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·综述·

口腔微生物组在口腔鳞状细胞癌中的研究进展

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【摘要】 口腔微生物组稳态对维持宿主健康至关重要，其失衡可促进口腔及全身疾病发生。口腔微生物组可通过多种机制影响口腔鳞状细胞癌(oral squamous cell carcinoma，OSCC)的发生和发展：①口腔微生物可直接作用于口腔上皮细胞，诱导细胞周期紊乱、DNA损伤和表观遗传重编程，促进细胞增殖和上皮-间质转化。例如，具核梭杆菌可通过黏附素FadA与E-cadherin结合，激活β-catenin信号通路，直接促进肿瘤细胞增殖与上皮-间质转化，牙龈卟啉单胞菌能调节脂质合成，增强OSCC细胞的的干性特征；②口腔微生物及其代谢物可影响肿瘤组织免疫细胞的密度、亚群比例和功能，重塑了肿瘤免疫抑制微环境，牙周病原微生物所致慢性口腔炎症状态，可激活MAPK/ERK、NF-κB等信号通路，间接促进OSCC进展；③口腔内细菌与病毒存在协同作用，细菌生物膜和蛋白酶有助于病毒的激活和感染，细菌代谢物如丁酸可通过增强组蛋白乙酰化，促进潜伏病毒裂解复制；④微生态层面，口腔共生菌减少与厌氧致病菌扩增破坏了群落代谢网络，通过复杂的种间互作共同塑造一个促癌生态位，从多层面推动OSCC进展。未来研究应整合多组学分析与纵向临床队列数据，探索关键菌群的功能因果网络，并发展针对微生态的个体化靶向干预策略。

【关键词】 口腔微生物组；　口腔鳞状细胞癌；　肿瘤微环境；　肿瘤免疫；　表观遗传；　细菌；　具核梭杆菌；　牙龈卟啉单胞菌；　病毒；　上皮-间质转化；　组蛋白乙酰化；　NF-κB信号通路

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Research progress on oral microbiome in oral squamous cell carcinoma

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【Abstract】 The homeostasis of the oral microbiome is essential for maintaining host health, and its disruption can contribute to the development of both oral and systemic diseases. The oral microbiome influences the initiation and progression of oral squamous cell carcinoma (OSCC) through multiple mechanisms. ① Oral microbes can directly act on epithelial cells, inducing cell-cycle dysregulation, DNA damage, and epigenetic reprogramming, thereby promoting cell proliferation and epithelial - mesenchymal transition (EMT). For example, *Fusobacterium nucleatum* binds to E-cadherin via its adhesin FadA, activating the β-catenin pathway and directly driving tumor-cell proliferation and EMT, while *Porphyromonas gingivalis* reprograms lipid synthesis to enhance the stemness of OSCC cells. ② Oral microbes

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and their metabolites reshape the tumor immune-suppressive microenvironment by altering the density, composition, and function of infiltrating immune cells. Periodontal pathogens induce a chronic inflammatory state in the oral cavity and activate signaling cascades such as MAPK/ERK and NF-κB, thereby indirectly accelerating OSCC progression. ③ Bacteria and viruses in the oral cavity exhibit synergistic interactions. Bacterial biofilms and proteases facilitate viral activation and infection, and microbial metabolites such as butyrate can enhance histone acetylation to promote the lytic reactivation of latent viruses. ④ At the ecological level, the depletion of commensals and expansion of anaerobic pathogens disrupt the metabolic network of the community, and complex interspecies interactions collectively shape a pro-carcinogenic niche that drives OSCC progression on multiple fronts. Future studies should integrate multi-omics analyses with longitudinal clinical cohorts to explore functional causal networks of key microbial communities and develop individualized targeted intervention strategies for microecology.

【Key words】 oral microbiome; oral squamous cell carcinoma; tumor microenvironment; tumor immunology; epigenetic; bacterial; *Fusobacterium nucleatum*; *Porphyromonas gingivalis*; virus; epithelial-mesenchymal transition; histone acetylation; NF-κB signaling pathway

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口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)占口腔恶性肿瘤的90%[1]。吸烟、饮酒和咀嚼槟榔是OSCC的主要危险因素。其他潜在危险因素包括病毒和真菌感染,以及慢性牙周炎[1]。OSCC发生发展与口腔微生物组紊乱密切相关。传统的研究多集中于单一微生物的作用,但随着研究的深入,逐渐认识到口腔微生物组作为一个复杂的生态系统,其微生物之间的协同与竞争作用,以及微生物群落功能的变化在癌症进展中扮演着更为重要的角色[2]。本综述分析了癌变过程微生物群落的变化,总结口腔微生物组在OSCC中的调控机制,以及群落失衡如何影响肿瘤的发生与发展。通过探讨微生物组在免疫调节、代谢改变、肿瘤微环境构建等方面的作用,为未来基于口腔微生物组的OSCC诊断和治疗提供新的理论支持和研究方向。

1　口腔微生物组稳态与OSCC

1.1　口腔微生物组

人体微生物组包括人体表面和体内发现的所有微生物。口腔微生物组是人体中仅次于肠道微生物组的第二大微生物组,健康的口腔微生物组是一个高度多样化和复杂的生态系统,由细菌、真菌、病毒和古细菌组成,其中细菌构成了主要群体,已鉴定的细菌种类超过700种[3]。主要细菌门类包括厚壁菌门、拟杆菌门、放线菌门以及变形菌门。真菌和病毒在口腔微生物组中的丰度较低,仅占微生物总数的不到0.1%[4]。值得注意的是,微生物在不同口腔部位的分布存在显著差异:例如舌背以链球菌属为主,而唾液中的优势菌属则为韦荣球菌属和奈瑟菌属[5]。口腔微生物稳态在维持屏障功能、免疫调节和代谢活动方面起着至关重要的作用。

1.2　口腔微生物组在OSCC中的生态失调特征

正常情况下,微生物与宿主保持平衡的状态,彼此互利。然而,在某些疾病状态下,口腔内某些共生微生物可能过度生长,同时其他微生物的数量减少。这种微生物群落的变化被称为生态失调(ecological dysbiosis)[6]。口腔微生物组的生态失调是全身性疾病的危险因素,包括炎症性疾病和癌症[7]。研究表明,OSCC患者的口腔菌群组成与健康人群存在显著差异,具体表现为微生物多样性下降、菌群结构重构以及促炎型菌群的富集[8]。

在菌群构成上,OSCC患者口腔中共生菌(如链球菌、放线菌)显著减少,而厌氧性和致病性菌株,如具核梭杆菌、牙龈卟啉单胞菌、中间普雷沃菌等相对丰度明显升高[9]。口腔中的假单胞菌属与肿瘤缺氧部位的相关性最强[10]。白色念珠菌是口腔癌中发现的主要真菌[11],最常见的病毒是爱泼斯坦-巴尔病毒(Epstein-Barr virus, EBV)和人乳头瘤病毒(human papillomavirus, HPV)[12]。

细菌在口腔潜在恶性疾病(oral potentially malignant disorders, OPMDs)和OSCC的整个阶段表现出不同的丰度和多样性。与对照组相比,OSCC中

的细菌多样性显著下降，而OPMDs通常未出现类似现象[13]。OSCC、OPMDs和健康对照者中口腔念珠菌检出率分别为72.2%、58%和20.5%，各类人群之间存在念珠菌属分布的差异[11]。在OSCC从I期进展到IV期的过程中，牙周梭杆菌、微小单胞菌等丰度逐渐增加，而放线菌门、温和链球菌和牙龈卟啉单胞菌的丰度则逐渐减少[14]。具核梭杆菌是早期和晚期定植者之间的关键生物[14]。

2　口腔微生物组介导的OSCC发生发展的分子与生态机制

近年来，大量研究揭示口腔微生物组不仅是宿主口腔健康稳态的重要组成部分，更通过多层次的分子互作在OSCC的发生与进展中发挥重要作用。微生物组可通过直接影响上皮细胞信号转导、间接重塑免疫微环境、微生物间协同感染及破坏生态平衡等途径共同推动肿瘤形成与恶性演化。

2.1　口腔微生物组对肿瘤细胞的直接作用

宿主遗传背景与微生物组之间存在复杂的双向调控关系。宿主基因变异不仅决定微生物组的组成与稳定性，反过来微生物群亦可通过信号通路干扰、染色质重塑及表观遗传修饰等机制调控宿主基因表达，影响细胞稳态与肿瘤易感性[15]。多种致病菌可通过黏附、侵入或分泌致癌分子直接作用于口腔上皮细胞，诱导细胞周期紊乱、DNA损伤、表观遗传重编程及上皮-间质转化（epithelial mesenchymal transition，EMT）等致癌事件。

在口腔环境中，具核梭杆菌通过其黏附性FadA蛋白（fusobacterial adhesin A，FadA）与上皮细胞E-钙粘蛋白相互作用，促进细菌入侵并激活Wnt/β-连环蛋白通路，从而上调致癌基因的表达[16]。具核梭杆菌感染还上调细胞周期蛋白D1与c-Myc表达，从而促进上皮细胞增殖与EMT[17]。牙龈卟啉单胞菌长期感染可通过microRNA-21/程序性细胞死亡蛋白4/激活蛋白1负反馈途径促进细胞周期蛋白D1表达，加速OSCC细胞增殖[18]。真菌和病毒感染同样可以通过直接作用参与OSCC进展。HPV的E6与E7癌蛋白分别促进肿瘤蛋白p53及视网膜母细胞瘤蛋白（retinoblastoma protein，Rb）降解，导致细胞周期蛋白依赖性激酶抑制剂2A上调与细胞周期失控[19-20]。

口腔微生物还能干扰OSCC细胞的基因稳定性和表观遗传调控。具核梭杆菌与OSCC细胞DNA错配修复和微卫星不稳定性相关，通过Toll样受体4（Toll-like receptor 4，TLR4）4/髓样分化初级反应蛋白88（myeloid differentiation primary response 88，MYD88）/miR-205-5p信号通路影响肿瘤细胞的表观遗传，促进DNA损伤和细胞增殖[21]。研究发现，长形口腔杆菌来源的细胞外囊泡可促进DNA修复基因乳腺癌基因1（breast cancer gene 1，BRCA1）与核酸外切酶1（exonuclease 1，EXO1）的转录[22]。E6/E7还可影响DNA甲基转移酶活性，导致特异性甲基化改变[23]。这些基因涉及细胞周期、瘤病毒感染、转录失调、肿瘤坏死因子信号传导、细胞骨架重排和凋亡等多种通路[23-24]。

研究表明口腔微生物诱导的上皮-间质转化与OSCC的进展密切相关，其中牙周病原体受到广泛关注。发生EMT的细胞表现出运动性、侵袭性和干性增强，这些变化营造了一个促肿瘤环境，并促进了OSCC的恶性转移[25]。具核梭杆菌和牙龈卟啉单胞菌的促癌机制有一定共性，两者通过Toll样受体与口腔上皮细胞直接相互作用来刺激肿瘤发生，通过上调白细胞介素-6（interleukin-6，IL-6），激活信号转导与转录激活因子3（signal transducer and activator of transcription 3，STAT3），进而诱导驱动OSCC生长和侵袭性的重要效应子[即细胞周期蛋白D1、基质金属蛋白酶（matrix metalloproteinases，MMP）、肝素酶等][26-27]。齿垢密螺旋体通过齿垢蛋白酶激活MMP8/9[28]，还通过TLR/MYD88和整合素αV/黏着斑激酶（integrin alpha V / focal adhesion kinase，integrinαV/FAK）信号通路[29]，增强肿瘤细胞的侵袭性和肿瘤干细胞特性，而乳酸链球菌素能抑制这一作用[29]。中间普雷沃菌通过干扰素刺激基因15（interferon-stimulated gene 15，ISG15）上调促进肿瘤增殖、侵袭、转移[30]。牙龈卟啉单胞菌与人OSCC标本中肿瘤干细胞标志物的表达呈正相关，Zang等[31]研究发现牙龈卟啉单胞菌调节硬脂酰辅酶A去饱和酶1（stearoyl-CoA desaturase 1，SCD1）依赖性脂质合成，增强OSCC的干细胞特性。牙周病原体也在肿瘤耐药机制中发挥作用。牙龈卟啉单胞菌的菌毛蛋白A靶向神经酰胺依赖性线粒体自噬，导致口腔肿瘤治疗耐药[32]。持续感染牙龈卟啉单胞菌的口腔癌细胞对紫杉醇表现出耐药性，且表现出更高的转移潜力，这由Notch受体1（Notch receptor 1，Notch1）激活介导[33]。

此外，微生物源性代谢物是介导其致癌效应

的关键因子。口腔中部分链球菌、念珠菌和牙龈卟啉单胞菌均能产生乙醛这一公认的致癌物[34-35]。唾液链球菌、缓症链球菌、金黄色葡萄球菌及白色念珠菌等产生的亚硝酸盐能够激活原癌基因[6]。中间普雷沃菌产生的挥发性硫化合物(硫化氢、甲硫醇)则通过诱导氧化应激与DNA损伤,为癌变创造条件[36]。牙周炎病原体伴放线聚集杆菌也能产生促炎细胞因子、硫化氢和甲硫醇,从而促进OSCC进展和血管生成[28]。

2.2　口腔微生物组在肿瘤进展中的间接作用

2.2.1　口腔微生物组介导的肿瘤免疫微环境重塑　越来越多的证据表明,肿瘤微环境被微生物或其衍生物以直接和间接的方式重塑,导致肿瘤进展、化疗耐药、放疗耐药和免疫抑制[37]。肿瘤免疫微环境(tumor immune microenvironment, TIME)是指围绕肿瘤组织的复杂免疫生态系统,主要由免疫细胞和细胞因子、趋化因子等共同组成[38]。多种口腔微生物已被证明影响免疫细胞的浸润、效应功能和极化,促进免疫抑制并破坏抗肿瘤反应。具核梭杆菌影响肿瘤浸润淋巴细胞的密度、亚群比例和功能,还诱导巨噬细胞的M2型极化和分泌。具核梭杆菌激活了OSCC细胞和巨噬细胞中的核因子κB(nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB)通路,导致C-X-C基序趋化因子配体2(C-X-C motif chemokine ligand 2, CXCL2)表达上调[39]。OSCC驻留的具核梭杆菌通过葡萄糖转运蛋白(glucose transporter 1, GLUT1)驱动的乳酸积累重构了免疫抑制的微环境[40]。牙龈卟啉单胞菌通过扩增髓源性抑制细胞和Tregs细胞来促进肿瘤相关免疫抑制[18]。牙龈卟啉单胞菌外膜囊泡(outer membrane vesicles, OMVs)抑制环鸟苷酸-腺苷酸合成酶/干扰素基因刺激蛋白(cyclic GMP-AMP synthase/stimulator of interferon genes, cGAS-STING)信号,从而抑制NK细胞和DC细胞募集[41]。Tsai等[42]研究发现变形链球菌的存在与OSCC患者标本中IL-6水平之间存在正相关,并增强了髓源性抑制细胞募集。中性粒细胞胞外诱捕网是由DNA、组蛋白和抗菌蛋白组成的网络结构。在口腔癌变中呈现双重作用:早期通过捕获致瘤菌抑制肿瘤发生,后期则通过释放促瘤因子加速进展[43]。这些证据表明口腔微生物通过重塑免疫抑制的肿瘤微环境间接参与肿瘤进展。

来自微生物组的代谢物也参与调控肿瘤免疫微环境。其中,色氨酸代谢通路是微生物干预免疫应答的关键途径之一。厚壁菌门细菌所表达的吲哚胺2, 3-双加氧酶1,可将色氨酸分解为犬尿氨酸,后者通过减少活化T细胞、树突状细胞与自然杀伤细胞数量,并诱导Th1细胞凋亡,进而促进免疫稳态向耐受方向偏移[44]。另一方面,具核梭杆菌来源的外膜囊泡可携带色氨酸酶,通过色氨酸-2, 3-双加氧酶2/芳香烃受体(tryptophan 2, 3-dioxygenas/aryl hydrocarbon receptor, TDO2/AhR)轴诱导巨噬细胞向M2型极化,进一步强化免疫抑制微环境[45]。值得注意的是,慢性应激引发的口腔菌群失调亦可导致宿主代谢组重塑,促使犬尿氨酸积累;后者通过稳定AhR表达,加速$CD8^+$ T细胞功能耗竭[46]。这些机制共同揭示,微生物来源的代谢物通过干预免疫细胞功能,在塑造抑制性肿瘤微环境中发挥重要作用。

免疫检查点抑制剂在OSCC中的应用已成为近年来免疫治疗的热点,但其疗效仍存在显著局限性,这与肿瘤免疫抑制性微环境有关。既往研究表明,在OSCC中牙龈卟啉单胞菌和具核梭杆菌均能增加癌细胞表面程序性死亡配体-1(programmed cell death 1 ligand 1, PD-L1)的表达[47]。牙龈卟啉单胞菌以受体相互作用丝氨酸/苏氨酸蛋白激酶2依赖性的方式诱导PD-L1表达,从而抑制抗肿瘤免疫,有助于肿瘤细胞逃脱免疫监视[48]。具核梭杆菌的代谢产物丁酸通过抑制$CD8^+$ T细胞组蛋白去乙酰化酶,抑制程序性死亡受体-1(programmed cell death protein 1, PD-1)表达,减少了T细胞耗竭,增敏抗PD-1疗法[49];相反,另一研究发现该菌衍生的琥珀酸通过抑制cGAS-STING-IFN-β信号通路,限制$CD8^+$ T细胞向肿瘤微环境的浸润,从而诱导免疫治疗耐药[50]。此双重效应揭示了菌群代谢调控免疫微环境的复杂性。可能的解释是,虽然具核梭杆菌诱导肿瘤细胞中PD-L1上调增强了免疫逃逸,但在免疫治疗期间上调PD-L1表达可以将“冷肿瘤”转化为“热肿瘤”,从而改善免疫治疗反应[51]。然而,驱动具核梭杆菌不同代谢产生的条件尚不清楚,厘清特定代谢物增强或损害疗效的具体情境,才能开发出相应的靶向策略来优化免疫治疗。

2.2.2　口腔微生物通过系统性调控影响肿瘤进展　微生物组失调引起全身炎性改变,通过代谢、免疫及神经调节等系统性途径,对远隔部位的肿瘤发展产生深远影响。慢性牙周炎是一种由细菌

生态失调引起的进展性炎症性疾病，通常与口腔卫生不良有关，其标志是多种细菌的富集，例如伴放线聚集杆菌、牙龈卟啉单胞菌、福赛斯拟杆菌、齿垢密螺旋体、中间普雷沃菌和具核梭杆菌等[52-53]。慢性牙周炎会导致全身性慢性炎症，这种状态是多种癌症（如肺癌、乳腺癌、前列腺癌、结直肠癌）的已知风险因素[54-57]。病例对照研究[58]和系统评价[18]揭示了牙周炎与口腔癌之间的联系，研究表明牙周炎是口腔癌的独立危险因素。如前文所述，这些牙周病原微生物通过直接或间接作用调控上皮细胞信号转导，从而影响OSCC的增殖、迁移、侵袭、转移、耐药和免疫逃逸。失调的微生物组通过维持慢性炎症，塑造了一个复杂的微环境，通过激活丝裂原活化蛋白激酶/细胞外信号调节激酶（mitogen-activated protein kinase / extracellular signal-regulated kinase，MAPK/ERK）等信号通路促进细胞的增殖和分化[59]。具核梭杆菌激活NF-κB和NOD样受体热蛋白结构域相关蛋白3（NOD-like receptor family pyrin domain containing 3，NLRP3）导致IL-1β上调，从而促进OSCC增殖[60]。慢性炎症不仅促进细胞增殖，还通过调节B淋巴细胞瘤-2基因（B-cell lymphoma-2，Bcl-2）家族的表达来破坏细胞存活和细胞死亡之间的正常平衡[61]。脂多糖（lipopolysaccharide，LPS）是参与口腔细菌代谢的关键外源性毒力因子[62]。LPS会引发强烈的免疫反应并导致严重感染，尤其是诱导牙周组织的炎症和铁死亡[63]。OSCC与正常组织细菌组成的比较分析发现，LPS在肿瘤组织中富集[62]，多组学分析也提示OSCC中22种代谢途径过表达，特别是脂多糖生物合成[64]。LPS和LPS诱导的促炎细胞因子（IL-22、IL-6、IL-2、C-C基序趋化因子配体5IL-1β、α干扰素等[64]）能改变宿主基因表达谱，激活下游信号通路，从而增强肿瘤的发生和发展[65]（表1）。

表1　口腔鳞状细胞癌发生发展中的代表性牙周病原菌及其作用机制

Table 1　Representative periodontal pathogenic bacteria and their mechanisms in the initiation and progression of oral squamous cell carcinoma

Representative bacteria	Key molecules and pathways	Oncogenic mechanisms
Fusobacterium nucleatum	FadA adhesin activating E-cadherin/β-catenin signaling[16]	Tumor proliferation, tumor invasion
	TLR4/MYD88/miR-205-5p signaling pathway, DNA damage[21]	Tumor proliferation
	Activation of NF-κB and NLRP3, leading to upregulation of IL-1β[60]	Tumor proliferation
	Activation of p38 protein kinase, promoting secretion of MMP-13/9[27]	Tumor invasion
	Induction of macrophage M2 polarization, upregulation of CXCL2 expression[39]	Immunosuppression
	OMVs modulating the tryptophan metabolism pathway[45]	Immunosuppression
Porphyromonas gingivalis	Modulation of miR-21/PDCD4/AP-1 signaling, upregulation of Cyclin D1[18]	Tumor proliferation
	Upregulation of SCD1, increasing lipid synthesis[31]	Tumor stemness
	Activation of Notch1[33]	Tumor stemness, chemoresistance
	FimA protein targeting ceramide-dependent mitophagy[32]	Tumor drug resistance
	Modulation of MDSCs and Tregs via Mfa1 and FimA fimbriae[18]	Immunosuppression
	OMVs inhibiting cGAS-STING signaling, suppressing NK and DC cell recruitment[41]	Immunosuppression
	OMVs activating RIP2 and MAPK-dependent signaling, upregulating PD-L1[48]	Immunosuppression
Prevotella intermedia	Upregulation of ISG15[30]	Tumor proliferation, invasion, metastasis, immunosuppression
Aggregatibacter actinomycetemcomitans	Production of pro-inflammatory cytokines, hydrogen sulfide, and methanethiol[28]	Tumor proliferation, migration, angiogenesis
Treponema denticola	Dentilisin-mediated activation of MMP8/9[28]	Tumor invasion
	TLR4/MYD88; integrin αV/FAK signaling[29]	Tumor migration, tumor stemness

FadA: fusobacterial adhesin A; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: nucleotide-binding oligomerization domain-like receptor protein 3; MMP: matrix metalloproteinase; CXCL2: C-X-C motif chemokine ligand 2; OMVs: outer membrane vesicles; SCD1: stearoyl-CoA desaturase 1; FimA: fimbrillin A (major fimbriae subunit); MDSCs: myeloid-derived suppressor cells; Mfa1: minor fimbrial antigen 1 (minor fimbriae subunit); RIP2: receptor-interacting serine/threonine-protein kinase 2; MAPK: mitogen-activated protein kinase; ISG15: interferon-stimulated gene 15; MYD88: myeloid differentiation primary response 88; TLR4: Toll-like receptor 4; PD-L1: programmed death-ligand 1; PDCD4: programmed cell death protein 4; AP-1: activator protein 1; cGAS-STING: cyclic GMP-AMP synthase-stimulator of interferon genes; NK cell: natural killer cell; DC cell: dendritic cell; IL-1β: interleukin-1 beta; Mfa1: minor fimbrial antigen 1 (minor fimbriae subunit); αV/FAK: integrin alpha V/focal adhesion kinase

肠道菌群作为关键的“代谢工厂”,能将代谢物通过循环系统作用于远端器官,并影响对应部位的肿瘤发生发展[66-67]。类似的,口腔微生物组被发现与OSCC、结直肠癌和胰腺导管腺癌存在密切关联。口腔微生物在咀嚼、刷牙和使用牙线等常规口腔卫生习惯后,通过循环系统到达远处的身体部位[68]。这种作用机制在过去的研究中被总结为“口-肠轴”这一概念[69]。更为间接的途径是,肠道菌群通过“肠-脑轴”影响中枢神经系统及宿主心理状态,激活奖赏系统可通过减弱骨髓来源抑制性细胞的免疫抑制功能,激发抗肿瘤免疫[55, 70]。这些发现揭示了微生物组通过代谢物循环与神经-免疫互作网络,实现其对肿瘤的远距作用,为开发基于菌群干预的癌症治疗新策略提供了理论依据。当前,关于口腔微生物与OSCC互作的认知,现有成果仍多局限于对局部菌群构成与局部免疫微环境相互作用的描述,而系统性神经-免疫互作是否影响OSCC发生发展的系统性视角尚无充分的实验证据。

2.3　病毒-细菌的协同效应

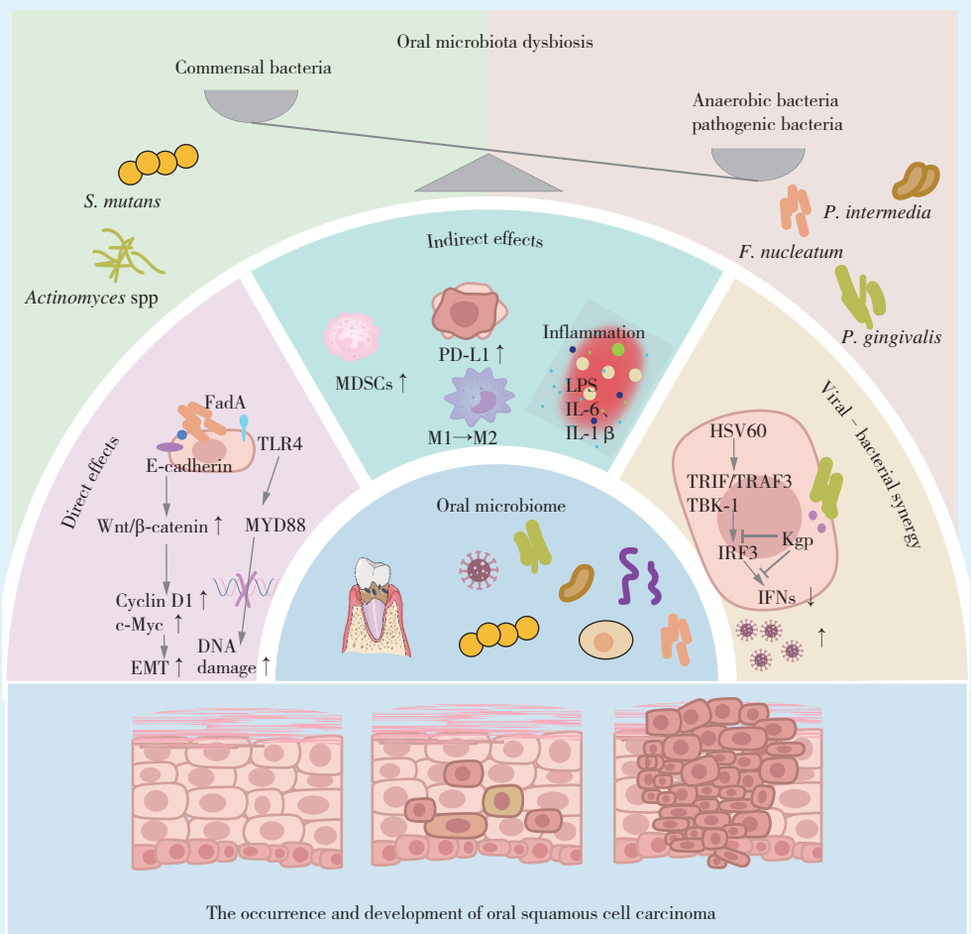
人体病毒组主要由约98%的噬菌体和2%真核病毒组成[71],病毒组特征谱可作为癌症发展的生物标志物[72]。目前已知有7种致癌病毒,包括乙型肝炎病毒、人乳头瘤病毒、EB病毒、卡波西肉瘤相关疱疹病毒、丙型肝炎病毒、人类T细胞白血病病毒1型和人类免疫缺陷病毒,它们主要通过病毒基因表达直接转化、编码癌蛋白等来发挥其生物学功能[73]。除了真核病毒,噬菌体也可以作为癌症的调节剂。噬菌体可以通过菌株特异性捕食显著塑造生态系统结构,并通过裂解宿主细菌介导水平基因转移[74]。

在口腔微生态中,病毒与细菌并非孤立存在,它们之间形成的复杂互作网络是驱动癌变的重要协同因素。HPV^-肿瘤的致癌细菌丰度明显高于HPV^+肿瘤,高致癌细菌丰度与HPV^+肿瘤的不良预后呈正相关[75]。病毒和细菌的这种协同效应主要体现在病毒为细菌的定植与致病创造有利条件,而细菌的慢性炎症环境反过来促进病毒的持续感染与癌基因表达,共同加速肿瘤的发生与发展。以具核梭杆菌和中间普雷沃菌为代表的口腔来源微生物易位至鼻咽部,参与瘤内浸润和肿瘤微环境重塑,与上皮EBV感染密切相关[76]。放线菌与单纯疱疹病毒1型(herpes simplex virus-1, HSV-1)共感染显著增加口腔上皮细胞中病毒的产生,这可能是两种微生物共享信号通路调控的结果,如磷脂酰肌醇3激酶(phosphatidylinositol 3 kinase, PI-3K)/蛋白激酶B(protein kinase B, PKB)信号通路的激活[77]。牙龈卟啉单胞菌的赖氨酸特异性银杏蛋白酶通过催化干扰素通路关键蛋白的水解,导致口腔黏膜抗病毒能力受损,从而促进了HSV-1感染[78]。在体外培养中也证实了具核梭杆菌能诱导EBV病毒的再激活[79]。此外,牙周细菌衍生的小型细胞外囊泡(small extracellular vesicles, sEVs)和代谢物也能激活病毒的复制。Qin等[80]发现与非HPV驱动头颈癌患者相比,HPV驱动的头颈癌患者介导子复合物27亚基(mediator complex subunit 27, MED27)mRNA水平更高,这可能与牙周细菌衍生的sEVs中MED27上调有关。牙龈卟啉单胞菌的代谢产物丁酸能介导表观遗传调控,诱导潜伏的EBV进入裂解复制。丁酸可增强组蛋白乙酰化,促进EBV裂解复制周期关键转录因子的表达,从而使病毒由潜伏状态被激活并扩增[81]。

2.4　口腔微生物组的生态学视角:群落失衡与代谢网络

口腔微生物组在OSCC中的作用,并非单一病原体的致病机制所能概括,其本质是整体微生物生态系统从共生稳态向菌群失调的崩溃性转变。这种生态失衡不仅体现在物种构成的改变,更伴随着群落功能与代谢网络的整体性偏移,共同塑造了一个支持肿瘤发生和发展的微环境[82]。首先,在OSCC的发生发展过程中菌群结构发生规律性更迭,其特定的失调模式或能为从微生态角度理解癌症的家族聚集倾向提供新视角,这在鼻咽癌中已经得到证实[83]。研究还发现长生存期的胰腺癌患者的肿瘤微生物组具有更高的α多样性[84],而富集环境通过调节肠道菌群(如上调乳杆菌属)抑制胰腺癌[85]。其次,在生态系统层面,口腔微生物并非孤立致癌,而是通过复杂的种间互作共同塑造一个促癌生态位。例如,具核梭杆菌能通过其特有的黏附能力,作为“基石菌”促进其他条件致病菌的共聚集与生物膜形成[86]。牙龈卟啉单胞菌的菌毛结构可介导其与链球菌属、韦荣菌属及伴放线聚集杆菌的共聚集[87],进一步强化微生物间的协同感染效应。白色念珠菌为牙龈卟啉单胞菌提供低氧微环境,促进后者的定植,二者又相互黏附促进口腔生物膜形成[88]。更为关键的是,它们之间存在着代谢协同:菌种的代谢废物可作为其他菌种的营养底物[89]。口腔共生菌戈登链

球菌通过鸟氨酸外排，促进具核梭杆菌的生物膜形成[90]。这种生态学互作极大增强了整个微生物群落的定植能力、免疫逃逸和对宿主组织的破坏力。最后，抗生素的使用改变微生物组稳态，广谱抗生素可能会导致真菌过度生长，从而降低放疗效率[91]。而万古霉素通过消耗参与短链脂肪酸和胆汁酸代谢的细菌来改善肿瘤治疗效果[92]。然而，即使是特定的抗生素也会引起微生物群组成的广泛变化，这可能对癌症治疗产生负面影响。这些发现提示，微生物群落通过动态平衡维持着宿主微环境稳态，而其生态失调则可能通过改变菌群互作网络，影响肿瘤发展（图1）。



The oral microbiome promotes OSCC development through multidimensional mechanisms. ① Direct effects: *Fusobacterium nucleatum* interacts with E-cadherin via its adhesin FadA, activating the Wnt/β-catenin pathway and upregulating Cyclin D1 and c-Myc, thereby enhancing epithelial cell proliferation and EMT; F. nucleatum also induces DNA damage through the TLR4/MYD88/miR-205-5p signaling axis. ② Indirect effects: microorganisms indirectly promote tumor progression by shaping an immunosuppressive tumor microenvironment and maintaining chronic inflammation. ③ Virus – bacteria synergy: the lysine-specific gingipain (Kgp) of *Porphyromonas gingivalis* cleaves key proteins in the interferon signaling pathway, impairing mucosal antiviral defenses and facilitating HSV-1 infection. ④ Ecological level: reduced commensals and expansion of pathogenic bacteria lead to microbial dysbiosis. EMT: epithelial-mesenchymal transition; FadA: fusobacterial adhesin A; MDSCs: myeloid-derived suppressor cells; WNT: Wingless-related integration site; LPS: lipopolysaccharide; IL-6: interleukin-6; IL-1β: interleukin-1β; DNA: deoxyribonucleic acid; c-Myc: cellular myelocytomatosis oncogene; MYD88: myeloid differentiation primary response 88; TLR4: Toll-like receptor 4; PD-L1: programmed death-ligand 1; M1: M1 macrophages; M2: M2 macrophages; HSV60: heat shock protein 60; TRIF: TIR-domain – containing adaptor-inducing interferon-β; TRAF3: TNF receptor-associated factor 3; TBK-1: TANK-binding kinase 1; IRF3: interferon regulatory factor 3; IFNs: interferons; *Actinomyces* spp: *Actinomyces* species; *S. mutans*: *Streptococcus mutans*; *P. gingivalis: Porphyromonas gingivalis; F. nucleatum: Fusobacterium nucleatum; P. intermedia: Prevotella intermedia*

Figure 1　Multidimensional mechanisms of initiation and progression of oral squamous cell carcinoma driven by oral microbiota dysbiosis

图1　口腔微生物生态失调驱动口腔鳞状细胞癌发生发展的多维度机制

3　口腔微生物组在OSCC治疗中的应用前景与挑战

3.1　诊断和预后生物标志物开发

口腔微生物组作为非侵入性生物标志物在OSCC早期诊断和预后评估中展现出重要潜力[93]。利用高通量测序与机器学习算法构建的菌群特征模型，可实现对高危人群的早期识别，能够预测肿瘤转移、复发、治疗反应及生存期[2, 94-96]。采集OSCC和健康对照受试者的唾液样本，采用16S rDNA测序分析显示，OSCC患者唾液微生物多样性与临床病理特征相关，影响肿瘤免疫和患者生存[97]。结合唾液[98]、龈沟液[99]等非侵入性样本检测，有望建立简便、敏感且特异性高的微生物标志物体系，为OSCC的精准诊断与个体化治疗提供参考。尽管目前研究尝试利用16S rRNA测序分析口腔菌群以预测OSCC，但由于样本类型、DNA提取流程、测序区域、分析方法缺乏标准化，菌群结构指标目前在诊断或预后预测中的效能仍然十分有限[100]。

3.2　微生物组干预策略

靶向口腔微生物组的治疗策略为OSCC防治提供了新思路。目前主要干预手段包括：益生菌补充[101]、致病菌靶向清除、工程菌改造、噬菌体疗法[102]以及个性化菌群移植等。但是针对OSCC的研究目前仍较少。研究表明，消化链球菌属的高丰度与OSCC患者良好预后相关，据此开发的银纳米颗粒水凝胶可选择性促进其定植并抑制竞争菌增殖，从而增强PD-1疗效[103]；锌介导的金属免疫疗法能有效清除牙龈卟啉单胞菌并协同免疫治疗[104]。然而微生物组的个体差异性、外源菌株定植效率及长期安全性等问题仍是临床转化的主要挑战[105-106]。

4　小　结

本综述阐明了口腔微生物组与OSCC发病机制之间的复杂关系，部分微生物具有直接促癌作用，部分微生物通过“菌群-免疫-代谢”网络参与OSCC发生发展，而微生物群落的生态失调影响肿瘤进展和治疗的各个环节。口腔微生物组作为诊断标志物和干预策略已展现出重要临床价值。

【Author contributions】 Gong JJ wrote the article. Li B collected the references, revised the article. Li LJ conceptualized and reviewed the article. All authors read and approved the final manuscript as submitted.

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