显著减少[31]。从唾液中分离的克雷伯菌属和肠杆菌属可激活辅助性T细胞1（T helper cell 1，Th1）、Th17和炎症小体，促进结肠炎发展[32-33]。本课题组

发现，清除肠道菌群可减轻牙周炎对糖代谢的影响，提示肠道菌群可能在牙周炎与全身性疾病之间起到桥梁作用[34]。在牙周炎小鼠中，*P. gingivalis*可通过色氨酸代谢途径加剧牙槽骨损伤，导致口腔和肠道菌群失调[35]。口服*P. gingivalis*可增加拟杆菌门丰度，降低厚壁菌门等丰度，进而加剧结肠炎[36]。此外，清除肠道菌群能够改善小鼠结肠炎诱导的焦虑样行为，粪菌移植实验进一步证明，牙周炎患者唾液菌群灌胃小鼠的粪菌可加剧结肠炎诱导的焦虑样行为[5, 37]。这些研究均提示肠道菌群是牙周致病菌影响IBD的关键因素。

3　牙周炎通过肠道菌群影响IBD的机制

肠道共生菌是宿主肠道内长期稳定存在的微生物，可激活免疫反应、维持免疫细胞稳态并调节免疫系统。当共生菌的平衡遭到破坏时，多种肠道功能受到影响，包括免疫反应、肠道代谢物的生成以及肠道屏障功能的完整性。牙周炎通过肠道菌群影响上述三者间的相互作用，进而影响IBD的发生发展。

3.1　免疫反应

微生物结构中的保守成分即病原相关分子模式（pathogen-associated molecular patterns，PAMP）能够穿越肠道屏障并异位至其他组织，刺激Toll样受体（Toll-like receptors，TLR）和NOD样受体等模式识别受体，进而激活免疫反应[38-39]。生理状态下，肠道菌群通过提供抗原激活T淋巴细胞、树突状细胞等免疫细胞，维持肠道免疫耐受性或发挥免疫应答作用。然而，当肠道稳态被破坏时，肠道菌群来源的PAMPs会激活宿主的模式识别受体，启动信号传导通路，促进炎症反应。Zhan等[40]发现，小韦荣氏球菌可通过LPS-TLR4途径诱导M1型巨噬细胞活化，释放大量促炎因子，进一步加重肠道菌群失调和炎症进展。Wang等[41]研究发现，3型固有淋巴细胞通过分泌IL-22调控肠道菌群，限制病原菌感染。因此，肠道菌群与免疫反应相互作用，参与疾病进程。

牙周炎可加剧局部氧化应激、促进免疫逃避和损害肠道屏障功能，致使微生物产物和炎症介质进入循环，进而加重全身性炎症反应。研究表明，相较于健康个体，牙周炎患者龈沟液、血清和唾液中的炎症介质和免疫细胞发生变化，如IL-1β、IL-6、TNF-α及中性粒细胞数量显著升高，对全身性疾病的发展产生重要影响[42-43]。牙周致病菌可能构成牙周炎和IBD之间的微生物桥梁。研究显示，在小鼠牙周炎合并结肠炎模型中，口腔内的适应性免疫被激活，牙周致病菌产生大量Th17，Th17迁移到肠道淋巴结并被异位至肠道的牙周致病菌所诱导，从而促进结肠炎的发展[32]。*P. gingivalis*释放的毒力因子可诱导原始$CD4^+$ T细胞转化为Th17，增加IL-17产生，同时抑制调节性T细胞（regulatory T cells，Treg）及IL-10产生，加剧结肠炎的严重程度[44]。*P. gingivalis*还通过改变肠道菌群构成和增加小肠$IL\text{-}9^+$ $CD4^+$ T细胞数量，破坏上皮屏障功能，间接诱发肠道炎症[45]。*F. nucleatum*则通过感染肠上皮细胞分泌IL-8，提高中性粒细胞的趋化性，加重肠道屏障损伤，导致疾病恶化[46]。这种口腔与肠道免疫反应之间的作用可能是双向的。Nagao等[47]证明肠道内异位定植的*P. gingivalis*能够激活Th17，使其在派尔集合淋巴结中分化，并在口腔感染时迁移到口腔部位并聚集，提示牙周致病菌可通过肠道免疫加剧牙周炎。这些微生物及其介导的免疫反应共同扰乱免疫平衡，推动IBD的发生发展。

3.2　肠道代谢物

肠道菌群在进行多种代谢活动时，会产生大量代谢产物。这些代谢产物不仅影响肠道功能，还能进入体循环，影响远端宿主免疫反应。目前，研究较多的肠道代谢物包括短链脂肪酸、色氨酸和胆汁酸相关代谢物。

短链脂肪酸主要由厌氧微生物发酵膳食纤维产生，为肠上皮细胞提供能量并参与调节肠道免疫。研究表明，肠道菌群来源的短链脂肪酸可抑制γδ T细胞中IL-17的产生，且可能通过组蛋白去乙酰化酶依赖性方式调节γδ T细胞[48]。丁酸盐和丙酸盐作为主要的短链脂肪酸之一，大量证据表明其在调节免疫反应和改善上皮屏障功能方面具有重要作用[49-50]。回归分析发现，牙周炎症表面积与肠道菌群失调有关，主要是产生短链脂肪酸的细菌数量减少[51]。牙周致病菌*P. gingivalis*可破坏肠道菌群的组成，减少短链脂肪酸产生和紧密连接蛋白表达，影响肠道功能[13]。

色氨酸代谢物是另一类备受关注的肠道代谢物。肠道菌群可将外源性色氨酸直接转化为芳香烃受体（aryl hydrocarbon receptor，AhR）的配体，调节宿主免疫稳态及肠道屏障功能[52]。研究显示，将富含色氨酸的肠道菌群移植到经过抗生素预处理的小鼠，可显著减轻葡聚糖硫酸钠（dextran sul-

fate sodium，DSS）诱导的结肠炎症状[53]。本团队前期研究发现，牙周炎患者唾液菌群灌胃后，小鼠肠道菌群紊乱，影响色氨酸-AhR信号轴的表达，损伤肠道屏障功能[54-55]。

胆汁酸在小肠内促进脂质吸收或排泄，并作用于多个器官影响机体代谢与免疫功能，与IBD的发生发展密切相关[56-57]。*F. nucleatum*可诱发肠道炎症、上皮屏障功能障碍、肠道菌群失调和胆汁酸代谢紊乱，加剧结肠炎症状[30]。此外，*P. gingivalis*灌胃可引起肠道菌群结构紊乱和亚油酸水平下降，补充亚油酸则以AhR依赖性方式缓解结肠炎症状及Th17/Treg失衡[36]。本团队研究还发现，牙周炎患者唾液菌群通过改变肠道和大脑代谢组学中的组氨酸代谢，直接影响宿主肠道菌群，加剧结肠炎诱导的焦虑样行为[37]。综上所述，肠道菌群衍生的代谢物对于维护肠道稳态、预防黏膜和全身感染至关重要。牙周炎通过影响肠道代谢物，参与IBD的发生发展。

3.3　肠道屏障

肠道屏障是机体抵御外界微生物及抗原入侵的关键防线。生理状态下，肠道共生菌的鞭毛蛋白、LPS和肽聚糖等PAMPs通过与表面识别受体结合，激活先天免疫反应，促进抗菌肽产生，维持肠上皮细胞中紧密连接蛋白的正常分布，从而维护肠道屏障功能[58]。一旦上皮细胞受损，机械屏障通透性增加，会直接引发肠道局部炎症、感染、IBD和乳糜泻等反应。例如，沙门氏菌等病原体可破坏肠上皮结构完整性，导致水和电解质流失至肠腔引发腹泻；而胃肠道感染可促使细菌异位至肠黏膜，产生炎症，进一步加重肠道屏障功能障碍，形成恶性循环[59]。从CD患者肠系膜脂肪组织中分离出的克雷伯菌可抑制ZO-1的表达，损害肠道屏障[60-61]。肠道黏液层位于肠上皮与肠道微生物之间，主要由杯状细胞分泌的黏蛋白2组成，既能抵御细菌入侵，也为肠道菌群提供营养[62]。Foxo1是调节杯状细胞分泌黏液的关键因子，Foxo1缺陷会导致黏蛋白2减少，肠道菌群中产生短链脂肪酸的菌群数量减少，进而破坏肠上皮的紧密连接，增加机体对肠道炎症的易感性[63]。有研究指出，*F. nucleatum*可显著降低正常肠上皮细胞间紧密连接蛋白的表达水平，并通过其LPS激活结肠炎小鼠肠上皮细胞的自噬性死亡，加剧肠道炎症[64]。此外，*F. nucleatum*衍生的细胞外囊泡可下调抗炎细胞因子和细胞间紧密连接蛋白ZO-1和Occludin的表达，损害肠道屏障功能[65-66]。因此，牙周炎可通过扰乱肠道菌群稳态，破坏肠道屏障功能，增加疾病易感性。

4　以牙周致病菌为靶点的治疗策略

牙周炎与IBD之间紧密关联，牙周致病菌可通过影响肠道菌群促进IBD的疾病进程。以牙周致病菌为靶点，通过牙周治疗和益生菌等策略，有望在牙周炎和IBD治疗中实现协同作用。

牙周治疗通过清除感染灶、减少致病菌负荷，阻断其向肠道的传播，为IBD管理提供了新方向。研究表明，在ApoE$^{-/-}$小鼠中，非手术牙周治疗具有改善肠道菌群和牙周炎诱导的肠黏膜屏障损伤的趋势[25]。消除牙周炎症可减少结肠炎大鼠固有层中的炎症细胞数量，恢复肠道上皮屏障[67]。牙周炎与嘌呤代谢异常有关，嘌呤降解酶抑制剂有可能作为一种免疫调节剂，调节肠道菌群失调，通过抑制炎症、氧化应激反应和抗破骨作用，对牙周炎起到辅助治疗作用[68]。此外，外泌体治疗可改善牙周炎，同时恢复IBD的免疫反应[69]。两项临床试验也证实，牙周干预可缓解口腔菌群失调并改变肠道菌群[70-71]。这些研究揭示了牙周干预通过重塑口腔和肠道菌群稳态进而调控IBD的潜在作用，为个性化治疗方案的制定提供依据，以优化治疗效果。

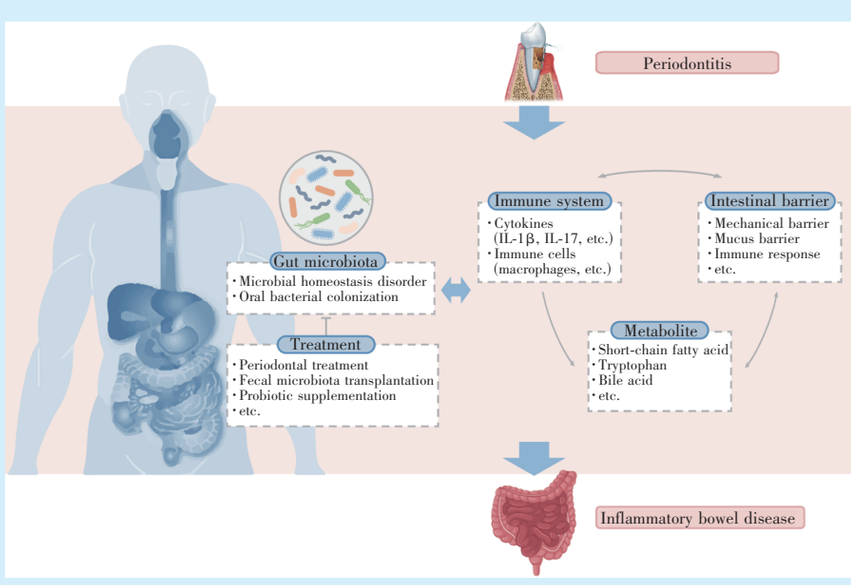
如前所述，牙周致病菌可通过唾液进入肠道，因此针对肠道菌群的治疗也不容忽视。目前，肠道菌群的治疗包括粪菌移植和益生菌补充等，能够通过调节肠道菌群，增强机体免疫力。粪菌移植是一种将健康供体粪便中的菌群移植到患者消化道中的治疗方法，通过调节肠道菌群及其代谢物，改善IBD[72-73]。研究显示，粪菌移植可修复肠道菌群及肠道屏障，降低口腔菌群的致病性，缓解牙槽骨的流失[74]。益生菌是一类能够定植于肠道并改变宿主微生物群落的有益活性微生物，其主要功能包括维持肠道菌群稳态、增强肠道屏障功能以及调节免疫反应。鼠李糖乳杆菌通过调节肠道菌群和血液代谢物恢复高脂血症背景下牙周缺损的骨再生能力[75]。双歧杆菌等益生菌通过调节肠道菌群和骨免疫反应来有效减轻雌激素缺乏下的牙槽骨流失[76]。嗜黏蛋白阿克曼氏菌可改善*P. gingivalis*引起的牙周组织损伤[77-78]。此外，Nijakowski等[79]研究发现，用生物制剂治疗UC患者也会改善口腔宿主防御功能。肠道代谢物氧化三甲胺-N-氧化物通过调节肠道菌群结构以及肠道免

疫功能，诱发肠道慢性炎症，而降低氧化三甲胺-N-氧化物的水平则有效延缓牙周炎的进展[80]。尽管粪菌移植和益生菌等在牙周炎治疗上显示出一定应用潜力，但目前在粪菌移植供体的筛选、粪菌的制备、给药频率和途径，以及益生菌的最佳剂量、治疗方案、作用机制等实际应用环节尚未达成共识。相关领域的研究数量有限，其长期安全性以及标准化流程的构建仍需进一步明确和完善。

5　总结与展望

综上所述，牙周致病菌可以通过唾液菌群进入胃肠道，影响肠道菌群的组成与功能。肠道菌群在维护肠道屏障功能、维持肠道免疫稳态以及调节肠道代谢物等方面发挥关键作用，影响IBD的发展。因此，肠道菌群可能是牙周炎影响IBD的关键因素。本研究总结了牙周炎与IBD的关系（图1），探讨了可能机制，为探究牙周炎与全身系统性疾病的发病机制和防治提供了新思路。

尽管牙周炎与IBD的关联研究已取得显著进展，但仍需进一步探索。首先，牙周炎影响肠道菌群的具体机制仍需探讨，如牙周致病菌在肠道中的定植机制、细菌间和细菌-宿主间的相互作用机制等。其次，目前多数研究基于DSS诱导的结肠炎模型，但该模型与临床IBD的发病机制存在差异，相关成果的普适性仍需验证。此外，目前大多数研究针对单一细菌的作用，牙周炎状态下口腔/肠道菌群失调对疾病的影响机制仍未探明。最后，在治疗策略方面，针对牙周致病菌的干预措施包括牙周治疗、粪菌移植和益生菌等，现有研究已初步揭示其在牙周炎与IBD共病治疗中具备协同增效的潜在价值，但仍需更多临床研究进一步探索验证相关机制并优化治疗方案。未来研究应聚焦于治疗方法创新、作用机制阐明以及模型优化等方面，以推动该领域研究向纵深发展。



IL-1β: interleukin-1β. IL-17: interleukin-17

Figure 1　Periodontitis is associated with inflammatory bowel disease

图1　牙周炎与炎症性肠病具有相关性

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