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牙龈卟啉单胞菌促进口腔鳞状细胞癌进展的分子机制的研究现状

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摘　要

牙龈卟啉单胞菌(*Porphyromonas gingivalis*, Pg)作为牙周病的主要致病菌，近年被证实与口腔鳞状细胞癌(OSCC)的发生、发展及预后密切相关。Pg通过炎症微环境、免疫逃逸、代谢重编程等机制促进OSCC发展。本文综述了Pg参与OSCC进展的分子机制，为OSCC的治疗策略提供理论依据。

关键词

口腔鳞状细胞癌，牙龈卟啉单胞菌，肿瘤微环境，上皮－间质转化，口腔微生物群

Research Advances on the Molecular Mechanisms of *Porphyromonas gingivalis* in Promoting Oral Squamous Cell Carcinoma Progression

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Abstract

***P. gingivalis*, a primary pathogenic bacterium in periodontitis, has been increasingly implicated in the onset, progression, and prognosis of oral squamous cell carcinoma (OSCC). Porphyromonas gingivalis promotes the development of OSCC through mechanisms including inflammatory microenvironment modulation, immune escape, and metabolic reprogramming. This review summarizes the molecular mechanisms by which *P. gingivalis* contributes to OSCC development, providing a theoretical basis for therapeutic strategies against OSCC.**

Keywords

Oral Squamous Cell Carcinoma, *Porphyromonas gingivalis*, Tumor Microenvironment, Epithelial-Mesenchymal Transition (EMT), Oral Microbiota

1. 引言

口腔鳞状细胞癌(OSCC)占头颈部恶性肿瘤的 90%，其发生与吸烟、饮酒等传统危险因素相关[1] [2]。近年研究发现，口腔微生物群失调(如 Pg 的慢性感染)通过诱导慢性炎症和基因突变参与 OSCC 的癌变过程。Pg 作为牙周炎的主要致病菌，可通过多种途径促进 OSCC 的侵袭和转移，成为肿瘤微环境(TME)的重要调控者。本文对 Pg 促进 OSCC 的分子机制进行了总结。

2. 炎症与免疫逃逸

Pg 通过多种炎症调控机制影响 OSCC 进展。Pg 分泌的毒力因子如脂多糖(LPS)和牙龈蛋白酶(gingipains)可直接破坏宿主细胞屏障，促进上皮－间质转化(EMT)，增强肿瘤侵袭性[3] [4]。还可激活 Toll 样受体(TLR)及 NOD1 信号通路，诱导 NF-κB 和 MAPK 通路活化，促进致炎因子(IL-6、IL-8、TNF-α)的释放，形成慢性炎症微环境[5]-[9]。Omori 等发现 OSCC 患者肿瘤组织中，PD-L1 高表达与细菌感染标志物(如 LPS 水平)呈正相关，此外，使用牙龈卟啉单胞菌脂多糖处理口腔鳞状细胞癌细胞系发现 LPS 通过 TLR4 信号诱导 OSCC 细胞 PD-L1 表达，并通过外泌体(EXOs)传递 PD-L1 至周围微环境[10]。Guo 等发现 Pg 通过激活中性粒细胞 TLR2 受体及 ROS/ERK 信号通路，驱动胞外诱捕网(NETs)的形成和释放，增强 OSCC 细胞侵袭和迁移能力，促进 EMT，重塑肿瘤免疫微环境[11]。现有研究多聚焦单一通路(如 TLR4-PD-L1)，但对不同炎症信号(如 TLR2 vs TLR4)的时空特异性调控缺乏深入探讨。

Pg 通过多种途径抑制抗肿瘤免疫应答。Pg 抑制巨噬细胞对肿瘤细胞的吞噬功能，同时诱导分泌 IL-10 等免疫抑制因子[12] [13]。Yao 等发现 Pg 通过上调 ASC 和 caspase-1 (分别增加 6 倍和 4 倍)，激活 NLRP3 炎性小体，释放 IL-1β 和 IL-18，形成慢性炎症微环境[14]。这种炎症反应与肿瘤相关巨噬细胞(TAMs)向 M2 型极化相关，进一步抑制抗肿瘤免疫[14] [15]。此外，Pg 通过 CXCL2/CXCR2 轴招募肿瘤相关中性粒细胞(TANs)，并通过 DOK3 信号促进 TAMs 的促瘤表型，抑制 CD8+ T 细胞活性[16]-[18]。

3. 细胞增殖与凋亡失衡

Pg 可激活促增殖信号通路。其 LPS 结合 TLR2/4 或 NOD1 受体，激活 PI3K/AKT 和 Wnt/β-catenin 通

路，上调 Cyclin D1、c-Myc 等细胞周期蛋白，促进肿瘤细胞增殖，其效应与 Fn (具核梭杆菌)的 FadA 蛋白协同增强，这种跨物种通路激活提示微生物群可能共享致癌信号节点[3] [5] [6] [19] [20]。此外还可抑制 p53 功能，导致细胞周期检查点失控[4] [13]。

Pg 通过多种途径调控肿瘤细胞凋亡。Pg 分泌的磷酸乙醇胺二氢神经酰胺(PEDHC)抑制酸性神经酰胺酶(ASAH1)表达，导致细胞内神经酰胺累积，最终通过抑制 caspase-3 活化阻止凋亡[21]。Yuan 等的研究报道 Pg 通过抑制 mTOR 通路(降低磷酸化 mTOR 水平)和激活 AMPK 信号，显著增强 OSCC 细胞的自噬活性，通过清除细胞内受损细胞器和氧化应激产物，维持肿瘤细胞在微环境压力下的存活[9]。此外，Liu 等发现 Pg 通过外膜囊泡(OMVs)高效递送 sRNA23392 至 OSCC 细胞，直接靶向桥粒胶蛋白 DSC2，破坏细胞间黏附并抑制凋亡，sRNA23392-DSC2 轴通过激活 TGF-β/Smad 通路进一步驱动 EMT 进程[22]。

4. 微生物群协同作用

Pg 与口腔微生物群的协同效应是促进 OSCC 发展的重要机制。1、Pg 与其他微生物交叉激活致癌信号通路。Shao 等发现 Fn 通过上调 ZEB1、Snail 等转录因子诱导 pEMT 表型，促进 OSCC 细胞侵袭[23]。Kamarajan 等指出 Pg 与齿垢密螺旋体(Treponema denticola, Td)通过 TLR/MyD88 信号激活整合素 αV/FAK 通路，增强细胞迁移和肿瘤形成[24]。2、Pg 与产酸菌的协同代谢调控。研究报道口腔菌群失调(如 Pg 与乳酸杆菌、链球菌共存)可导致微环境酸化，促进 DNA 损伤和基因组不稳定性[25] [26]。Isono 等发现 Pg 的代谢产物(如丁酸)可能与其他菌群的短链脂肪酸协同抑制宿主免疫应答，加速肿瘤生长[27]。3、Pg 协同微生物群共同调控免疫抑制微环境。Pg 与 Fn 共同诱导 M2 型巨噬细胞极化、Treg 细胞扩增及 PD-L1 表达上调，形成免疫抑制微环境，抑制 CD8+ T 细胞活性，从而促进 OSCC 免疫逃逸[20] [25] [27]。有研究报道了 EB 病毒(EBV)与 Pg 形成“病毒–细菌”正反馈环路，协同促进癌变，EBV 感染通过上调口腔黏膜细胞中细菌黏附分子(如 ICAM-1)，增强 Pg 的定植能力，同时 Pg 的炎症信号(如 NF-κB)激活 EBV 潜伏感染[28]。此外，Pg 与 EB 病毒(EBV)协同上调 IL-6 和 COX-2，形成慢性炎症微环境，加速基因组不稳定性[26]-[28]。

5. 代谢重编程与肿瘤微环境调控

Pg 通过多途径驱动 OSCC 的代谢重编程。1、脂质代谢重编程：Pg 通过 NOD1/KLF5 轴上调硬脂酰辅酶 A 去饱和酶 1 (SCD1)，促进单不饱和脂肪酸合成，增强肿瘤干细胞(CSCs)特性(如肿瘤球形成能力、化疗耐药性)，SCD1 抑制剂可逆转 Pg 诱导的干细胞表型[29]。Lu 等使用人永生化口腔上皮细胞建立 Pg 的长期感染模型，发现长期 Pg 感染通过抑制 ZFP36 蛋白(一种 RNA 结合蛋白，参与 mRNA 稳定性调控)表达，激活 CCAT1/MK2 复合物，促进 KLF5 依赖性脂代谢基因转录，增强肿瘤进展[30]。2、表观遗传调控与基因表达改变：Pg 感染导致抑癌基因(如 p53)失活，解除对代谢检查点的调控，同时激活癌基因(Cyclin D1)，促进细胞周期进展[26] [31] [32]。Baraniya 等发现 Pg 可能通过诱导 CD36 基因启动子区域的 DNA 高甲基化(如 DNMTs 活性增强)，抑制脂肪酸转运蛋白 CD36 转录，从而减少癌细胞对游离脂肪酸的摄取，迫使癌细胞转向依赖内源性脂质合成(如 FASN 上调)以满足能量需求[33] [34]。此外，Pg 与 Fn 的协同代谢产生短链脂肪酸(SCFAs)等物质，抑制组蛋白去乙酰化酶(HDACs)，影响表观遗传调控[35]。3、微生物群代谢产物：Pg 通过分泌毒力因子(如牙龈蛋白酶)产生致癌代谢物(如琥珀酸、丁酸)，直接促进肿瘤细胞增殖和侵袭。这些代谢物可激活缺氧诱导因子(HIF-1α)，增强糖酵解(Warburg 效应)和能量代谢[32] [36]。Pg 与口腔微生物群(如具核梭杆菌)协同形成生物膜微环境，产生局部缺氧和酸性代谢产物，进一步驱动 HIF-1α 依赖的代谢适应[23] [24] [35]。此外，Pg 通过外膜囊泡(OMVs)传递毒力因子，直接干扰宿主线粒体功能，促进 ROS 积累和氧化磷酸化失调[37] [38]。OMVs 还可递送脂质代谢相关分子，调

控宿主细胞代谢[20]。

6. 小结

综上，牙龈卟啉单胞菌通过多维度机制驱动口腔鳞状细胞癌的恶性进展。该致病菌被证实可激活上皮–间质转化、抑制宿主免疫监控系统、增强肿瘤细胞增殖速率，并显著提升其侵袭转移潜能等机制，从而系统性地加剧口腔鳞癌的病理恶化过程。值得注意的是，Pg 并非独立发挥作用，其调控的炎症反应、代谢适应与免疫抑制间存在复杂的交互作用，并与共生微生物形成致癌网络。这些分子机制的研究具有重要的临床意义，为靶向治疗提供了潜在干预点。本文总结了这些分子机制，为 OSCC 的诊治提供了重要的理论依据。

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