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在线全文

牙周炎通过口-肠轴影响系统性疾病的研究进展与展望*

张树伟，李玉超，杨 泽，黄海凤，潘亚萍△
中国医科大学附属口腔医院 牙周病科（沈阳 110002）

【摘要】 牙周炎作为全球高发的慢性感染性炎症疾病，其危害已远超口腔局部，大量研究表明牙周炎与糖尿病、心血管疾病、炎症性肠病、类风湿性关节炎等多种全身疾病存在密切关联。口-肠轴作为连接口腔与全身的关键通路，通过唾液菌群异位定植、肠道微生态失衡、肠道屏障破坏与全身性炎症，成为牙周炎影响全身健康的重要机制。本文梳理了近年来国内外聚焦牙周炎通过口-肠轴影响牙周共病的相关研究，包括临床研究、动物实验、体外研究等，综述牙周炎通过口腔致病菌异位定植、免疫炎症、宿主因子调控及代谢紊乱等扰动肠道稳态，经由口-肠轴途径影响系统性疾病的研究进展，为牙周炎相关全身疾病的防治提供新视角。

【关键词】 牙周炎 口-肠轴 异位定植 肠道菌群 系统性疾病 综述

Recent Research Progress and Prospects on Periodontitis Affecting Systemic Comorbidities via the Oral-Gut Axis

ZHANG Shuwei, LI Yuchao, YANG Ze, HUANG Haifeng, PAN Yaping△. *Department of Periodontics, School and Hospital of Stomatology, China Medical University, Shenyang 110002, China*
△ Corresponding author, E-mail: yppan@cmu.edu.cn

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[Abstract] Periodontitis is a prevalent chronic infectious and inflammatory disease worldwide, which imposes harms extending far beyond the oral cavity. A large body of research has demonstrated that periodontitis is closely associated with various systemic diseases, such as diabetes mellitus, cardiovascular diseases, inflammatory bowel disease, and rheumatoid arthritis. Serving as a crucial pathway connecting the oral cavity to the entire body, the oral-gut axis becomes the core mechanism through which periodontitis affects systemic health, primarily via the ectopic colonization of salivary microbiota, intestinal dysbiosis, intestinal barrier disruption, and systemic inflammation. This review summarizes recent studies focusing on how periodontitis influences systemic comorbidities via the oral-gut axis, encompassing clinical studies, animal experimental and *in vitro* research. We summarize the research progress regarding how periodontitis perturbs intestinal homeostasis through ectopic colonization of oral pathogenic bacteria, immunoinflammation, host factor regulation, and metabolic disorders, and eventually affects systemic diseases via the oral-gut axis. This review aims to provide a new perspective for the prevention and treatment of periodontitis-related systemic comorbidities.

[Key words] Periodontitis Oral-gut axis Ectopic colonization Gut microbiome Systemic comorbidities Review

牙周炎是一种破坏牙齿支持组织的炎症性疾病，全球患病率超过60%，是影响口腔健康和全身健康的公共卫生问题[1]。牙周炎与全身系统性疾病的关联及其作用机制一直是学者们关注的热点，尽管近年来相关研究已取得长足进展，但其相互作用的核心调控通路、因果关系验证及临床转化应用等关键科学问题仍未完全阐明，亟待进一步深入探究。根据牛津大学循证医学中心的证据分级标准，目前已明确牙周病是糖尿病（A级证据）和心血管疾病（B级证据）的独立危险因素。牙周病还与类风湿性关节炎（rheumatoid arthritis, RA）（B级证据），消化系统疾病尤其是炎症性肠病（inflammatory bowel disease, IBD）（B级证据）等关系密切[2]。此外，牙周病还与骨质疏松症、阿尔茨海默病等全身疾病相关[3-6]，但证据尚不充分。近年来，随着“口-肠轴”理论的兴起，越来越多研究表明，牙周炎引发的口腔菌群失调、致病菌移位及宿主炎症反应，通过口-肠轴途径重塑肠道微生态，破坏肠道屏障完整性，进而诱发或加重IBD、2型糖尿病（type 2 diabetes mellitus,T2DM）、心血管疾病、类风湿性关节炎、代谢相关脂肪性肝病（metabolic dysfunction-associated fatty liver disease, MAFLD）、神经退行性疾病等多种全身系统性疾病[3,7-11]（图1）。唾液途径被认为是牙周病与全身

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△ 通信作者，E-mail: yppan@cmu.edu.cn
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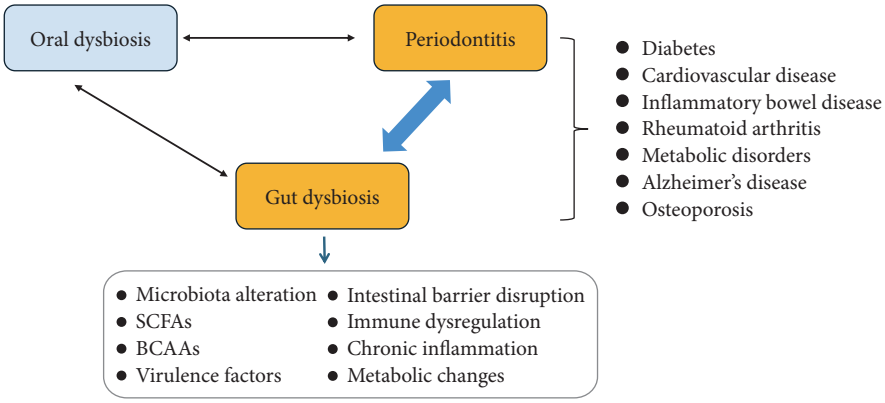

图 1 牙周炎通过口-肠轴途径影响系统性疾病

Fig 1 Periodontitis affects systemic comborbidities via oral-gut axis

SCFAs: short chain fatty acids; BCAAs: branched chain amino acids.

疾病关联途径之一[12]。口腔内约有700种微生物,致病菌可能随着吞咽唾液进入肠道并在肠道存活,调节肠道菌群。然而口腔微生物的定植机制及其在引发或加重其他器官疾病中所发挥的作用目前尚未完全阐明。本文主要基于近年来发表的临床研究、动物实验、体外研究等多类型研究证据,就牙周炎通过"口-肠轴"调控牙周炎共病的最新研究进展做一综述,以期为牙周炎相关全身疾病的早筛及防治提供理论支撑。

1 口-肠轴介导牙周炎全身影响的核心机制

口腔与肠道作为消化道的两端,同属于黏膜免疫系统,是人体中最复杂的两个微生态系统,在维持人体各种生理平衡中发挥重要作用[12]。口腔中包含700多种细菌,主要以生物膜形式定植于口腔黏膜、唾液、牙菌斑等位置,多样化的口腔微生物群与宿主免疫系统共同维持口腔稳态[13]。口腔与肠道在解剖结构上连续,为口腔致病菌易位及其代谢物通过肠道传播提供可能。健康人口腔菌群以有益菌为主,迁移至肠道后难以定植,对肠道微生态影响微弱[14]。而牙周炎患者唾液中致病菌丰度显著升高,特别是牙龈卟啉单胞菌(*P. gingivalis*)、具核梭杆菌(*F. nucleatum*)等通过吞咽进入肠道后可实现异位定植,细菌脂多糖、菌毛、外膜囊泡等毒力因子异常扩散改变肠道微生态,导致肠道菌群失衡,代谢改变,肠道屏障功能受损和免疫失衡,进而影响全身性疾病的进展[15-18]。最近一项观察性研究利用PacBio单分子长读长测序结合扩增子序列变体(ASV)分析精准验证了"唾液-肠道共享菌株",提示口腔细菌迁移可能关联肠道菌群结构,改变肠道菌群功能[19]。因此,目前研究认为口-肠轴调控核心构成包括微生物转运、肠道屏障破坏及免疫失衡炎症传导三大环节,其功能紊乱是局部疾病引发全身效应的关键媒介,为牙周炎的全身效应提供了结构与功能基础[20]。

1.1 牙周致病菌肠道定植

口腔作为消化道的起始部分,口腔微生物群可直接通过吞咽进入消化系统,改变肠道微生物群落组成。人体每日通过唾液吞咽摄入的细菌数量可达10^{12}个[21],牙周健康人群的肠道菌群中,仅0.6%来源于唾液;而牙周炎患者的这一比例会升高至5.88%[22]。牙周炎状态下,牙龈上皮溃疡、血管通透性增加导致口腔屏障破损,牙周致病菌可通过血流途径进入全身循环扩散至靶器官,间接定植于肠道[23-24]。此外,研究还发现部分口腔细菌可在树突状细胞、巨噬细胞等免疫细胞内存活,将其作为"特洛伊木马",实现细菌从口腔黏膜向肠道黏膜的播散[25]。有学者认为肠道菌群失衡是口腔致病菌定植的前提条件,KITAMOTO等[15]在研究口腔与肠道的因果关系时提出,当口腔和肠道均存在炎症时,口腔致病菌可沿消化道显著定植于肠道,通过口腔致病菌的摄入加速疾病进展。然而也有证据表明口腔致病菌可主动破坏肠道屏障,但需要炎症参与或菌群失调作为肠道定植前提[26]。READ等[27]在2021年发表的一篇综述中详尽阐述了口腔细菌,如*F. nucleatum*、肺炎克雷伯菌(*Klebsiella pneumoniae*)、简明弯曲杆菌(*Campylobacter concisus*)从口腔迁移至肠道,直接加重IBD的病理进程,在此不再赘述。此外,BAO等[22]研究发现牙周炎患者唾液中的致病菌可定植至小鼠肠道,诱导小鼠肠道菌群失调,证实口腔致病菌的肠道定植是口-肠轴调控的关键起始环节。

1.2 肠道微生态与屏障功能的双重紊乱

牙周炎介导的口-肠轴失调最终体现为肠道菌群结构与功能的异常,破坏肠道屏障。研究发现,与灌胃牙周健康人群唾液的小鼠相比,灌胃牙周炎患者的唾液后小

鼠肠道菌群β多样性发生明显改变, 卟啉单胞菌和梭杆菌数量明显增加[28]。另外一项研究将牙周炎患者的唾液灌胃结肠炎模型小鼠后, 小鼠肠道菌群α多样性增加, 炎症性肠道疾病相关菌群发生改变[29]。除了灌胃牙周炎患者唾液, 灌胃单一的牙周致病菌也可改变小鼠肠道菌群组成。KOMAZAKI等[30]研究发现灌饲伴放线团聚杆菌(*Aggregatibactera actinomycetemcomitans, Aa*)6周可改变小鼠肠道微生物群组成, 导致厚壁菌门中*Turicibacter*菌减少, 该菌可产生丁酸盐, 其减少与胰岛素敏感性降低有关。灌饲*P. gingivalis* 16 h后即可在小鼠结肠检测到*P. gingivalis* DNA, 持续灌胃5周后小鼠肠道菌群中拟杆菌(*Bacteroidales*)比例增加, 厚壁菌门比例降低, 且这一变化与小鼠胰岛素抵抗增强及全身炎症反应加剧同时发生[31]。重度牙周炎未经治疗最终会导致牙齿丧失, 2025年一项研究探究了牙齿缺失后口腔与肠道菌群的具体变化及关联机制, 牙齿缺失小鼠口腔菌群失调, 表现为α多样性下降, 同时也造成肠道菌群失调, 且牙齿缺失组小鼠口腔与肠道菌群变化存在显著相关性, 小鼠牙齿缺失通过破坏口腔-肠道菌群轴影响肠道健康[32]。

肠道屏障由黏液层、肠道上皮细胞及紧密连接蛋白构成, 是阻止肠道菌群及毒素入血的关键防线。口腔致病菌在肠道定植会抑制有益菌生长, 导致肠道菌群改变, 肠道细菌短链脂肪酸(short chain fatty acids, SCFAs)合成减少, 削弱肠道屏障的能量供应与抗炎能力, 肠道上皮屏障破坏, 增加通透性和炎症[33-34]。SUN等[35]研究观察到结扎联合*P. gingivalis*灌胃诱导的牙周炎小鼠肠道产SCFAs细菌(*Lactobacillus*、*Ligilactobacillus*、*Allobucalum*)数量减少, 厚壁菌门(Firmicutes)和放线菌门(Actinobacteriota)丰度也明显下降, 黏蛋白分泌减少, 肠道屏障完整性破坏。口腔致病菌及其毒力因子可通过降解紧密连接蛋白表达, 破坏肠道上皮完整性, 同时可诱导肠道炎症, 促进促炎因子释放, 间接破坏黏液层与上皮细胞连接, 最终导致肠道通透性增加, 最终造成肠道内的毒素、炎症因子等进入血液循环, 引发全身低度炎症, 为全身共病的发生提供病理基础[36-38]。

1.3　宿主免疫失衡与炎症因子扩散

一旦口腔致病菌定植于肠道, 就可能成为致病原, 诱导肠道产生异常免疫反应, 激活局部炎性巨噬细胞和适应性免疫, 促进肠道炎症[39]。BOONYALEKA等[40]研究发现*F. nucleatum*灌胃5%葡聚糖硫酸钠(DSS)诱导的结肠炎小鼠可加重小鼠结肠组织炎症浸润, 炎症因子IL-1α、IL-1β和IL-18生成显著增加。持续灌胃*P. gingivalis* 5周可使小鼠发生内毒素血症, 并导致肠道中促炎因子IL-6、IL-12和IFN-γ增加[31]。JIA等[41]研究发现*P. gingivalis*灌胃可抑制肠道菌群的亚油酸代谢通路, 导致Th17/Treg失衡, 加剧肠道炎症。口腔引流淋巴结可产生能识别口腔致病菌的致敏Th17细胞, 其迁移至肠道后可被移位至肠道定植的口腔致病菌激活, 促进结肠炎发生。同时, 牙周炎小鼠肠道中的Th17细胞会向Th1表型转变, 肠道巨噬细胞接触口腔来源*K. aerogenes*后分泌IL-1β等炎症因子[14-15, 42]。牙周炎引发的口腔局部炎症可通过口-肠轴途径放大, 激活全身免疫反应, 导致靶器官的炎症反应与代谢失衡[14](图2)。

2　牙周炎通过口-肠轴关联的主要系统性疾病

2.1　糖尿病

糖尿病是因胰岛素分泌缺陷、胰岛素作用缺陷或两者兼而有之导致的以慢性高血糖为特征的代谢性疾病。流行病学证据充分表明, 牙周炎患者出现血糖异常和胰岛素抵抗的风险升高。2018年, 欧洲牙周病联盟(EFP)与国际糖尿病联盟(IDF)发布共识指南更新了牙周炎与T2DM双向关联的证据基础[43]。口肠菌群失调与T2DM密切相关。目前研究认为口腔微生物导致胰岛素抵抗增加的机制可能涉及肠道微生态失衡、肠道通透性增加、炎症及代谢紊乱。灌饲*P. gingivalis*小鼠可表现为糖耐量异常、胰岛素抵抗, 其可能机制为灌饲*P. gingivalis*改变了小鼠结肠肠道微生物组, 导致胰高血糖素样肽(glucagonlikepeptide-1, GLP-1)表达下调, 从而干扰小鼠血糖水平[44-45]。近期一项研究结果显示从糖尿病前期到T2DM进展过程中口腔菌群失调, 口腔*Firmicutes-C*升高, 肠道*Bacteroidota*升高, *Escherichia*在T2DM患者口腔和肠道微生物中显著富集, 可能通过促进炎症反应加剧胰岛素抵抗[46]。此外, 研究发现*P. gingivalis*或结扎诱导牙周炎小鼠肠道中嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*)和产丁酸类细菌含量减少, 丁酸生成减少与胰岛素抵抗增加相关[47-48], 而另一项研究证实灌胃牙周炎患者唾液不会造成糖尿病无菌小鼠胰岛素抵抗, 也进一步说明肠道微生物在调节口腔细菌影响糖尿病中的重要作用[49](图2)。肠道微生态失衡可进一步导致色氨酸代谢、胆碱代谢紊乱, 肠道微生物衍生代谢物在*P. gingivalis*诱导的糖尿病进展中扮演关键致病角色[50]。

2.2　心血管疾病

心血管疾病(cardiovascular diseases, CVD)包括冠心病、脑卒中、心律失常等, 是全球主要致死原因之一。动脉粥样硬化(atherosclerosis, AS)是CVD的核心病理基础,

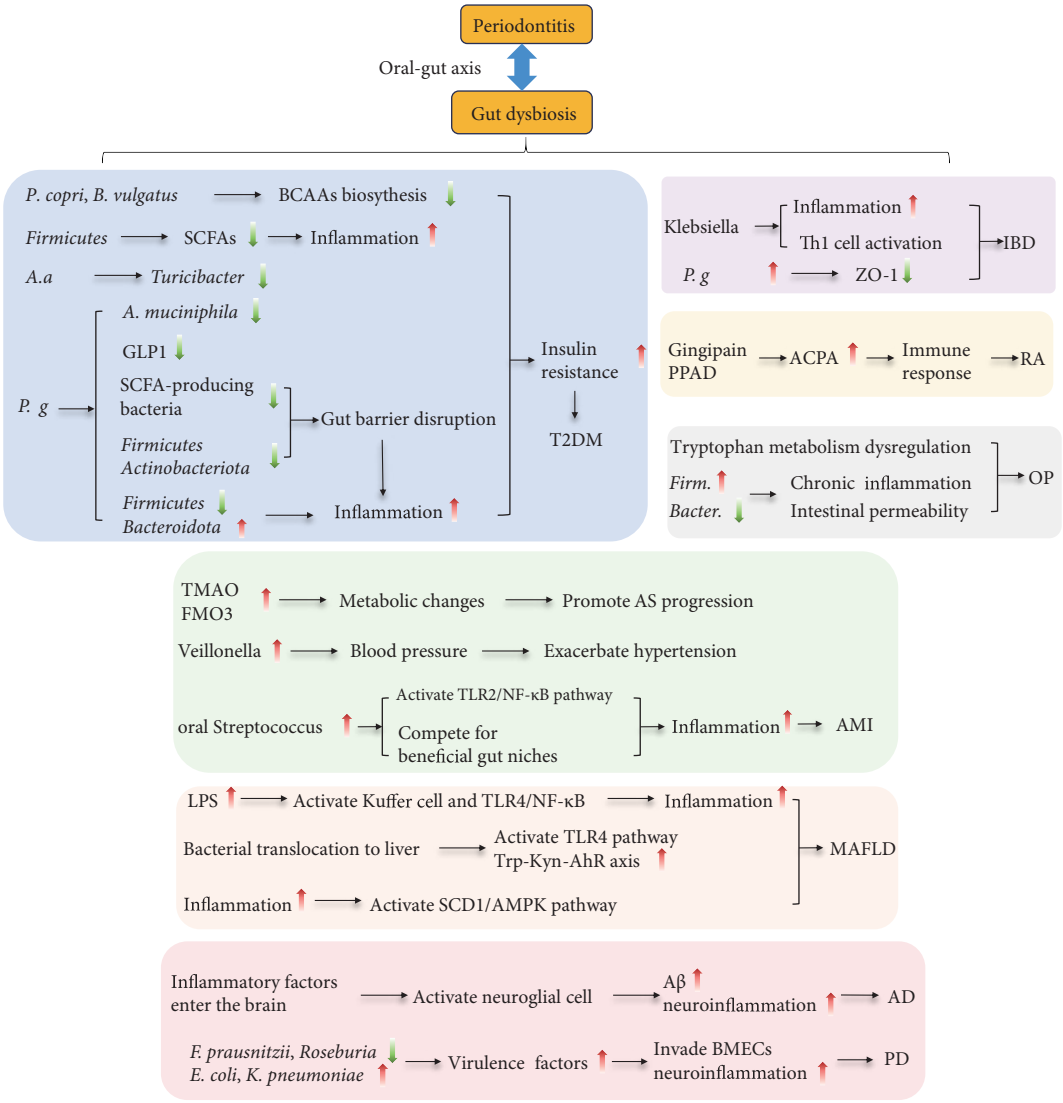

图 2 牙周炎通过口-肠轴途径影响系统性疾病的关键致病菌及调控通路

Fig 2 Key pathogens and regulatory pathways mediating the impact of periodontitis on systemic diseases via oral-gut axis

BCAAs: branched chain amino acids; SCFAs: short chain fatty acids; GLP1: glucagonlikepeptide-1; T2DM: type 2 diabetes mellitus: ZO-1: zonula occludens 1; IBD: inflammatory bowel disease; PPAD: peptidylarginine deiminase; ACPA: anti-citrullinated peptide antibodies; RA: rheumatoid arthritis; OP: osteoporosis; TMAO: trimethylamine N-Oxide; FMO3: flavinmonooxygenase 3; AMI: acute myocardial infarction; LPS: lipopolysaccharides; MAFLD: metabolic dysfunction-associated fatty liver disease; AD: Alzheimer's disease; PD: Parkinson's disease.

表现为动脉壁脂质斑块沉积引发的血管狭窄和硬化，最终引发心肌梗死、脑卒中等不良事件。研究表明，牙周炎与动脉粥样硬化性心血管疾病密切相关，肠道菌群紊乱可加速AS进展[12]，其中肠道菌群代谢产物氧化三甲胺(trimethylamine N-Oxide,TMAO)可能介导二者关联[51-52]。XIAO等[53]研究发现，ApoE$^{-/-}$牙周炎模型小鼠外周血TMAO水平升高，肝脏黄素单加氧酶3(flavin monooxygenase 3, FMO3)表达增加，且肠道菌群组成及丰度改变，提示牙周炎可能通过诱导肠道菌群失调及代谢异常促进AS进展(图2)。

高血压是CVD的首要危险因素。CHEN等[54]通过临床横断面队列研究，结合16S rRNA测序、宏基因组测序及动物实验证实，牙周炎患者收缩压/舒张压显著高于非牙周炎患者，且该差异持续存在；高血压患者口腔及肠道菌群组成显著改变，其中韦荣球菌属(*Veillonella*)是稳定富集于高血压患者的传递菌。*Veillonella*作为关键硝酸盐还原菌，可通过促进NO生成降低血压。灌胃高血压患者唾液可加剧血管紧张素Ⅱ诱导的小鼠高血压，且人类唾液来源的*Veillonella*可在小鼠肠道定植，其定植量与血压正相关，提示口腔-肠道菌群传递可能是高血压的重要致病机制(图2)。

急性心肌梗死(acute myocardial infarction, AMI)发病率及死亡率高，是心力衰竭和心源性死亡的主要诱因。肠道微生物动态变化及口腔微生物群均与AMI发生

发展相关[55-56]。一项纳入37例AMI患者与36例健康对照者的研究, 通过口腔唾液、龈下菌斑与肠道粪便样本16S rRNA全长测序结合动物实验证实, AMI患者口腔微生物α多样性显著升高, 而肠道微生物α多样性降低; 口腔链球菌可通过口-肠轴异位定植于肠道, 并显著加剧小鼠心肌梗死程度[57]。其潜在机制为: 口腔链球菌的肽聚糖、脂磷壁酸等致病因子定植肠道后可激活TLR2/NF-κB炎症通路, 促进TNF-α、IL-6等促炎因子入血, 加重冠状动脉内皮损伤及血栓形成; 同时竞争产丁酸菌等有益菌的肠道生态位, 导致丁酸生成减少、肠道屏障功能受损, 增加内毒素入血风险, 进一步加剧全身炎症和心肌损伤(图2)。

2.3　IBD

IBD是一类以慢性肠道炎症为核心特征的疾病, 主要包括溃疡性结肠炎(UC)和克罗恩病(CD), 其与牙周炎存在共同的炎症机制, 口-肠轴菌群失调是二者关联的核心。临床研究证实, IBD患者牙周炎患病率显著升高, 牙周致病菌(*P. gingivlis*和*F. nucleatum*)在肠道内丰度增加[58]。另一项纳入60例IBD患者和45例健康对照的前瞻性研究(12个月随访)通过16S rRNA测序分析唾液及肠道菌群, 发现IBD口腔与肠道微生物群相似度显著高于健康对照组, 提示口腔细菌肠道异位定植增加, 且早期牙周炎可能与部分CD患者症状恶化相关[59], 但该研究仅检测了唾液微生物而未分析牙周袋局部菌群, 可能遗漏关键致病菌。动物实验进一步揭示了二者关联的机制: ATARASHI等[60]通过将2例CD患者、2例健康受试者及2例活动性UC患者的唾液灌胃移植到无菌小鼠, 证实口腔来源克雷伯氏菌属菌株肠道异位定植是诱导Th1细胞活化及炎症反应的关键诱因。另有研究向2.5% DSS诱导的结肠炎小鼠灌饲三种主要牙周致病菌(*P. gingivalis*、*P. intermedia*和*F. nucleatum*), 发现仅*P. gingivalis*可显著加重结肠炎, 其核心机制为通过下调紧密连接蛋白ZO-1的表达破坏肠道上皮屏障, 增加肠道通透性及血清内毒素水平, 而*P. gingivalis*牙龈素突变株则丧失该加重效应, 提示*P. gingivalis*可直接作用于易感宿主的肠道上皮屏障, 加剧胃肠道炎症[61], 为牙周炎与IBD的关联提供了机制证据(图2)。

2.4　类风湿性关节炎

RA是一种以滑膜炎症、骨侵蚀为特征的自身免疫性疾病, 病因涉及遗传、环境及免疫紊乱等多种因素。RA与牙周炎存在双向流行病学关联, 口-肠轴调控紊乱为关键关联机制之一。研究表明, 早期RA患者和RA高危人群口腔菌群组成显著异常, 唾液中*Veillonella*、普雷沃菌属(*Prevotlla*)、坦纳菌属(*Tannerella*)丰度升高, 而*Defluviitaleaceae UCG-011*、口腔奈瑟菌(*Neisseria oralis*)丰度降低[62]。此外, 肠道微生物群与肠道相关淋巴组织共同参与宿主免疫稳态维持, 对RA发生发展具有重要调控作用[63], 灌胃*P. gingivalis*可扰乱小鼠肠道菌群及肠道免疫稳态, 进而加重关节炎症状[18]。目前研究已明确*P. gingivalis*牙龈素和肽基精氨酸脱亚氨酶(peptidylarginine deiminase, PPAD)可协同产生瓜氨酸化自身抗原, 诱导抗瓜氨酸化蛋白抗体(anti-citrullinated peptide antibodies, ACPA)生成, 激活异常免疫反应参与RA发病[64]。近期一项前瞻性队列研究评估了RA锚定药物甲氨蝶呤(MTX)与非手术牙周治疗(non-surgical periodontal therapy, NSPT)对RA患者口腔-肠道菌群的影响, 结果显示MTX可降低口腔-肠道菌群α多样性, 改变口腔菌群β多样性, 但对牙周指数无显著影响; 而NSPT可显著恢复口腔菌群多样性[65]。该研究提示肠道菌群或可作为RA治疗响应的潜在标志物, 且口腔致病菌与RA疾病活动度评分(Disease Activity Score in 28 Joints, DAS28)相关联, 进一步验证了口-肠轴在RA病理进程中的核心作用(图2)。

2.5　代谢相关脂肪性肝病

MAFLD又称非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD), 目前已成为影响全球1/3成年人口的第一大慢性肝病。口腔作为消化系统入口, 通过口腔-肠道-肝脏轴(口-肠-肝轴)与肝脏构成关联。其核心致病路径为: 口腔致病菌经吞咽定植于肠道后破坏肠道屏障, 内毒素(如LPS)等经门静脉靶向肝脏, 激活肝脏Kuffer细胞及TLR4/NF-κB通路, 促进IL-6、TNF-α等炎症因子释放, 进而加剧肝脂肪变性、纤维化及肝损伤[66]。动物实验进一步证实该轴的调控作用: KURAJI等[67]通过局部接种多种牙周致病菌构建小鼠牙周炎模型, 发现乳酸链球菌素可通过调节口-肠-肝轴菌群失调, 减少致病菌肝脏易位, 抑制肝内炎症, 显著改善牙周炎相关MAFLD的肝脂肪变性及线粒体氧化应激。WANG等[68]在高脂饮食诱导的肥胖小鼠模型中, 经灌胃给予20例重度牙周炎患者唾液菌群, 证实该菌群可通过加剧肠道屏障功能障碍、促进细菌肝内易位激活TLR4炎症通路, 上调肝脏色氨酸-犬尿氨酸-AhR轴, 进而加重肝脂肪变性, 且伴随肠道菌群组成显著改变, 为牙周炎与MAFLD的关联提供了口-肠-肝轴介导的机制证据。此外, 大鼠牙周炎模型动物研究显示, 牙周炎可诱导大鼠肝损伤与脂肪变性, 伴随肠道菌群失调(*Firmicutes*/*Bacteroidetes*比值升高, *Ruminococcus*富集, 异杆菌属*Allobaculum*减少)、肠道紧密连接蛋白表达下调及肠道屏障破坏, 血清IL-1β与LPS水平升高引发全身炎症, 结合体外细胞证实, 牙周炎可能通过口-肠-肝轴介

导肠道菌群失调,激活肝脏SCD1/AMPK信号通路,最终诱发肝损伤与脂肪变性[69](图2)。

2.6 神经系统疾病

近年研究表明,口-肠轴介导的菌群-炎症通路是神经退行性疾病的重要诱因。阿尔茨海默病(Alzheimer's disease, AD)作为常见中枢神经系统退行性疾病,以β-淀粉样蛋白(Aβ)沉积及神经炎症为核心病理特征,其病理改变可早于痴呆症状,出现于遗忘型轻度认知障碍(amnestic mild cognitive impairment, aMCI)阶段。QIU等[70]通过16S rRNA测序分析32例AD患者、32例aMCI患者及32例认知正常人群的龈下菌斑菌群,并结合LC-MS/MS检测龈沟液代谢组,多组学整合结果显示:AD患者牙周炎严重程度显著高于aMCI患者及认知正常人群,牙周微生物失调与代谢紊乱可能参与AD的发生发展。动物实验进一步证实,在APPswe/PS1ΔE9转基因AD小鼠模型中,牙周炎患者唾液菌群经灌胃可肠道定植,诱导肠道菌群失衡及屏障损伤,全身炎症因子通过血脑屏障侵入中枢神经系统,激活神经胶质细胞,促进Aβ斑块堆积及神经炎症(GFAP$^+$星形胶质细胞、Iba1$^+$小胶质细胞激活),最终加重认知障碍[71]。此外,*P. gingivalis*的毒力因子可直接通过肠道-血液-脑通路迁移至大脑,进一步放大神经损伤[72]。

多项研究聚焦肠道微生物组在帕金森病(Parkinson's disease, PD)中的调控作用,证实肠道微生物代谢物及毒力因子可通过诱导神经炎症与氧化应激加剧神经退行性性变。CLASEN等[73]最新研究发现,PD认知障碍患者存在显著口-肠菌群轴失调,表现为肠道内产丁酸有益菌(如*Faecalibacterium prausnitzii*、*Roseburia*)减少、致病菌(如*Escherichia coli*、*Klebsiella pneumoniae*)增多,口腔中*P. endodontalis*富集;且口腔菌群向肠道移位可导致肠道内口腔来源毒力因子(如ompA、gmhA)富集,这些毒力因子可通过侵袭脑微血管内皮细胞、激活神经炎症参与PD认知功能下降,证实口-肠-脑轴介导的菌群失调是PD认知障碍的关键机制。

2.7 骨质疏松症

骨质疏松症(osteoporosis, OP)表现为骨量降低、骨小梁微结构破坏,绝经后女性高发。观察性研究提示牙周炎可能是骨质疏松症的危险因素,但因果关联证据不足。近期一项动物实验研究探究了两者的关联机制,通过将18例牙周炎患者唾液菌群灌胃去卵巢(OVX)大鼠2周发现牙周炎患者唾液菌群可显著加重OVX大鼠股骨骨丧失,但牙槽骨无显著变化。同时,牙周炎唾液菌群异位定植肠道,破坏肠道屏障,加剧肠道炎症并改变肠道菌群组成。肠道菌群失调进一步导致色氨酸代谢紊乱,最终加剧长骨丢失[74]。该研究证实牙周炎可通过口-肠轴加重OVX大鼠长骨丢失,为口-肠轴介导两者关联提供有力证据。ApoE$^{-/-}$小鼠自发高脂血症,骨稳态受损但未发展为骨质疏松症,是研究“牙周炎-肠道菌群-骨稳态”的理想模型。LI等[75]利用该模型研究发现,牙周炎可诱导小鼠肠道菌群失调(*Firmicutes*升高、*Bacteroidetes*降低),伴随结肠低度炎症及肠道通透性增加;肠道菌群移植实验证实其因果介导作用,最终明确牙周炎可通过调控肠道菌群破坏ApoE$^{-/-}$小鼠全身骨稳态(图2)。

3 总结与展望

尽管牙周炎通过口-肠轴影响全身共病的相关研究日益增多,但仍存在诸多不足。当前研究证据多来自动物模型,啮齿类动物的急性牙周炎模型难以模拟人类慢性牙周炎的长期病理过程,需要在人体中进一步验证。更值得注意的是,目前研究横断面研究占比高,更多是探究牙周炎与全身共病的相关关系,缺乏纵向队列研究,未能提供强有效的因果关系证据,且部分研究样本量较小,存在地域与种族偏倚,口腔菌群存在高度个体差异性,单一的研究结论可能不具有普适性。另外,在研究过程中还需要控制饮食、生活方式等混杂因素的影响。目前尚无针对口-肠轴的靶向干预临床试验,缺乏“治疗牙周炎改善牙周共病”的直接证据。在机制研究方面,宿主介质与菌群的交互作用、不同致病菌的特异性致病通路仍需深入解析。未来可利用单细胞测序、类器官模型、宏基因组学、代谢组学等多组学技术及多学科交叉研究深入解析牙周炎影响共病的机制,同时聚焦关键致病菌的毒力因子、宿主介质等信号通路,明确不同牙周共病的特异性调控网络。开展多中心大规模前瞻性队列研究和干预性研究,通过长期追踪牙周炎患者的肠道菌群、屏障功能及全身疾病发生风险,进一步明确口-肠轴的因果作用。开发针对口-肠轴的精准防治策略,如益生菌、靶向抗生素和粪菌移植等手段促进临床转化。另外,开发基于口腔-肠道菌群的共病风险预测模型,为牙周炎相关全身疾病的早期预防、精准诊断及有效治疗提供新策略。

* * *

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