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· 综述 ·

牙龈卟啉单胞菌在肿瘤发生发展中作用的研究进展

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【摘要】 牙周炎是一种慢性炎症性疾病，牙周炎致病菌的异位定植可影响全身健康引起全身性疾病。牙龈卟啉单胞菌(*Porphyromonas gingivalis*，*P. gingivalis*)作为牙周炎的关键病原体，已被证实与口腔鳞状细胞癌(oral squamous cell carcinoma，OSCC)、肺癌、食管癌、胰腺癌、结直肠癌、宫颈癌和前列腺癌的发生发展有关。*P. gingivalis*通过多种机制参与调控OSCC的发生发展：*P. gingivalis*直接调控细胞周期和凋亡相关蛋白促进肿瘤细胞增殖、诱导分化簇44(cluster of differentiation 44，CD44)和分化簇133(cluster of differentiation 133，CD133)的表达增强肿瘤干细胞特性、激活炎性小体和P38/c-Jun NH2末端激酶1(c-Jun N-terminal kinase，JNK)通路以及调控肿瘤相关中性粒细胞(tumor-associated neutrophil，TAN)极化重塑肿瘤微环境、调控上皮-间充质转化(epithelial-mesenchymal transition，EMT)促进肿瘤转移、调控巨噬细胞功能逃避宿主免疫反应、诱导肿瘤细胞耐药以及调控与共生菌间的相互作用等参与OSCC的进展。此外，*P. gingivalis*通过促进细胞增殖、抑制细胞凋亡、诱导慢性炎症、逃避宿主免疫监视等促进食管癌、胰腺癌、结直肠癌和前列腺癌的进展。然而，口腔微生物组是一个复杂的系统，*P. gingivalis*并非独立存在，口腔微生物之间的相互作用是否影响肿瘤的进展有待进一步的研究。

【关键词】 牙龈卟啉单胞菌；　牙周炎；　肿瘤；　口腔鳞状细胞癌；　系统性疾病；　菌群失调；　致癌机制；　早期诊疗；　口腔健康
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Research progress on the role of *Porphyromonas gingivalis* in the progression of tumor

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【Abstract】 Periodontitis is a chronic inflammatory disease. The heterotopic colonization of periodontal pathogens results in the development of several systemic diseases. *Porphyromonas gingivalis* (*P. gingivalis*), a key pathogen for periodontitis, has been linked to the development of various cancers, such as oral squamous cell carcinoma (OSCC), lung cancer, esophageal cancer, pancreatic cancer, colorectal cancer, cervical cancer, and prostate cancer. *P. gingivalis* promote the progression of tumor through various mechanisms, *P. gingivalis* regulates proteins targeting cell cycle and apoptosis to promote proliferation of tumor cells directly, enhances tumor stemness by upregulating the expression of cluster of differentiation 44 (CD44) and cluster of differentiation 133 (CD133), activates inflammasome and p38/c-Jun

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N-terminal kinase 1(JNK) pathways, regulates tumor-associated neutrophil (TAN) polarization to remodel the tumor microenvironment, regulates epithelial-mesenchymal transition (EMT) to promote tumor metastasis, remodel macrophage function to evade host immune response, and regulates multi-communicating with symbiotic bacteria. In addition, *P. gingivalis* accelerates the progression of esophageal cancer, pancreatic cancer, colorectal cancer, and prostate cancer by promoting cell proliferation, inhibiting apoptosis, inducing chronic inflammation, and escaping immunity. However, the oral microbiome is a complex system, whether the interactions between oral bacteria affect tumor progression needs to be further investigated.

【Key words】 *Porphyromonas gingivalis*; periodontitis; tumor; oral squamous cell carcinoma; systemic diseases; dysbacteriosis; carcinogenic mechanisms; early diagnosis and treatment; oral health

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研究表明，约13%的癌症发病与微生物感染有关[1-2]。牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P. gingivalis*）是革兰氏阴性厌氧的牙周炎致病菌，被证实与肿瘤发生发展相关[3]。*P. gingivalis*主要毒力因子包括菌毛（FimA）、脂多糖（lipopolysaccharide，LPS），牙龈蛋白酶、血凝素（hemagglutinin，HA）和外膜囊泡（outer membrane vesicles，OMVs）等[4-6]。口腔菌群稳态对口腔和全身健康均有重要作用，口腔菌群失衡可引起局部慢性炎症和免疫抑制，不仅可以导致口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）[7]，还可以通过异位定植，参与肺癌[8]、食管癌[9]、胰腺癌[10]、结直肠癌[11]、宫颈癌[12]和前列腺癌[13]的进展（表1）。其促癌机制涉及调控肿瘤细胞增殖与细胞周期、抑制肿瘤细胞凋亡、促进肿瘤细胞侵袭、诱导炎症反应和化学耐药以及共生菌之间的相互作用。本文将对*P. gingivalis*与肿瘤进展的相关性及其病理机制进行综述。

表1 口腔菌群失衡与全身性疾病

Table 1 Oral dysbacteriosis and systemic disease

Disease	Oral bacteria
Chronic periodontitis	*Porphyromonas gingivalis*[14-15]; *Tannerella forsythia*; *Treponema denticola*; *Prevotella intermedia*[14]; *Aggregatibacter actinomycetemcomitans*[14, 16]
Ooral squamous cell carcinoma	*Porphyromonas gingivalis; Treponema denticola*[14]; *Fusobacterium nucleatum*[7, 14]; *Prevotella intermedia*[7, 17]
Pneumonia	*Porphyromonas gingivalis*[18-20]; *Fusobacterium nucleatum*; *Aggregatibacter actinomycetemcomitans*[18]; *Prevotella intermedia*[21]
Chronic obstructive pulmonary disease	*Porphyromonas gingivalis*[22-23]; *Prevotella intermedia*[22]
Asthma	*Prevotella intermedia*[24]
Lung cancer	*Prevotella intermedia; Fusobacterium nucleatum*[22];*Veillonella*[25]
Breast cancer	*Fusobacterium nucleatum*[26-27]; *Streptococcus mutans*[26, 28-29]
Esophageal cancer	*Porphyromonas gingivalis*; *Fusobacterium nucleatum*[30]
Gastric cancer	*Prevotella intermedia*[31-32]; *Streptococcus oralis*; *Veillonella parvula*[31]; *Fusobacterium nucleatum*[33-34]
Pancreatic cancer	*Porphyromonas gingivalis*[10, 14]; *Aggregatibacter actinomycetemcomitans*[14]
Colorectal cancer	*Porphyromonas gingivalis*[35-36]; *Fusobacterium nucleatum*[35-38]
Cervical cancer	*Porphyromonas gingivalis*; *Prevotella intermedia*; *Campylobacter rectus*[12]
Prostate cancer	*Porphyromonas gingivalis*[13]
Atherosclerosis	*Porphyromonas gingivalis*[14, 39]; *Prevotella intermedia*; *Prevotella nigrescens*; *Prevotella nigrescens*; *Campylobacter rectus*[14]; *Fusobacterium nucleatum*[40-41]
Alzheimer's disease	*Porphyromonas gingivalis*[14, 42-44]; *Treponema denticola*[14, 45]
Diabetes mellitus	*Treponema denticola*; *Streptococcus sanguinis*; *Streptococcus intermedius*; *Streptococcus oralis*; *Prevotella nigrescens*[14]

1 *P. gingivalis* 在口腔鳞状细胞癌发生发展中的作用机制

与健康个体相比，OSCC患者肿瘤组织中*P. gingivalis*显著富集[7, 46-47]，是正常组织的600倍[48]。Chang等[46]发现*P. gingivalis*与OSCC患者临床晚分期、低分化及淋巴结转移呈正相关，且*P. gingivalis*可通过结肠癌相关转录因子1/三四脯氨酸/丝裂原活化蛋白激酶激活的蛋白激酶2感染口腔上皮细胞抑制锌指蛋白36的表达，从而促进其恶性转化[49]。综上，表明*P. gingivalis*与OSCC之间可能存在着密切的关系(图1)。

1.1 *P. gingivalis*促进细胞增殖

肿瘤细胞具有无限增殖的能力，细菌可通过增强肿瘤细胞增殖而促进肿瘤的进展[50]。*P. gingivalis*通过调控miR-21/程序性细胞死亡4(programmed cell death 4，PDCD4)/激活蛋白1(activator protein 1，AP-1)负反馈通路，驱动细胞周期蛋白(cyclin)D1的表达，诱导细胞周期阻滞于S期[51-52]。同时，*P. gingivalis*的毒力因子牙龈蛋白酶通过激活NOTCH信号传导促进细胞增殖。*P. gingivalis*还可通过促进细胞自噬[53]和抑制凋亡蛋白Bad并激活B淋巴细胞瘤-2(B-cell lymphoma 2，Bcl-2)的表达抑制细胞凋亡促进OSCC细胞增殖[54]。此外，*P. gingivalis*可以通过上调钙结合蛋白1(calbindin 1，CALB1)表达诱导牙龈上皮癌细胞增殖[55]。Zeng等[56]发现*P. gingivalis*-OMVs可能通过下调抑癌基因锌指蛋白292(zinc finger protein 292，ZNF292)和ATRX(alpha thalassemia/mental retardat)表达促进OSCC细胞增殖。研究表明FimA通过依赖磷酸化蛋白激酶B 1(phosphorylated protein kinase B 1，pAkt1)、磷酸化叉头状转录因子O1(phosphorylated forkhead box transcription factor O1，pFOXO1)通路[57]以及靶向结合微管相关蛋白1轻链3B(microtubule-associated protein 1 light chain 3 B，LC3B)-鞘氨醇(ceramide)复合物抑制线粒体自噬[58]，促进OSCC细胞增殖。研究发现*P. gingivalis*分泌的核苷二磷酸激酶可增加细胞外三磷酸腺苷(adenosine triphosphate，ATP)水解，从而激活ATP-嘌呤能离子通道(purinergic ligand-gated ion channel 7，P2X7)信号通路，上调P2X7的表达和激活钙离子通道，导致细胞内钙离子累积促进OSCC细胞增殖[59]。目前尚未报道*P. gingivalis*其他毒力因子对OSCC细胞增殖影响的机制，需要进一步研究。

1.2 *P. gingivalis*增强肿瘤干细胞特性

脂质是细胞的重要组成部分，其代谢异常有助于癌细胞获得干细胞特性。脂质硬脂酰辅酶A去饱和酶1(stearoyl-coA desaturase 1，SCD1)是一种参与脂质去饱和的酶，是癌细胞生存的重要调节因子[60]。Zang等[61]发现*P. gingivalis*通过含核苷酸结合寡聚结构域蛋白1(nucleotide-binding oligomerization domain-containing protein 1, NOD1)/Krüppel样因子5(Krüppel-like factor 5，KLF5)轴上调SCD1的表达，促进OSCC细胞脂质合成，诱导癌症干细胞标志物簇分化抗原(cluster of differentiation 44，CD44)和簇分化抗原(cluster of differentiation 133，CD133)的表达，增强OSCC的干性和致瘤性，提示*P. gingivalis*在OSCC发生发展中具有重要的作用。靶向SCD1抑制肿瘤细胞干性有望抑制肿瘤进展、复发和耐药。

1.3 *P. gingivalis*重塑炎性微环境

研究发现*P. gingivalis*感染口腔内皮细胞后促进口腔内皮细胞分泌促炎OMVs，激活Toll样受体4(Toll-like receptor ，TLR4)/核因子-κB(nuclear factor kappa B，NF-κB)信号通路，诱导炎症反应[62]。同时还发现*P. gingivalis*通过激活炎性小体NLRP3过表达引起白细胞介素(interleukin，IL)-1β(IL-1β)大量释放，形成慢性炎症微环境[52]，其毒力因子LPS通过激活P38/c-Jun NH2末端激酶1(c-Jun N-terminal kinase，JNK)通路，促进炎症反应[63]。此外，*P. gingivalis*诱导免疫细胞分泌趋化因子，C-C趋化因子2(C-C motif ligand 2，CCL2)和C-X-C趋化因子2(C-X-C motif chemokine ligand 2，CXCL2)以及细胞因子IL-6、IL-8等，激活髓系抑制细胞(myeloid-derived suppressor cells，MDSC)[64]和肿瘤相关中性粒细胞(tumor-associated neutrophil，TAN)[54]，TAN可通过释放中性粒细胞外陷阱(neutrophil extracellular traps ，NETs)改变肿瘤微环境从而促进OSCC进展[65]。TAN分为肿瘤抑制型TAN1和肿瘤促进型TAN2，有研究发现*P. gingivalis*下调黏蛋白-1和C-X-C趋化因子17(C-X-C motif ligand 17，CXCL17)的表达[66]，其中CXCL17可能激活N1型TAN，释放活性氧和活性氮直接杀死肿瘤细胞，从而抑制OSCC生长，提示*P. gingivalis*在OSCC发生发展中具有双重作用。因此，通过诱导TAN极化为TAN1，从而可能开发基于TAN极化的肿瘤治疗新方法。

1.4　*P. gingivalis* 促进肿瘤细胞侵袭

P. gingivalis 介导IL-8上调基质金属蛋白酶1（matrix metalloprotease 1，MMP-1）和基质金属蛋白酶10（matrix metalloprotease 10，MMP-10）的表达[67]，增强OSCC侵袭。同时，*P. gingivalis* 菌毛蛋白FimA激活锌指E-box结合同源框1蛋白表达，上调间充质标志物如波形蛋白和基质金属蛋白酶9的表达，诱导上皮-间充质转化（epithelial-mesenchymal transition，EMT）[68]，协同增强OSCC细胞迁移和侵袭的能力。Liu等[69]首次发现 *P. gingivalis*-OMVs中sRNA23392可下调OSCC细胞中桥粒蛋白2（desmocollin-2，DSC2），进一步促进EMT、细胞迁移和侵袭。本课题组[70]还发现 *P. gingivalis*-OMVs可以通过NF-κB信号通路抑制铁死亡从而促进OSCC的EMT进程。此外，精氨酸特异性半胱氨酸蛋白酶R牙龈蛋白酶（arginine-specific cysteine proteinase R gingipain，Rgp）通过降解宿主屏障蛋白促进细胞侵袭和诱导细胞凋亡[71]。LPS还可以诱导程序性死亡配体1（programmed death ligand 1，PD-L1）的表达和EMT促进OSCC的侵袭[72]。不同毒力因子对肿瘤细胞侵袭能力的调控不同，抑制或敲除促癌成分（FimA、Rgp、OMVs和LPS）是达到精准治疗目的的有效途径。肿瘤细胞侵袭表型的获得是肿瘤细胞从原发灶向远处转移的基础，也是治疗失败的主要原因。基于上述，发现 *P. gingivalis* 毒力因子在OSCC进展中发挥着重要作用，因此通过靶向 *P. gingivalis* 毒力因子抑制细胞的侵袭可能可以提高治疗效果。

1.5　*P. gingivalis* 促进肿瘤细胞逃避宿主免疫反应

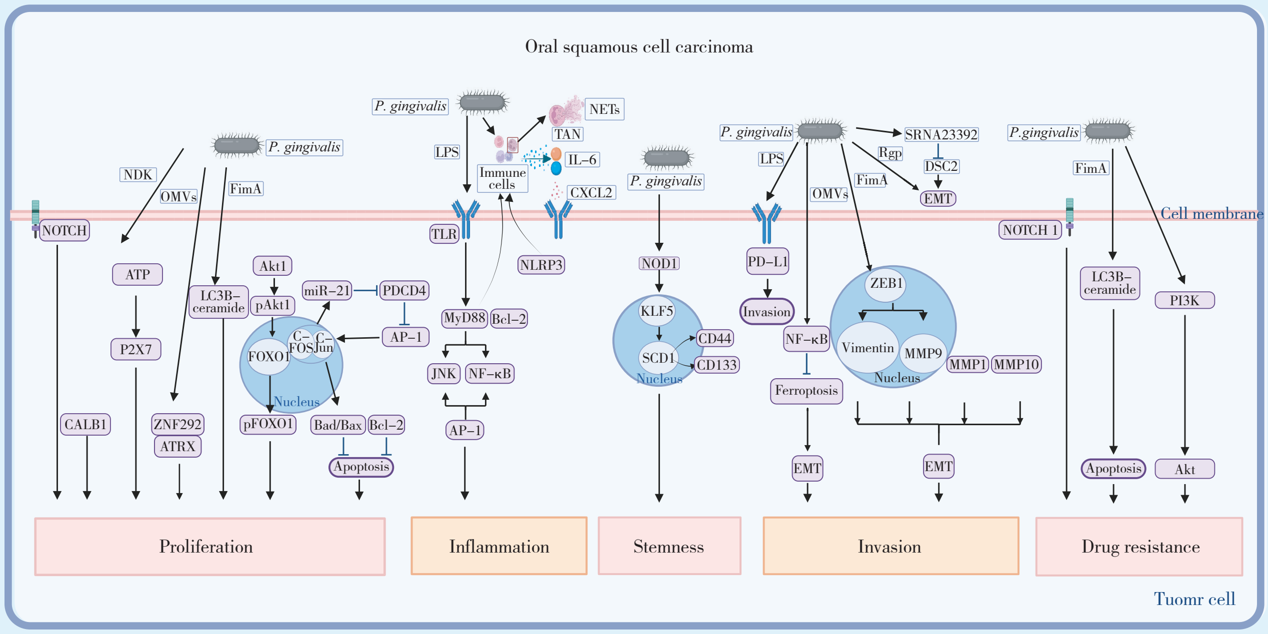
研究发现 *P. gingivalis* 在OSCC免疫逃避中具有重要作用，*P. gingivalis* 上调巨噬细胞中的DOK3[73]，抑制巨噬细胞对OSCC细胞的吞噬作用，并诱导巨噬细胞极化为M2肿瘤相关巨噬细胞[74]，有助于OSCC免疫逃逸从而促进OSCC进展。此外，Ren等[75]发现 *P. gingivalis* 可通过蛋白激酶B（protein kinase B，Akt）-信号转导与转录激活因子3（signal transducer and activator of transcription 3，STAT3）信号通路上调树突状细胞上的PD-L1的表达，促进PD-1与其配体PD-L1结合，抑制CD8+ T细胞毒性以逃避免疫攻击；同时，*P. gingivalis* 细胞壁表面的肽聚糖可激活受体相互作用蛋白激酶2（receptor-interacting protein kinase 2，RIP2）-丝裂原活化激酶（mitogen-activated protein kinases，MAPK）轴，上调PD-L1的表达[76]，从而促进肿瘤细胞逃逸。此外，*P. gingivalis* 通过募集趋化因子受体6（chemokine receptor 6，CCR6）阳性（$CCR6^+$）调节性T（regulatory T cells，Treg）细胞以减少 $CD8^+$ T细胞的占比[77]，而 $CD8^+$ T细胞是抑制OSCC进展的重要防线和预后指标，因此，靶向抑制 *P. gingivalis* 有望抑制OSCC进展。

1.6　*P. gingivalis* 诱导化学耐药

研究发现，*P. gingivalis* 通过FimA与膜联蛋白A2（annexin A2，ANXA2）结合，靶向OSCC细胞中的LC3B-ceramide复合物抑制线粒体自噬，导致OSCC细胞产生耐药[58]。*P. gingivalis* 感染OSCC后诱导OSCC细胞中NOTCH1的激活导致OSCC细胞对紫杉醇耐药[78]。同时，*P. gingivalis* 还可通过磷脂酰肌醇-3-激酶（phosphoinositide 3-kinase，PI3K）/Akt信号通路诱导口腔角质细胞失巢凋亡耐药[79]。此外，还发现 *P. gingivalis* 可以引发小鼠炎症反应且促进肿瘤生长，炎症是肿瘤耐药的促进因素，抗炎治疗不仅可以抑制 *P. gingivalis* 的聚集，还可以增强荷瘤的小鼠对化疗药物的敏感性[80]，提示控制 *P. gingivalis* 及其相关炎症对治疗OSCC耐药具有重要作用。

1.7　*P. gingivalis* 与口腔共生菌间的相互作用

研究发现 *Fn* 与OSCC进展密切相关[81]，将 *P. gingivalis* 和 *Fn* 共培养后，*Fn* 通过激活烟酰胺腺嘌呤二核苷酸磷酸氧化酶1（nicotinamide adenine dinucleotide phosphate oxidase，NOX1）和烟酰胺腺嘌呤二核苷酸磷酸氧化酶2（nicotinamide adenine dinucleotide phosphate oxidase，NOX2）[82]，增加 *P. gingivalis* 对牙龈上皮的黏附和侵袭能力，促进OSCC进展，但Zhang等[83]发现，*P. gingivalis*–OMVs中的蛋白酶通过降低 *Fn* 表面黏附相关蛋白梭杆菌黏附素A（Fusobacterium adhesin A，FadA）和具核梭杆菌外膜蛋白A（*Fusobacterium nucleatum* outer membrane protein A，FomA）的表达，抑制 *P. gingivalis* 侵入口腔上皮细胞，从而可能抑制OSCC进展。此外，Fukuda等[84]还发现奈瑟球菌属也能通过其与 *P. gingivalis* 之间的相互作用抑制 *P. gingivalis* 侵入上皮而抑制OSCC进展，尤其是黏液奈瑟球菌和延长奈瑟球菌抑制效果最显著，但 *P. gingivalis* 与奈瑟球菌属之间相互作用的机制尚不清楚需要深入研究，以期为治疗OSCC寻找新策略。因此，深入研究细菌间的相互作用对控制OSCC的发生发展具有重要作用，但目前对于 *P. gingivalis* 与口腔其他细菌间的作用研究较少。



P. gingivalis: *Porphyromonas gingivalis*; OMVs: outer membrane vesicles; LPS: lipopolysaccharide; Rgp: arginine-specific cysteine proteinase R gingipain; PDCD4: programmed cell death 4; AP-1: activator protein 1; Bad: Bcl-2 antagonist of cell death; Bax: Bcl-2 associated X protein; Bcl-2: B-cell lymphoma 2; CALB1: Calbindin 1; ZNF292: zinc finger protein 292; ATRX: alpha thalassemia/mental retardat; LC3B- ceramide: microtubule-associated protein 1 light chain 3 B-ceramide; FOXO1: forkhead box transcription factor O1;Akt1: protein kinase B 1;pAkt1: phosphorylated Protein kinase B 1;pFOXO1: phosphorylated Forkhead box transcription factor O1;C-Fos: cellular oncogene Fos;C-Jun: c-jun proto-oncogene; miR-21: microRNA-21; SCD1: Stearoyl-CoA desaturase 1; NOD1: nucleotide-binding oligomerization domain-containing protein 1; KLF5: Krüppel-like factor 5; CD44: cluster of differentiation 44; CD133: cluster of differentiation 133; IL-1β: interleukin-1β; JNK: c-Jun N-terminal kinase; TLR: Toll-like receptor; CXCL2: C-X-C motif chemokine ligand 2; MyD88: myeloid differentiation primary response protein 88; NLRP3: nucleotide-binding domain, leucine-rich repeat containing family, pyrin domain-containing 3; MDSC: myeloid-derived suppressor cells; TAN: Tumor-associated neutrophil; NETs: neutrophil extracellular traps; MMP-1: matrix metalloprotease 1; MMP-10: matrix metalloprotease 10; MMP-9: matrix metalloprotease 9; EMT: epithelial-mesenchymal transition; ZEB1: zinc finger E-box binding homeobox 1; SRNA23392: small RNA 23392; DSC2: desmocollin-2; NF-κB: nuclear factor kappa B; PD-L1: programmed death ligand 1; PI3K: phosphoinositide 3-kinase; Akt: protein kinase B

Figure 1　The role of *Porphyromonas gingivalis* in the progression of oral squamous cell carcinoma

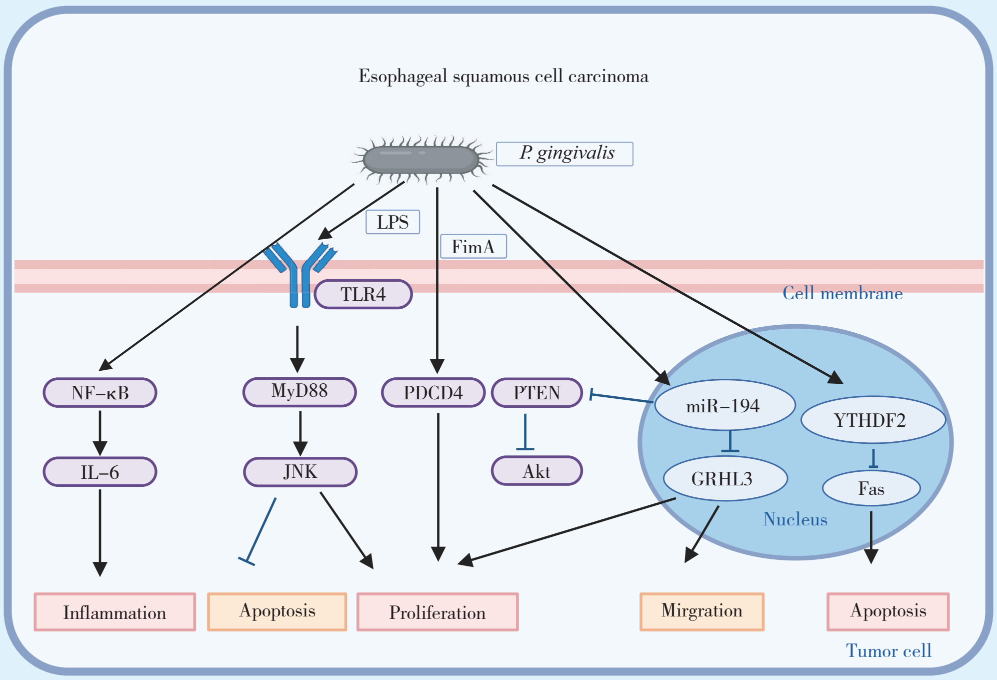
图1　牙龈卟啉单胞菌在口腔鳞状细胞癌发生发展中的作用

2 *P. gingivalis* 在其他癌症发生发展中的作用机制

P. gingivalis 除了可参与OSCC进展外，还可通过异位定植影响肺癌、消化道及生殖系统肿瘤的发生发展。根据2022年的国际癌症研究机构报告，肺癌已超过乳腺癌、前列腺癌等成为全球癌症死亡的主要原因[85]。Liu等[8]对三种类型肺癌组织和癌旁组织进行免疫组织化学染色，首次在肺癌组织中检测到 *P. gingivalis*，且 *P. gingivalis* 阳性的肺癌患者5年生存率和中位生存时间显著低于阴性组，提示 *P. gingivalis* 可能与肺癌患者不良预后相关，但是 *P. gingivalis* 具体的致癌机制尚未明确，需要进一步深入研究，从而提高患者的生存率及改善患者的预后。

研究发现 *P. gingivalis* 激活Sonic hedgehog信号通路诱导正常食管上皮恶性转化，表明高丰度的 *P. gingivalis* 可能会增加食管癌发生的风险[86]。Meng等[87]通过16S rRNA基因测序和LEfSe分析比较正常人和食管鳞状细胞癌（esophageal squamous cell carcinoma，ESCC）患者唾液细菌，发现 *P. gingivalis* 在ESCC患者中显著富集，表明 *P. gingivalis* 与ESCC之间可能存在关联。另一研究发现唾液中的 *P. gingivalis* 可作为食管癌的特征性标志物[88]，因此，研究 *P. gingivalis* 的致癌机制对于治疗食管癌具有重要作用。研究指出，*P. gingivalis* 通过抑制程序性细胞死亡因子4（programmed cell death factor 4，PDCD4）的表达，增强ESCC细胞干性和耐药[89]，同时通过FimA、毒力因子LPS激活TLR4/髓

样细胞分化因子(Myeloid differentiation factor 88,MyD88)/JNK信号通路[90]以及上调MicroRNA-194,抑制果蝇头状因子(Grainy head-like 3,GRHL3)/磷酸酯酶与张力蛋白同源物(phosphatase and tensin homolog, PTEN)/Akt信号通路[91]促进ESCC增殖[89,92]。同时,*P. gingivalis*定植引起菌群失调诱导食管黏膜慢性炎症[93],激活NF-κB[87],促进IL-6分泌[94],形成慢性炎症微环境促进ESCC进展。此外,*P. gingivalis*还通过YTH N6-甲基腺苷RNA结合蛋白2(YTH N6-methyladenosine RNA binding protein 2,YTHDF2)抑制凋亡相关因子Fas的表达,协助ESCC细胞逃避宿主免疫监视,从而促进ESCC的进展[95](图2)。食管微生物失衡可作为检测食管疾病的标志物,直接靶向FimA或MicroRNA-194可能是治疗食管癌的新策略。



P. gingivalis: *Porphyromonas gingivalis;* LPS: lipopolysaccharide; PDCD4: programmed cell death factor 4; MyD88: Myeloid differentiation factor 88; JNK: c-Jun N-terminal kinase; GRHL3: grainy head-like 3; TLR4: Toll-like receptor 4; MiR-194: microRNA-194; PTEN: phosphatase and tensin homolog; Akt: protein kinase B; NF-κB: nuclear factor kappa B; IL-6: interleukin-6; YTHDF2: YTH N6-methyladenosine RNA binding protein 2; Fas: Fas Antigen

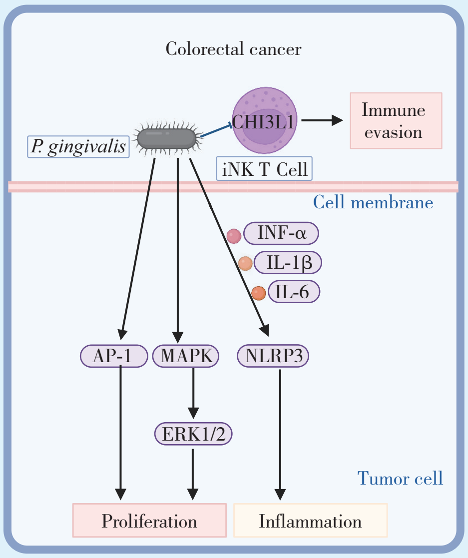
Figure 2　The role of *Porphyromonas gingivalis* in the progression of esophageal squamous cell carcinoma

图2　牙龈卟啉单胞菌在食管鳞状细胞癌发生发展中的作用

牙周病主要是由口腔正常菌群生态失调引起,最近研究发现牙周病可增加胰腺癌的发病风险[96]。一项荟萃分析表明*P. gingivalis*与胰腺癌相关[10]。Tan等[97]发现*P. gingivalis*通过诱导趋化因子募集中性粒细胞,促进中性粒细胞弹性蛋白酶分泌,加速胰腺癌的进展。*P. gingivalis*还可激活Toll受体(Toll-like receptor,TLR)信号通路,TLR9诱导胰腺癌细胞纤维化并产生刺激上皮细胞增殖的细胞因子,促进肿瘤纤维化和上皮细胞异常增殖[98]。虽然*P. gingivalis*能促进胰腺癌的发生发展,但目前仍缺乏明确口腔微生物可以作为胰腺癌风险评估的研究。

研究发现*P. gingivalis*在结直肠癌(colorectal cancer,CRC)组织中富集[35,99],其可通过血行或经肠道途径在肠道定植[100]。Mu等[101]通过建立侵袭CRC感染模型,发现*P. gingivalis*激活丝裂原活化激酶(mitogen-activated protein kinases,MAPK)/细胞外调节蛋白激酶(extracellular regulated protein kinases,ERK)信号通路促进CRC细胞增殖,同时上调AP-1的表达调节肿瘤细胞周期。还可通过募集IL-1β、IL-6和干扰素α,激活炎性小体NLRP3形成炎性微环境,促进CRC进展[11]。此外*P. gingivalis*上调几丁质酶3-like-1蛋白(Chitinase 3-like-1 protein,CHI3L1)表达,损害抑制性天然T细胞毒性功

能,促进肿瘤免疫逃避[102](图3)。因此,开发靶向CHI3L1的治疗策略有望克服CRC免疫逃避。



P. gingivalis: *Porphyromonas gingivalis*; MAPK: mitogen-activated protein kinases; ERK1/2: extracellular regulated protein kinases 1/2; AP-1: Activator protein 1; INF-α: interferon-α; IL-1β: interleukin-1β; IL-6: interleukin-6; CHI3L1: Chitinase 3-like-1 protein; iNK T Cell: invariant Natural Killer T Cell; Caspase-1: Cysteine aspartate specific protease-1; NLRP3: nucleotide-binding domain, leucine-rich repeat containing family, pyrin domain-containing 3

Figure 3　The role of *Porphyromonas gingivalis* in the progression of colorectal cancer

图3　牙龈卟啉单胞菌在结直肠癌发生发展中的作用

有研究表明阴道细菌与宫颈癌(cervical cancer,CC)之间存在一定的联系,Wu等[12]通过分析宫颈黏液微生物,发现*P. gingivalis*是CC的生物标志物之一,然而目前对于*P. gingivalis*如何定植于阴道的研究有限,其致癌机制尚未明确,需要进一步探索*P. gingivalis*在CC发生发展中的作用。

最近一项荟萃分析明确了牙周炎与前列腺癌(prostate cancer,PCa)风险的相关性[103],*P. gingivalis*通过肽聚糖介导PCa细胞中PD-L1的表达,诱发慢性炎症和肿瘤细胞免疫逃避促进PCa的进展[13]。前列腺与口腔在生理上没有连续性,如果能够明确*P. gingivalis*与前列腺癌之间的致癌机制,则可以此为靶点引入新的治疗方法。

3　小　结

本文综述了*P. gingivalis*与肿瘤发生发展之间的密切关系及其作用机制。该菌不仅可以通过多种机制参与OSCC的发生发展,还可通过异位定植影响肺癌、消化道及生殖系统肿瘤的发生发展。目前对于*P. gingivalis*在肺癌、宫颈癌和前列腺癌中的致癌机制研究相对较少,需要深入探索具体机制,寻找特异性靶点。在致癌过程中,唾液中细菌群落组成在定性和定量上都会发生变化,收集唾液或牙菌斑简单且无创,分析唾液或牙菌斑中的细菌群落组成,有望成为癌症风险评估的一种有效检验手段。因此,明确*P. gingivalis*在全身肿瘤中发生发展的生物机制至关重要,为未来治疗癌症提供诊断和治疗的新思路,还有助于通过识别相应部位致病性微生物。

【Author contributions】 Feng Y wrote the article. Feng Y and Yu L conceptualized and reviewed the article. All authors read and approved the final manuscript as submitted.

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