

ROLE OF *FUSOBACTERIUM NUCLEATUM* AND *PORPHYROMONAS GINGIVALIS* IN ORAL CANCER: A LITERATURE REVIEW

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Abstract: Oral cancer, predominantly oral squamous cell carcinoma (OSCC), is a multifactorial disease influenced by genetic, environmental, and microbial factors. Among the emerging contributors to oral carcinogenesis, *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, two Gram-negative anaerobic bacteria that reside in the human oral cavity as part of the normal microbiota, have gained attention for their pathogenic roles. Both species play key roles in periodontal disease and exhibit significant tumour-promoting activities through distinct and synergistic mechanisms. They modulate the tumor microenvironment by promoting the release of pro-inflammatory cytokines, facilitating immune evasion, and contributing to microbial dysbiosis. Clinical studies have identified their presence in OSCC tissues, correlating with advanced tumor stages, lymph node metastasis, and poor prognosis. Their involvement underscores the critical interplay between oral microbiota and host-pathogen interactions in cancer development. This review highlights the molecular mechanisms through which *F. nucleatum* and *P. gingivalis* contribute to oral carcinogenesis, emphasizing the need for further research to explore their diagnostic and therapeutic potential in oral cancer management. Addressing these microbial drivers could pave the way for innovative strategies in cancer prevention and treatment.

1. Introduction. 2. *Fusobacterium nucleatum* and *Porphyromonas gingivalis* – characteristic features. 3. Association between *Fusobacterium nucleatum*, *Porphyromonas gingivalis* and oral cancer. 4. Carcinogenesis mechanisms of *Fusobacterium nucleatum* and *Porphyromonas gingivalis*. 5. Migration and Invasion. 6. Proliferation. 7. Change in the Local Tumor Microenvironment. 8. Conclusions.

Keywords: carcinogenesis, *Fusobacterium nucleatum*, oral microbiota, oral squamous cell carcinoma (OSCC), *Porphyromonas gingivalis*,

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity, accounting for over 90% of oral cancers (Li et al. 2024). OSCC ranks among the top 10 cancers worldwide, with an annual incidence exceeding 300,000 cases. Higher rates are observed in South Asia, parts of Africa, and the Middle East. It predominantly affects individuals over 40 years of age, with a higher prevalence in males. However, cases in younger populations, particularly women, are

increasing. Five-year survival rates range from 50% to 60%, depending on the stage at diagnosis (Shao et al. 2021). OSCC arises from the squamous epithelium lining the oral cavity and is characterized by its aggressive growth, as well as a tendency for local invasion and metastasis. The anatomical distribution of OSCC includes the anterior two-thirds of the tongue, lower and upper gingiva, buccal mucosa, hard palate, floor of the mouth, retromolar triangle, and vermilion mucosa (Li et al. 2024). Some OSCCs may arise *de novo*, whilst others arise from oral potentially malignant

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disorders (OPMDs), such as leukoplakia and erythroplakia (Warnakulasuriya et al. 2020). Traditional risk factors, such as tobacco use, alcohol consumption, betel nut chewing, and human papillomavirus (HPV) infection, are well-recognized. Other factors, including infections resulting from poor oral hygiene, exposure to ionizing radiation, and environmental pollutants, may also play a significant role. Moreover, emerging evidence highlights the role of microbiota in carcinogenesis (Shao et al. 2021). However, around 15% of OSCC cases develop without any of these known risk factors (Singh et al. 2023). Some evidence suggests that the imbalance of oral microbiota plays a crucial role in the onset, progression, and prognosis of OSCC, thereby offering potential biomarkers for the disease. The oral microbiota can elicit chronic inflammation, generate inflammatory mediators and carcinogenic agents, and influence cell proliferation and apoptosis. Among oral pathogens, *Porphyromonas gingivalis* and *Fusobacterium nucleatum* have garnered attention for their potential role in the development, progression, and metastasis of OSCC (Nie et al., 2024; Pang et al., 2024).

This review aims to enhance our understanding of the molecular mechanisms underlying the initiation and progression of OSCC to inform the development of more effective preventive measures. Furthermore, it seeks to expand our understanding of the intricate relationship between microorganisms and cancer development.

2. *Fusobacterium nucleatum* and *Porphyromonas gingivalis* – characteristic features.

F. nucleatum is a non-motile, Gram-negative bacteria belonging to the *Fusobacteriaceae* family and is characterized by its spindle-shaped form (Bolstad et al. 1996) (Moraes et al. 2002). It is also known for its remarkable ability to co-aggregate with diverse bacterial species and adhere to host tissues. These traits enable *F. nucleatum* to serve as a “bridging organism” in biofilms, facilitating the integration of early and late colonizers in the oral microbial community (Chen et al. 2022). *F. nucleatum*'s pathogenic potential is attributed to several virulence factors: adhesins - *Fusobacterium* adhesion A (FadA) and *Fusobacterium* outer membrane protein A (FomA). FadA promotes adhesion and invasion of epithelial and endothelial cells. FomA facilitates biofilm formation and microbial co-aggregation (Chen et al. 2022). The bacteria produce short-chain fatty acids (SCFAs) such as butyrate and propionate, which influence cell signalling and apoptosis (Dahlstrand Rudin et al. 2021). It also suppresses immune

responses by inhibiting neutrophil activity and down-regulating inflammatory pathways and induces the production of pro-inflammatory cytokines such as IL-6 and TNF- α , contributing to chronic inflammation (Wang et al. 2023). Recent research has linked *F. nucleatum* to various systemic conditions, underscoring its potential role as a pathobiont in colorectal cancer (CRC) (Galasso et al. 2025). It has also been linked to cardiovascular disease, adverse pregnancy outcomes and endometriosis (Fan et al. 2022; Selvaraj et al. 2024; Muraoka et al. 2023).

Porphyromonas gingivalis is a Gram-negative, non-motile, obligately anaerobic bacterium belonging to the Porphyromonadaceae family (Shah and Collins 1988; Hahnke et al. 2018). A notable feature of *P. gingivalis* is its black pigmentation, which results from the accumulation of iron-containing heme compounds on its cell surface, contributing to both its virulence and survival within the periodontal environment (Shah and Collins 1988; How et al. 2016). The pathogenic potential of *P. gingivalis* stems from its wide range of virulence factors, including fimbriae, lipopolysaccharides (LPS), gingipains and a capsule (Singh et al. 2011; Jia et al. 2019). Fimbriae play a critical role in adhesion to host epithelial cells, oral tissues, and other bacterial species, thereby promoting biofilm formation and persistence within the oral cavity (Horvat Aleksijević et al. 2022). The lipopolysaccharides (LPS) of *P. gingivalis* are structurally diverse, a feature that helps the bacterium evade immune surveillance and modulate inflammatory responses (Wang and Ohura 2002). Gingipains, a family of cysteine proteases, significantly contribute to pathogenicity by degrading host proteins, disrupting immune responses, and directly contributing to tissue destruction (How et al. 2016; Bi et al. 2023). A polysaccharide capsule protects the bacterium from phagocytosis and enhances its survival in the host. These factors allow *P. gingivalis* to invade gingival tissues, manipulate host immune pathways, and establish chronic infection. *P. gingivalis* is often described as a “keystone pathogen” because its small numbers can disproportionately influence the microbial ecosystem and disease progression (Li et al. 2024). It achieves this by interfering with the complement system, subverting neutrophil activity, and producing toxins that exacerbate tissue damage. Emerging research links *P. gingivalis* to systemic diseases beyond the oral cavity, for instance, cardiovascular disease (Xie et al. 2020), rheumatoid arthritis (Ahmadi et al. 2023) and Alzheimer's Disease (Kanagasingam et al. 2020). A comparison of *Fusobacterium nucleatum* and *Porphyromonas gingivalis* is presented in Table 1.

Table I. Comparison of *Fusobacterium nucleatum* and *Porphyromonas gingivalis*.

Feature	<i>Fusobacterium nucleatum</i>	<i>Porphyromonas gingivalis</i>
Cell Morphology	Long, spindle-shaped rod (Chen et al. 2022)	Short rod (coccobacillus) (Lamont and Jenkinson 2000)
Gram Stain	Gram-negative (Shao et al. 2021)	Gram-negative (Shah and Collins 1988; How et al. 2016)
Oxygen Requirements	Obligate anaerobe (Shao et al. 2021)	Obligate anaerobe (Shah and Collins 1988; How et al. 2016)
Motility	Non-motile (Bolstad et al. 1996)	Non-motile (Shah and Collins 1988; How et al. 2016)
Production of pathognomonic enzymes or chemoattractants	Produces short chain fatty acids (SCFAs), e.g. acetate and butyrate (Dahlstrand Rudin et al. 2021).	Produces proteases (gingipains) (Singh et al. 2011; Jia et al. 2019)
Key Virulence Factors	Adhesins (FadA) (Chen et al. 2022), endotoxin (LPS) (Shao et al. 2021)	Gingipains, LPS, fimbriae (Singh et al. 2011; Jia et al. 2019)
Role in Diseases	Periodontal disease (Chen et al. 2022), colorectal cancer (Galasso et al. 2025), preterm birth (Shao et al. 2021), endometriosis (Muraoka et al. 2023)	Periodontal disease (Shah and Collins 1988; How et al. 2016), cardiovascular disease (Xie et al. 2020), rheumatoid arthritis (ahmadi et al. 2023), Alzheimer's Disease (Kanagasingam et al. 2020)
Natural Habitat (Niche)	Human oral cavity (Chen et al. 2022), gut (Galasso et al. 2025), placenta (Wang et al. 2013; Chen et al. 2022)	Oral cavity, subgingival plaque (Horvat Aleksijević et al. 2022)
Clinical Significance	Involved in polymicrobial infections, biofilm formation (Chen et al. 2022; Horvat Aleksijević et al. 2022)	Major pathogen in periodontitis (Horvat Aleksijević et al. 2022), linked to systemic diseases (Xie et al. 2020; Horvat Aleksijević et al. 2022; ahmadi et al. 2023)
Drug Resistance	Some resistance to beta-lactams (presence of β -lactamase-producing strains) (Bolstad et al. 1996)	Limited resistance to beta-lactams, resistance to macrolides (Conrads et al. 2021)
Capsule	Occasionally has a present capsule (Bolstad et al. 1996)	Has a polysaccharide capsule (Singh et al. 2011)

3. Association between *Fusobacterium nucleatum*, *Porphyromonas gingivalis* and oral cancer.

Approximately 15% of oral squamous cell carcinoma cases have no clear etiology but are linked to infectious agents, including viruses (e.g., human papilloma-virus, Epstein–Barr virus), fungi (*Candida albicans*), and bacteria. Chronic inflammation caused by infections is a significant contributor to carcinogenesis, with periodontitis and its associated pathogens playing a notable role (Kuper et al. 2001). Multiple studies highlight a strong association between periodontitis and OSCC, with chronic periodontal disease increasing the risk of premalignant lesions and progression to OSCC (Tezal et al. 2009; Laprise et al. 2016). *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, two prevalent opportunistic bacteria present in the oral cavity,

have garnered significant attention due to their abundance in periodontal plaque and their elevated levels in individuals with OSCC. Many publications indicate the presence of bacteria from the *Fusobacterium* genus (Nagy et al. 1998), particularly *F. nucleatum* (Al-Hebshi et al. 2017; Chang et al. 2018; Zhang et al. 2020; Su et al. 2021), as well as from the *Porphyromonas* genus (Nagy et al. 1998; Al-Hebshi et al. 2017; Zhang et al. 2020), especially *P. gingivalis* (Chang et al. 2018; Chen et al. 2021; Katz et al. 2011). An increase in the abundance of *Fusobacteria* may be more common in late-stage OSCC, as observed by Yang et al. They found that increased abundance occurs more often depending on OSCC staging, ranging from 2.98% in healthy controls to 7.92% in stage 4 OSCC (Yang et al. 2018). Similarly, when OSCC samples using immunostaining, it was found that all specimens were positive for *P. gingivalis*,

whereas adjacent healthy oral tissues tested negative. Among the cancer samples, 69.5% exhibited strong positivity, while 30.5% were weakly positive (Li et al. 2024).

Several studies have aimed to characterize the microbial species associated with OSCC tumor tissues compared to non-tumorous controls, utilizing various detection methods. Studies applying NGS analysis of both V1-V3 DNA regions (Al-hebshi et al. 2017) and V3-V4 (Chang et al. 2018) DNA regions of OSCC samples, as well as quantitative PCR (Chang et al. 2018) and immunohistochemical staining (Katz et al. 2011; Li et al. 2024) has shown this increase of the abundance of both bacteria in cancerous tissue. In addition, Park et al. reported that serum levels of *P. gingivalis* IgG were significantly elevated in OSCC patients compared to non-OSCC controls (Park et al. 2019). In OSCC samples with an increased abundance of the bacteria, the most commonly detected subspecies of *F. nucleatum* at the tumor site include *F. nucleatum* subspecies *polymorphum* (Al-hebshi et al. 2017), *F. nucleatum* subspecies *vincentii* (Pushalkar et al. 2012) and *F. nucleatum* subspecies *nucleatum* (Hooper et al. 2006). However, in the case of the last subspecies, *F. nucleatum* subspecies *nucleatum*, other studies have shown different results, finding that *F. nucleatum* subspecies *nucleatum* is predominantly present in non-tumorous regions (Pushalkar et al. 2012). Other changes in the microbiota of OSCC tissue were also observed, including a reduction in the *Streptococcus* genus (Su et al. 2021) and the *Actinobacteria* phylum (especially *Rothia*) (Schmidt et al. 2014), while *Prevotella* and *Alloprevotella* were enriched (Ganly et al. 2019). Interestingly, studies exploring the abundance of *P. gingivalis* and *F. nucleatum* in premalignant lesions, such as leukoplakia, have found no significant differences between affected patients and healthy controls (Shridhar et al. 2021).

F. nucleatum-high cases were significantly associated with non-white ethnicity and more infiltrative tumor lesions (Fernandes et al. 2024). In contrast, *P. gingivalis* was significantly associated with tobacco use, poor oral hygiene, and inadequate periodontal health. Moreover, it showed associations with larger tumor size, low tumor differentiation, advanced T stage and clinical stage, lymph node metastasis, and higher mortality rates (Li et al. 2024). In addition, other investigations have identified correlations between *P. gingivalis* infection and adverse clinical outcomes, including late-stage disease, poor tumor differentiation, lymph node metastasis, and reduced overall survival in OSCC patients (Wen et al. 2020; Xie et al. 2020). On the other hand, Neuzillet et al. found that *F. nucleatum*-positive tumors showed lower recurrence rates with fewer

metastatic relapses compared to *F. nucleatum*-negative tumors. *F. nucleatum*-associated OSCC occurs more often in older, non-drinking patients and is linked to a favorable prognosis (Neuzillet et al. 2021). Similarly, Chen et al. demonstrated that *F. nucleatum* enrichment in head and neck squamous cell carcinoma (HNSCC) tissues correlated with improved cancer-specific survival, lower relapse rates, and lower tumour and nodal staging, highlighting its potential as a prognostic biomarker (Chen et al., 2020). These findings are unexpected, given the association of *F. nucleatum* with poor prognosis in other cancer types. However, despite these conflicting studies, there might be a potential role of *P. gingivalis* and *F. nucleatum* as biomarkers for disease progression and prognosis in OSCC.

4. Carcinogenesis mechanisms of *Fusobacterium nucleatum* and *Porphyromonas gingivalis*

The specific roles of *F. nucleatum* and *P. gingivalis* in inducing the carcinogenesis of oral cancer, as well as their underlying mechanisms remain incompletely understood, with only a few studies providing preliminary insights. The first experimental evidence suggesting that *F. nucleatum* and *P. gingivalis* could induce malignant transformation in the oral cavity was presented by Binder Gallimindi et al., who used a mouse model of periodontal infection-associated oral tumorigenesis. This study demonstrated the effects of *P. gingivalis* and *F. nucleatum* on human oral cavity SCC cells *in vitro*. These pathogens were shown to activate Toll-like receptor (TLR) signalling in both precancerous and cancerous oral epithelia, leading to the overexpression of epithelial-derived IL-6. Exposure to *P. gingivalis* or *F. nucleatum*, either individually or in combination, significantly increased IL-6 expression in epithelial-like cells isolated from the tongues of SCC patients, as well as in the SCC-25 and CAL27 cell lines. Notably, TLR2 inhibition markedly reduced pathogen-induced IL-6 expression, whereas TLR4 inhibition did not, emphasizing the predominant role of TLR2 in this response. *In vivo* infection with *P. gingivalis* and *F. nucleatum* induced nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) signalling, a key pathway implicated in tumorigenesis (Gallimindi et al. 2015). *P. gingivalis* infection has also been shown to cause the increased production of other protumor molecules in OSCC cells, including suprabasin, IL-1R2, IL-18, and TGF- α (Liu et al., 2020). In addition, Groeger et al. reported that extracts from the *P. gingivalis* W83 membrane induced upregulation of oncogenesis-associated genes, including NF κ BIA and TRAF5, in infected OSCC cells. These genes are known to play critical roles in inflammatory signalling pathways linked to cancer progression (Groeger et al. 2022).

5. Migration and Invasion

F. nucleatum has been implicated in enhancing the migration and invasion of OSCC cells through various mechanisms, often involving interactions with host signalling pathways. Both *F. nucleatum* and *P. gingivalis* can produce matrix metalloproteinases (MMPs), such as MMP-1 and MMP-9, which are crucial for extracellular matrix remodelling and cancer cell invasion (Gallimidi et al. 2015; Harrandah et al. 2020). Harrandah et al. demonstrated that oral cancer cells co-infected with multiple pathogens showed upregulation of MMP1, MMP9, and interleukin-8 (IL-8), along with elevated expression of survival markers such as MYC, Janus kinase 1 (JAK1), signal transducer and activator of transcription 3 (STAT3), and epithelial-mesenchymal transition (EMT) markers zinc finger E-Box binding homeobox 1 (ZEB1) and transforming growth factor beta (TGF- β). Notably, the *F. nucleatum* culture supernatant, containing LPS, was sufficient to induce IL-8 secretion, suggesting that direct bacterial contact with cancer cells is not required for these effects. A 4-nitroquinoline-1-oxide (4NQO)-induced oral tumor model showed that bacterial infections resulted in significantly larger and more numerous lesions compared to non-infected mice, supporting the role of *F. nucleatum* in promoting OSCC progression (Harrandah et al. 2020). Inaba et al. demonstrated that *P. gingivalis* infection activates proMMP-9 in highly invasive SAS cells through protease-activated receptor 2 (PAR2) signalling pathways. Additionally, *P. gingivalis* has been shown to activate multiple kinase pathways, including NF- κ B, ERK1, and p38, leading to the overexpression of proMMP-9 (Inaba et al. 2013). Consistent findings were reported by Ha et al. and Woo et al., who observed overexpression of MMP-1, MMP-2, MMP-9, and MMP-10 in *P. gingivalis*-infected cells, accompanied by increased levels of IL-8. This IL-8 elevation was associated with the enhanced expression of MMPs, thereby further promoting cancer cell invasion and migration (Ha et al. 2015; Ha et al. 2016; Woo et al. 2017).

Another possible mechanism includes an increase of ZEB1 protein expression by gingival epithelial cells infected with *P. gingivalis*. ZEB1 protein, acting as a transcription factor, regulates multiple genes and has been implicated in activating metastasis in several types of cancer. Therefore, the elevated expression of ZEB1 after exposure to the bacterium was correlated with increased numbers of MMP-9 and vimentin proteins, resulting in increased cell migration (Sztukowska et al. 2016). ZFP36, also known as tristetraprolin (TTP), is a member of the zinc finger protein family that regulates numerous pro-inflammatory proteins, including itself.

It is recognized as a regulator of the inflammatory response. Lu et al. demonstrated that persistent infection with *P. gingivalis* suppresses ZFP36 by forming ZFP36/CCAT1/MK2 complexes, thereby enhancing the tumorigenic potential of human-immortalized oral epithelial cells (HIOECs). Clinical samples from patients with periodontitis and OSCC exhibit reduced ZFP36 expression. Furthermore, CCAT1 functions as a molecular scaffold, promoting the assembly of the ZFP36/CCAT1/MK2 complex, which strengthens MK2-mediated inhibition of ZFP36 phosphorylation. Reduced ZFP36 expression diminishes its inhibitory effect on cancer-associated biological processes such as proliferation, cell cycle regulation, apoptosis, migration, and invasion, thereby enhancing the tumorigenic capability of HIOECs (Chang et al. 2018; Lu et al. 2024).

Further studies have highlighted the involvement of *F. nucleatum* in EMT, a critical process for cancer metastasis. Cai et al. identified significant enrichment of *F. nucleatum* and other bacteria in OSCC, with *F. nucleatum* contributing to cellular invasion through interactions with the E-cadherin/ β -catenin signalling pathway, the TNF α /NF- κ B pathway, and matrix remodelling via the upregulation of the EMT transcription factor SNAI2 (Cai et al. 2024). Similarly, Zhang et al. found that infection with *F. nucleatum* increased cell migration and apoptosis while reducing E-cadherin expression. This was accompanied by elevated expression of lncRNA MIR4435-2HG and SNAI1, both of which are associated with OSCC progression (Zhang et al. 2020). Min et al. further showed that *F. nucleatum* activated EMT through upregulation of SNAI1 (Min et al. 2024).

Shao et al. revealed that both live and heat-inactivated *F. nucleatum* enhanced cancer cell invasiveness by upregulating pro-EMT genes, with the bacterial outer membrane proteins FadA and Fap2 playing significant roles in this process. LPS from *F. nucleatum* was also implicated in EMT induction through TLR signalling pathways (Shao et al. 2021). Uitto et al. observed that *F. nucleatum* stimulated the migration of epithelial cells, particularly at wound margins, and upregulated collagenase 3 expression via p38 MAPK activation. This highlights *F. nucleatum*'s ability to activate multiple cell signalling systems, leading to enhanced invasion and survival of infected epithelial cells (Uitto et al. 2005). Inflammasome activation also plays a role in *F. nucleatum*-induced OSCC pathogenesis. Aral et al. demonstrated that *F. nucleatum* promotes interleukin-1 β (IL-1 β) production by upregulating AIM2 and downregulating POP1, thereby contributing to chronic inflammation that facilitates the progression of HNSCC (Aral et al. 2020). Similarly, Abdulkareem et al. reported that *F. nucleatum* may induce

EMT in OSCC cells by elevating TGF- β , TNF- α , and epidermal growth factor (EGF) signalling pathways. Despite these findings, many studies remain at the *in vitro* stage, and the molecular mechanisms by which *F. nucleatum* promotes OSCC progression have not yet been thoroughly investigated (Abdulkareem et al. 2017). Kamarajan et al. highlighted the tumor-promoting effects of periodontal pathogens, including *F. nucleatum*, in a mouse model. Pathogen-challenged OSCC cells exhibited greater tumor burden compared to controls. The study also demonstrated that *F. nucleatum* enhanced OSCC cell migration, invasion, and tumor sphere formation via integrin α V and focal adhesion kinase (FAK) activation. Blocking α V or FAK expression inhibited these effects, while nisin therapy, an antimicrobial agent, was shown to modulate these pathogen-mediated processes, presenting a potential therapeutic strategy. Overall, these data underscore the role of *F. nucleatum* and other periodontal pathogens in promoting a highly aggressive cancer phenotype through crosstalk between TLR/Myeloid differentiation primary response 88 (MyD88) and integrin/FAK signalling pathways (Kamarajan et al. 2020). Extended exposure to *F. nucleatum* has a significant impact on epithelial cell behavior. Nakano et al. observed that continuous stimulation of human tongue SCC cells by *F. nucleatum* for two to four weeks led to increased proliferation, invasion, and migration. The cells underwent EMT, as indicated by a time-dependent decrease in epithelial markers and an increase in mesenchymal markers. Morphological changes, including the formation of spindle-shaped cell structures and a loss of cell-to-cell contact, were also noted. These processes were associated with the upregulation of CD44, a marker of cancer stem cells. Interestingly, dexamethasone treatment inhibited *F. nucleatum*-induced EMT, suggesting that anti-inflammatory agents may mitigate bacterial-driven tumor progression (Nakano et al. 2024). Selvarai et al. further explored the strain-specific effects of *F. nucleatum subsp. polymorphum* on OSCC-derived keratinocytes (H357 and H376). They reported enhanced transcriptional and cytokine responses related to cell migration and angiogenesis, with significant upregulation of MMP9 in H376 cells. This was linked to increased invasive phenotypes and secretion of pro-angiogenic factors such as vascular endothelial growth factor A (VEGF-A). Inhibition of VEGF-A signalling using resveratrol significantly reduced the formation of capillary-like structures by endothelial cells, underscoring the role of angiogenesis in *F. nucleatum*-mediated tumour progression (Selvaraj et al. 2024).

There is also a potential role of outer membrane vesicles (OMVs) of *P. gingivalis* and *F. nucleatum* in modulating host cell behavior. OMVs contain pack-

aged small RNAs (sRNAs) that have the potential to alert host mRNA function and/or stability. Liu et al. found that sRNA23392, one of the most commonly found sRNAs in OMVs of *P. gingivalis*, reduces the expression of desmocollin-2 (DSC2), a desmosomal cadherin family member, which results in the promotion of invasion and migration in OSCC cells (Liu et al., 2021). Chen et al. highlighted the role of *F. nucleatum* in promoting cancer metastasis. OMVs induced cancer cell invasion and migration both *in vitro* and *in vivo* by altering EMT-related protein expression. RNA sequencing revealed that OMVs activate intracellular autophagy pathways, and blocking autophagic flux with chloroquine significantly reduced the invasive capacity of cancer cells. This suggests that autophagy may play a crucial role in OMV-mediated tumor progression (Chen et al. 2024). Transcriptomic analysis by Zhang et al. revealed substantial dysregulation of mRNAs and lncRNAs in oral epithelial cells exposed to *F. nucleatum*. Functional analysis identified top hub genes (e.g., FYN, RAF1, ATM, VEGFA, JAK2) and lncRNA-hub gene co-expression networks involved in malignant transformation (Zhang et al. 2021).

6. Proliferation

Recent research highlights the role of *F. nucleatum* in promoting the proliferation of OSCC cells through various mechanisms. Li et al. demonstrated that *F. nucleatum* enhances OSCC cell proliferation both *in vitro* and *in vivo*. While the bacterium did not affect non-cancerous cells or alter E-cadherin CDH1 expression levels in CAL27 cells, it significantly increased tumor volume and Ki-67 proliferation indices in BALB/c nude mice. Interestingly, the overexpression of phosphorylated CDH1 in 293T cells did not influence β -catenin expression or the expression of cell cycle-related genes, suggesting that *F. nucleatum*'s effects may bypass canonical CDH1 signalling (Li et al. 2024). Nie et al. proposed that *F. nucleatum* contributes to OSCC progression by fostering tumor cell proliferation, recruiting macrophages, and promoting macrophages' M2 polarization. The interaction between OSCC cells and macrophages mediated by chemokine (C-X-C motif) ligand 2 (CXCL2) was identified as a key driver of the pro-tumorigenic activity of *F. nucleatum*. These findings highlight the bacterium's ability to influence the tumor microenvironment in favor of cancer progression (Nie et al. 2024). Geng et al. highlighted additional mechanisms by which *F. nucleatum* promotes the proliferation of OSCC cells. The bacterium induces DNA damage in infected cells, leading to accelerated cell cycle progression. Furthermore, the downregulation of *Ku70* and *p53*, genes critical for DNA repair

and cell cycle inhibition, suggests a link between *F. nucleatum* infection and genomic instability (Geng et al. 2020). *F. nucleatum* was also found to produce hydrogen sulfide, which promotes OSCC cell proliferation via activation of COX2, AKT, and ERK1/2 signalling pathways in a dose-dependent manner (Zhang et al. 2016). This finding aligns with earlier findings by Ma et al., which demonstrated that hydrogen sulfide accelerates the cell cycle in OSCC cell lines (Ma et al. 2014). Uitto et al. reported that *F. nucleatum* upregulates cyclin-dependent kinases (CDKs) 7 and 9, enhancing the proliferation of human immortalized keratinocytes (Uitto et al. 2005). Together, these studies highlight the multifaceted role of *F. nucleatum* in promoting OSCC cell proliferation through mechanisms that involve direct effects on tumor cells, modulation of the tumor microenvironment, and metabolic alterations. A study by Ha et al. found that repeated infections by *P. gingivalis* alter the morphology of OSCC cells. Cytokeratin 13 was underexpressed, while N-cadherin and α -SMA were increased, suggesting EMT at the molecular level. EMT influences the acquisition of cancer stemness, which induces resistance to chemotherapeutic drugs and results in higher cancer aggressiveness (Ha et al. 2015). Furthermore, Groeger et al. observed that the *P. gingivalis* membrane upregulates the expression of genes involved in downstream TLR, NF κ B and MAPK signalling pathways, associated with the pro-inflammatory immune response in primary and malignant oral epithelial cells, thus resulting in increased cancer proliferation (Groeger et al. 2017). OMVs may also play a role in accelerating cancer proliferation by up-regulating the expression of PD-L1 protein in infected OSCC. This effect is sustained in cancer cells even after the bacterium has been eradicated. Elevated PD-L1 expression depends on receptor-interacting protein kinase 2 (RIP2) signalling. Activation of PD-L1 has been shown to protect cancer cells from host immune response (Groeger et al. 2020). Interestingly, a study by Cho et al. found that *P. gingivalis* infection might reduce cancer cell proliferation by inhibiting the cell cycle at the G1 phase. Infected OSCC cells exhibited an increase in the expression of p21, a kinase inhibitor that regulates cell cycle progression through the G1 phase. Conversely, the expression levels of cyclin D1 and cdk4, both critical for cell cycle progression, were decreased. However, these effects were transient, being prominent within the first 24 hours post-infection and diminishing by the 72-hour mark. Additionally, *P. gingivalis* infection was found to promote autophagy in OSCC cells, suggesting a possible survival mechanism by which the bacteria exploit support its persistence and potentially contribute to carcinogenesis (Cho et al. 2014).

Both *F. nucleatum* and *P. gingivalis* are pathogens associated with both inflammatory diseases and cancer. They share common mechanisms of action, which suggests a synergistic effect on cancer development. The common mechanisms are presented in Table 2.

7. Change in the Local Tumor Microenvironment

F. nucleatum has been implicated in modulating the immune microenvironment of tumors, facilitating immune evasion, and contributing to cancer progression and resistance to therapy. One of the key mechanisms involves the bacterial outer-surface protein Fap2, which binds to and activates inhibitory receptors TIGIT and CEACAM1 expressed on T and Natural Killer (NK) cells. This interaction suppresses anti-tumor immune responses by inhibiting the activity of these immune cells. Gur et al. demonstrated that this immune inhibition could be targeted using TIGIT and CEACAM1 inhibitors, suggesting a potential therapeutic strategy for tumors colonized by *F. nucleatum* (Gur et al. 2019). In addition to immune suppression, *F. nucleatum* has been associated with resistance to chemotherapy. Rui et al. reported that patients with a higher abundance of *F. nucleatum* exhibited reduced responsiveness to induction chemotherapy. Using 16S rRNA sequencing and metagenomic shotgun analysis, the study revealed that *F. nucleatum* was enriched in the nonresponsive group. Functional analyses highlighted its association with the platinum drug resistance pathway, microRNAs involved in cancer, and RNA degradation pathways, indicating a role in mediating therapy resistance (Rui et al. 2021). Further evidence of its contribution to chemoresistance comes from the work of Da et al., who explored the effects of *F. nucleatum* on cisplatin resistance and migration in OSCC. Their findings showed that *F. nucleatum* activates the Wnt/NFAT signalling pathway, leading to the downregulation of tumor suppressors, including p53 and E-cadherin. Pretreatment of CAL-27 and HSC-3 cells with *F. nucleatum* significantly increased cell survival rates following cisplatin exposure. The bacterium induced higher expression of the Wnt pathway gene *wnt5a* and NFATc3. Inhibition of NFATc3 using the peptide VIVIT reversed these effects, restoring p53 and E-cadherin expression (Da et al. 2021). He et al. demonstrated that *F. nucleatum* is enriched in the stromal regions of tumors, where CD31+ blood vessels and inflammatory cells, including CD45+ leukocytes and CD68+ macrophages, are densely distributed. Cyclin D1 and β -catenin were primarily expressed in tumor cells and interstitial vascular endothelial cells, respectively, whereas E-cadherin expression was localized to tumor cell membranes. Notably, NF- κ B was highly expressed in the cytoplasm

Table II. The mechanisms promoting carcinogenesis of *F. nucleatum* and *P. gingivalis*.

Mechanism	Trigger factor	Explanation
Promotion of chronic inflammation	IL-6 (Gallimidi et al. 2015), IL-8 (Ha et al. 2016; Harrandah et al. 2020), TNF-α (Gallimidi et al. 2015; Liu et al. 2020)	Pro-inflammatory cytokines create a tumor-friendly microenvironment, promoting mutations and uncontrolled cell proliferation.
	<i>P. gingivalis</i> : IL-1R2, IL-18 (Liu et al. 2020)	
	<i>F.nucleatum</i> : IL-1β (Aral et al. 2020), TGF-β (Abdulkareem et al. 2017)	
Modulation of the immune response	Disruption of immune signaling (Wang and Ohura 2002; How et al. 2016; Bi et al. 2023)	Bacteria evade immune responses, leading to persistent infections and immune suppression.
Activation of the signal pathways associated with cancer development	NF-κB (Inaba et al. 2013; Gallimidi et al. 2015)	These pathways stimulate tumor growth, enhance survival and contribute to metastasis.
	<i>F.nucleatum</i> : Wnt/NFAT (Da et al. 2021), STAT3 (Harrandah et al. 2020)	
Increased invasion and metastasis	Epithelial-Mesenchymal Transition (EMT) (Ha et al. 2015; Harrandah et al. 2020), Matrix metalloproteinases (MMPs) (Gallimidi et al. 2015; Ha et al. 2016; Harrandah et al. 2020)	EMT enables cancer cells to detach and spread, while MMPs degrade the extracellular matrix, aiding metastasis.
Production of toxins and factors supporting tumor growth	Gingipains (<i>P. gingivalis</i>) (How et al. 2016; Bi et al. 2023), FadA (<i>F. nucleatum</i>) (Chen et al. 2022)	Gingipains disrupt cellular homeostasis, and FadA binds to E-cadherin, increasing epithelial permeability and promoting cancer progression.
Microbiota dysbiosis	Dysbiosis (Horvat Aleksijević et al. 2022; Cai et al. 2024)	Both bacteria contribute to changes in the microbiome , which promotes the proliferation of pathogenic microorganisms and increases the risk of developing cancer.

of tumor and stromal cells, while hypoxia-inducible factor 1-alpha (HIF-1α) was predominantly observed in the cytoplasm of stromal cells. HIF-1α expression was particularly high in areas with dense *F. nucleatum* distribution, suggesting that the bacterium exacerbates inflammation and hypoxia by interacting with NF-κB and HIF-1α signalling in OSCC tissues (He et al. 2023). These results underscore the role of *F. nucleatum* in promoting chemoresistance and enhancing cancer cell migration. Overall, *F. nucleatum* employs a multifaceted approach to evade immune surveillance and resist therapeutic interventions. By suppressing immune responses through TIGIT and CEACAM1 activation, modulating signalling pathways such as Wnt/NFAT, and contributing to drug resistance, *F. nucleatum* poses a significant challenge in the treatment of tumors it colonizes. Targeting these bacterial-mediated mechanisms presents a promising approach for enhancing cancer therapies (Da et al. 2021; Rui et al. 2021; He et al. 2023).

On the other hand, *Porphyromonas gingivalis* promotes OSCC progression by inducing the formation of neutrophil extracellular traps (NETs) within the tumor microenvironment (TME). These NETs enhance cancer cell migration, invasion, and colony formation. In vivo studies have further demonstrated that NETs play a crucial role in facilitating tumor metastasis (Guo et al., 2023). Furthermore, *P. gingivalis* promotes cancer progression by recruiting tumor-associated neutrophils through activation of the CXCL2/CXCR2 axis in the cancer microenvironment (Guo et al. 2022). Additionally, *P. gingivalis* inhibits macrophages from phagocytizing OSCC cells. Infection by a bacterium led to an increase in the polarization of M2 macrophages, which is tumor-promoting (Liu et al. 2020). Interestingly, Lan et al. investigated how *P. gingivalis* might suppress OSCC growth by downregulating MUC1 and CXCL17 expression, leading to the reversal of the immunosuppressive TME and thereby inhibiting OSCC progression (Lan et al. 2023).

8. Conclusions

The evidence presented in this review underscores the significant role of *Fusobacterium nucleatum* and *Porphyromonas gingivalis* in the pathogenesis of oral squamous cell carcinoma. These bacterial species contribute to tumor initiation and progression through shared mechanisms, including immune evasion, the upregulation of inflammatory mediators (e.g., IL-6, IL-8), and modulation of host cellular signalling pathways. In addition, they exhibit distinct but complementary virulence strategies, including the production of gingipains by *P. gingivalis* and FadA adhesin by *F. nucleatum*, which further support tumor development.

Their presence within the tumor microenvironment suggests potential diagnostic and prognostic relevance, particularly for *F. nucleatum*, which may serve as a biomarker of OSCC progression. Moreover, bacterial virulence factors offer promising targets for therapeutic intervention. However, further studies are required to elucidate the precise molecular mechanisms involved and to explore innovative antimicrobial and immunomodulatory strategies aimed at mitigating their oncogenic effects.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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