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REVIEW ARTICLE

Periodontal pathogens and cancer development

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Abstract

Increasing evidence suggests a significant association between periodontal disease and the occurrence of various cancers. The carcinogenic potential of several periodontal pathogens has been substantiated in vitro and in vivo. This review provides a comprehensive overview of the diverse mechanisms employed by different periodontal pathogens in the development of cancer. These mechanisms induce chronic inflammation, inhibit the host's immune system, activate cell invasion and proliferation, possess anti-apoptotic activity, and produce carcinogenic substances. Elucidating these mechanisms might provide new insights for developing novel approaches for tumor prevention, therapeutic purposes, and survival improvement.

KEYWORDS
cancer, carcinogenesis, cell invasion, cell proliferation, immune response, inflammation, periodontal pathogens

1 | INTRODUCTION

Periodontitis is a complex inflammatory disease with many etiologic and contributing factors.[1] It affects up to 90% of the global population.[2] The pathogenic processes primarily arise from the host's reaction to an oral microbial biofilm.[3] Oral microbiomes contain hundreds of aerobic and anaerobic bacteria that metabolically and physically interact. These interactions create a complex biofilm community. Certain viruses, bacteria, and parasites have been recognized as crucial risk factors for specific types of cancer.[4] Microbes existing in mucosal locations can integrate into the tumor microenvironment, impacting cancer growth and dissemination through various means. This includes influencing cell growth rates and affecting cancer genomic stability, metabolism, and immune responsiveness.[5] The link between periodontal disease and the overall cancer risk is attracting increasing attention. Research has shown a statistically significant correlation between periodontal disease and the risk of esophageal, breast, lung, pancreatic, prostate, colorectal, digestive tract, and head and neck cancers.[6] The complex interaction of periodontal pathogens with the host still warrants further investigation of the underlying mechanisms. This article reviews the properties of periodontal pathogens in association with cancer development.

2 | PERIODONTAL PATHOGENS

The oral microbiota is a substantial component of the human microbiota, comprising several hundreds to several thousands of diverse species.[7] The oral cavity is inhabited by almost 700 bacterial species, which are located in saliva, soft tissues like mucosa and tongue surface, hard tissues, and hard materials.[7,8] The Human Oral Microbiome Database (HOMD) lists 774 oral bacterial species and 2123 genomes representing 539 taxa (https://www.homd.org/). The oral cavity harbors a variety of bacterial genera, including *Treponema*, *Bacteroides*, *Porphyromonas*, *Prevotella*, *Capnocytophaga*, *Peptostreptococcus*, *Fusobaterium*, *Actinobacillus*, and *Eikenella*.[9] Notable high-risk periodontal pathogens associated with periodontitis include *Aggregatibacter actinomycetemcomitans*

(*A. actinomycetemcomitans*), *Porphyromonas gingivalis* (*P. gingivalis*), *Tannerella forsythia* (*T. forsythia*), *Treponema denticola* (*T. denticola*), and *Fusobacterium nucleatum* (*F. nucleatum*).[10]

Head and neck squamous cell carcinoma (HNSCC) originates from the squamous epithelium of the upper aerodigestive tract, with over 800 000 new cases and over 400 000 deaths in 2020, making it the most common cancer in this specific region.[11] Cancers of the oral cavity and oropharynx constitute the majority of cases of HNSCC.[12] Notably, oral squamous cell carcinoma (OSCC) is a significant contributor to morbidity and mortality in patients with head and neck cancers.[13] Globally, an estimated 377 713 new cases and 177 757 fatalities attributed to oral cavity cancer (including lip cancer) were reported in 2020.[11] Primary risk factors associated with the development of oral cavity cancer include inadequate oral hygiene, smoking, alcohol consumption, utilization of smokeless tobacco, and human papillomavirus (HPV) infection.[14–16]

Infection, chronic inflammation, or autoimmunity precede around 15%–20% of all cancer cases.[17–19] Chronic inflammation is primarily induced by bacterial infection. Associations between oral cancer and epithelial precursor lesions and bacteria from *Fusobacterium*, *Veillonella*, *Actinomyces*, *Clostridium*, *Haemophilus*, and *Enterobacteriaceae* genera have been established.[20] Chang et al.[21] tested 61 cancer tissues and their adjacent paracancerous tissues and 30 normal oral tissues. The findings indicated elevated levels of *P. gingivalis* and *F. nucleatum* in cancer tissue compared to normal tissues, consistent with the results of Nagy's and Schmidt.[20,22]

Dating back to the 1980s, Marshall and Warren's[23] publication provided the initial evidence of bacteria playing a direct role in cancer development. Figure 1 illustrates the timeline of notable discoveries and milestones in cancer microbiome research.[24] In the 19th century, the German pathologist Virchow proposed that inflammation was a promoter of carcinogenesis.[25] Inflammation triggered by microbes, although protective against pathogens, can paradoxically cause substantial secondary damage to host tissues. If this inflammation persists, it has the potential to lead to tissue fibrosis and carcinogenesis.[26] In vitro and in vivo studies have illustrated the carcinogenic potential of numerous bacteria. Enzymatic attacks by bacterial products have the capacity to inflict DNA damage, eliciting an inflammatory response that generates free radicals and may impact DNA repair mechanisms. Disruption of signaling by bacterial products can disturb the delicate equilibrium of growth, cell division, and apoptosis, potentially providing support for tumor promotion.[27] Despite most developments in understanding HNSCCs occurring in recent decades, clinically meaningful discoveries have yet to be fully realized, as depicted in Figure 2.[28]

3 | THE ASSOCIATION BETWEEN PERIODONTAL PATHOGENS AND CANCER

Substantial evidence highlights the connection between alterations in the oral microbiome and specific cancer types (see Table 1, Figure 3). Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of cancer mortality in women. By analyzing the microbiota of breast skin tissue, breast skin swabs, and buccal swabs, Hieken et al.[29] identified the malignancy correlated with enrichment in taxa of lower abundance including the genera *Fusobacterium*, *Atopobium*, *Gluconacetobacter*, *Hydrogenophaga*, and *Lactobacillus*. In another study, Wang et al.[30] reported that *Methylobacterium* was decreased in cancer patients relative to non-cancer patient samples. Breast cancer patients had increased levels of gram-positive organisms including *Corynebacterium*, *Staphylococcus*, *Actinomyces*, and *Propionibacteriaceae* in urine. Parhi et al.[31] showed that the occurrence of *F. nucleatum* gDNA in breast cancer samples correlates with high Gal-GalNAc levels.

Esophageal cancer (EC) poses a significant global health challenge, ranking as the seventh most prevalent and sixth most fatal malignancy worldwide.[32] Narikiyo et al.[33] observed a prevalent and frequent infection of the oral periodontopathic spirochete *T. denticola*, *Streptococcus mitis* (*S. mitis*), and *Streptococus anginosus* (*S. anginosus*), in EC across various geographic regions. These bacteria may exert notable influence on the carcinogenic process of numerous esophageal cancer cases by instigating inflammation

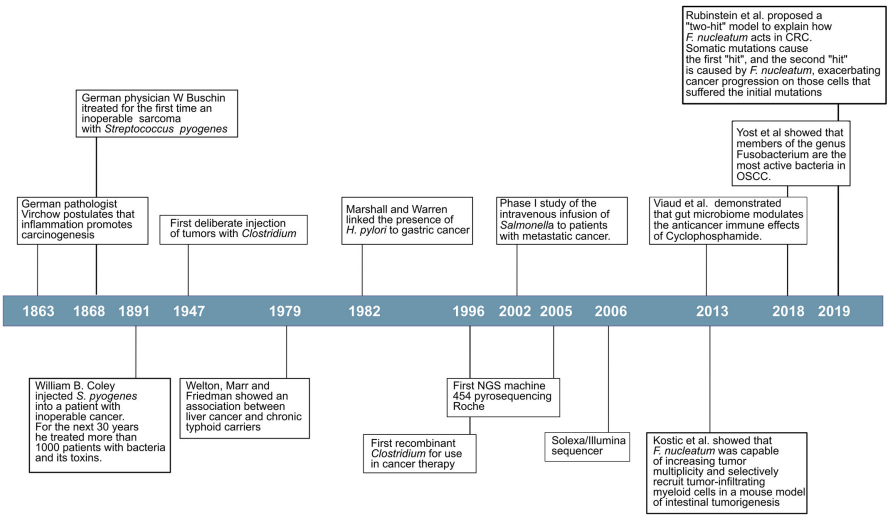

FIGURE 1 Timeline: Some significant discoveries and events in cancer microbiome research. *Reprinted from* Ref. [24].

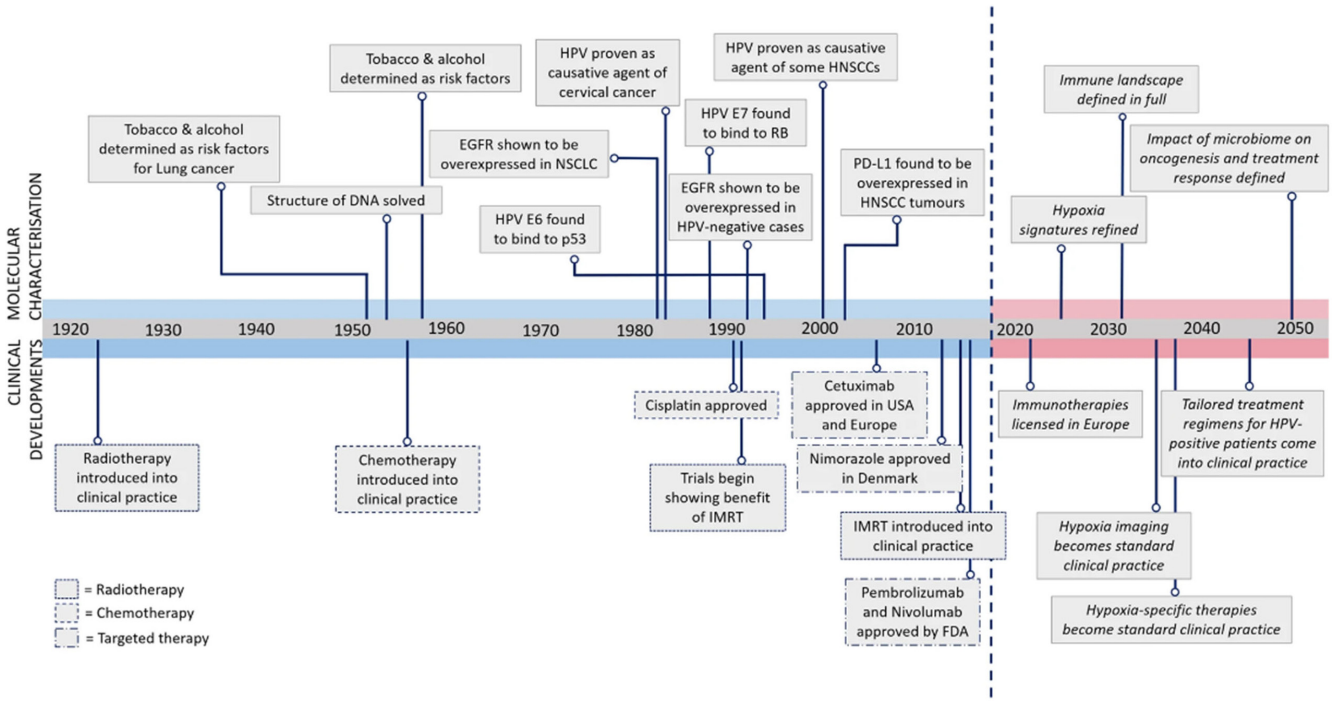

FIGURE 2 Timeline of molecular characterization, therapeutic innovations in head and neck cancers, and future perspectives.[28]

and facilitating carcinogenesis. Also, *F. nucleatum* and *P. gingivalis* are reported to be associated with EC and could be the biomarkers for this disease.[34,35] Kawasaki et al.[36] evaluated the prevalence and abundance of oral bacteria from subgingival dental plaque and saliva samples in patients with EC and individuals without any cancer. They found that in subgingival plaque, *A. actinomycetemcomitans*, *P. gingivalis*, *Prevotella intermedia* (*P. intermedia*), *T. forsythia*, *T. denticola*, and *S. anginosus* were more abundant and prevalent in the cancer group versus the control group. *A. actinomycetemcomitans* and *S. anginosus* were more abundant or prevalent in the salivary microbiota of the cancer group. The prevalence of *T. forsythia* and *S. anginosus* in dental plaque and of *A. actinomycetemcomitans* in saliva, as well as a drinking habit, was associated with a high risk of EC.

Measurements of antibodies against oral bacteria indicate previous infection and the level of immune response mounted by an individual's immune system. Håheim et al.[37] found that the lowest levels of antibodies for *T. forsythia* and *T. denticola* had a higher risk for bladder cancer. Low levels of *T. denticola* were also associated with increased risk of colon cancer. Moreover, *F. nucleatum* and *P. gingivalis* sequences were enriched in colorectal cancer (CRC) and are associated with shorter survival.[38–41] Besides, other oral microbiota have been reported to be associated with CRC, including *Gemella*, *Mogibacterium*, *Peptostreptococcus stomatitis*, and *Parvimonas micra*.[42–44]

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of cancer death worldwide.[45] The oral bacterial taxa enriched in the GC samples were predominantly represented by oral bacteria (such as *Peptostreptococcus*, *Streptococcus*, and *Fusobacterium*), while lactic acid-producing bacteria (such as *Lactococcus lactis* and *Lactobacillus brevis*) were more abundant in adjacent non-tumor tissues.[46] *Parvimonas micra*, *Slackia exigua* and *Dialister* also played important roles in GC progression.[47]

Pancreatic cancer's (PC) global burden has seen a significant surge in recent decades and is expected to remain a prominent contributor to cancer-related deaths.[48] *P. gingivalis* and *A. actinomycetemcomitans* were associated with a higher risk of PC.[49,50] Vogtmann et al.[51] and Farrell et al.[52] measured variations of salivary microbita in PC cases and controls, they found the presence of *Enterobacteriaceae*, *Lachnospiraceae G7*, *Bacteroidaceae*, *Staphylococcaceae*, *Neisseria elongata*, and *Streptococcus mitis* shown significant variation between patients with pancreatic cancer and controls.

The association between oral disease and increased risk of lung cancer (LC) has been reported in lots of studies. In 2016, a study investigated the tongue coat microbiome of liver cancer patients with cirrhosis based on 16S rRNA gene sequencing. The study found *Oribacterium* and *Fusobacterium* could distinguish LC patients from healthy subjects.[53] Yan et al.[54] found that the levels of *Capnocytophaga* and *Veillonella* were significantly higher in the saliva of LC patients. A higher abundance of *Streptococcus* and *Veillonella* was enriched in the lower airways of LC patients.[55] Furthermore, the non-small cell lung cancer (NSCLC) group exhibited significantly higher relative abundances of *Lautropia*, *Leptotrichia*, *Rothia*, and *Aggregatibacter* compared to the healthy control group.[56] Lu et al.[57] reported that the colonization rate of *P. gingivalis* in carcinoma tissues was significantly higher than that in adjacent lung tissues. The survival rate and median survival time of patients with *P. gingivalis* infection were significantly shortened.

TABLE 1 Detection of oral microbiota in cancerous sites.

Cancer type	Oral microbiome	Study design	Sample type	Numbers of samples	Microbial assessment platform	Major findings	References
Breast cancer	*Fusobacterium*, *Atopobium*, *Gluconacetobacter*, *Hydrogenophaga*, *Lactobacillus*	Prospective cohort	Breast skin tissue, breast skin swabs, and buccal swabs	Invasive breast cancer ($n=15$), benign breast disease without atypia ($n=13$)	16S rDNA hypervariable tag sequencing	Malignancy correlated with enrichment in taxa of lower abundance including the genera *Fusobacterium*, *Atopobium*, *Gluconacetobacter*, *Hydrogenophaga* and *Lactobacillus*	Hieken et al.[29]
	Methylobacterium, *Corynebacterium*, *Staphylococcus*, *Actinomyces*, *Propionibacteriaceae*	Cross-sectional	Urine, oral rinse and surgically collected breast tissue	Invasive breast cancer patients ($n=57$), healthy contorls ($n=21$)	16S rRNA gene sequencing	There were no significant differences in oral rinse samples. *Methylobacterium* was decreased in cancer relative to non-cancer patient samples. Independent of menopausal status, however, cancer patients had increased levels of gram-positive organisms including *Corynebacterium*, *Staphylococcus*, *Actinomyces*, and *Propionibacteriaceae* in urine	Wang et al.[30]
	F. nucleatum	Cross-sectional	FFPE samples from breast tumors, fresh forzen colon tumors	50 Breast tumors, 21 colon tumors	16S rRNA gene sequencing, flow cytometry, immunofluorescence microscopy	Gal-GalNAc levels increase as human BC progresses, and that occurrence of *F. nucleatum* gDNA in BC samples correlates with high Gal-GalNAc levels	Parhi et al.[31]
Esophageal cancer	*T. denticola*, *S. mitis*, *S. anginousus*	Cross-sectional	Tissue, saliva	20 Esophageal cancer tissues, 20 healthy volunteers	16S rRNA gene sequencing	*T. denticola*, *S. mitis*, and *S. anginousus* could have significant roles in the carcinogenic process of many cases of esophageal cancer by causing inflammation and by promoting the carcinogenic process, and that eradication of these three bacteria may decrease the risk of recurrence	Narikiyo et al.[33]
	P. gingivalis	Cross-sectional	Tissue	100 patients, 30 controls	Immunohistochemistry, qRT-PCR	*P. gingivalis* infects the epithelium of the esophagus of ESCC patients, establish an association between infection with *P. gingivalis* and the progression of ESCC, and suggest *P. gingivalis* infection could be a biomarker for this disease	Gao et al.[35]
	F. nucleatum	Longitudinal cohort	Tissue	325 FFPE EC specimens, 60 paired adjacent non-tumor tissues	Immunohistochemistry, qPCR	*F. nucleatum* in esophageal cancer tissues was associated with shorter survival, suggesting a potential role as a prognostic biomarker. *F. nucleatum* might also contribute to aggressive tumor behavior through activation of chemokines, such as CCL20	Yamamura et al.[34]
	T. forsythia, *Neisseria*, *Streptococcus pneumoniae*, *P. gingivalis*	Prospective cohort	Pre-diagnostic oral wash sample	$n=81/160$ EAC/ matched controls, $n=25/50$ ESCC/ matched controls	16S rRNA gene sequencing	*T. forsythia* to be associated with higher risk of EAC. The commensal genus *Neisseria* and the species *Streptococcus pneumoniae* were associated with lower EAC risk. Lastly, the abundance of the periodontal pathogen *P.gingivalis* trended with higher risk of ESCC	Peters et al.[65]

TABLE 1 (Continued)

Cancer type	Oral microbiome	Study design	Sample type	Numbers of samples	Microbial assessment platform	Major findings	References
	A. actinomycetemcomitans, *F. nucleatum*, *P. gingivalis*, *P. intermedia*, *T. forsythia*, *T. denticola*, *S. anginosus*	Cross-sectional	Subgingival dental plaque and unstimulated saliva	61 Patients, 62 matched controls	RT-PCR	In subgingival plaque, *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, *T. forsythia*, *T. denticola*, and *S. anginosus* were more abundant and prevalent in the cancer group versus the control group *A. actinomycetemcomitans* and *S. anginosus* were more abundant or prevalent in the salivary microbiota of the cancer group The prevalence of *T. forsythia* and *S. anginosus* in dental plaque and of *A. actinomycetemcomitans* in saliva, as well as a drinking habit, were associated with a high risk of esophageal cancer	Kawasaki et al.[36]
Bladder cancer, colorectal cancer	*T. forsythia*, *T. denticola*	Prospective cohort	Blood sample	Among the 621 participants with no prior cancer diagnoses, 221 men developed cancer	ELISA	Lowest levels of antibodies for the two oral bacteria *T. forsythia* and *T. denticola* had a higher risk of bladder cancer. Low levels of *T. denticola* were also associated with increased risk of colon cancer	Håheim et al.[37]
Colorectal cancer	*F. nucleatum*	Cross-sectional	Tissue	9 Tumor/normal pairs	qPCR, 16s rRNA gene sequencing, FISH	*Fusobacterium* sequences were enriched in CRC	Kostic et al.[38]
	Fusobacterium, *Porphyromonas*	Cross sectional	Fecal	47 CRC case subjects and 94 control subjects	16S rRNA sequencing	Increased carriage of *Fusobacterium* and *Porphyromonas* were found in case subjects compared with control subjects	Ahn et al.[40]
	Fusobacterium, *B. fragilis*, *Gemella*, *Peptostreptococcus*, *Parvimonas*	Cross-sectional	Tissue	47 Paired samples of adenoma and adenoma-adjacent mucosae, 52 paired samples of carcinoma and carcinoma-adjacent mucosae and 61 healthy controls	16S rRNA gene sequencing	In early-stage CRC, *Fusobacterium*, *Parvimonas*, *Gemella* and *Leptotrichia* were most significantly enriched	Nakatsu et al.[42]
	F. nucleatum	Prospective cohort	Tissue	1069 CRCs	PCR	The amount of *F. nucleatum* DNA in colorectal cancer tissue is associated with shorter survival, and may potentially serve as a prognostic biomarker	Mima et al.[39]
	Mogibacterium	Cross sectional	Fecal	233 Adenomas, 547 without adenomas	16S rRNA gene sequencing	Multiple taxa were significantly more abundant in patients with adenomas, including *Bilophila*, *Desulfovibrio*, proinflammatory bacteria in the genus *Mogibacterium*, and multiple Bacteroidetes species. Patients without adenomas had greater abundances of *Veillonella*, *Firmicutes* (Order Clostridia), and *Actinobacteria* (family Bifidobacteriales)	Hale et al.[43]

(Continues)

TABLE 1 (Continued)

Cancer type	Oral microbiome	Study design	Sample type	Numbers of samples	Microbial assessment platform	Major findings	References
	F. nucleatum, *Peptostreptococcus stomatitis, and Parvimonas micra*	Cross sectional	Oral swab, colonic mucosae, stool	CRC (99 subjects), colorectal polyps (32) or controls (103)	16S rRNA gene sequencing	Combining the data from fecal microbiota and oral swab microbiota increased the sensitivity of the model to 76% (CRC)/88% (polyps)	Flemer et al.[44]
	P. gingivalis	Cross sectional	Fecal and mucosal samples	247 CRC patients and 89 control subjects	qRT-PCR	*P. gingivalis* could be linked to patients with CRC and to a worse patient prognosis	Kerdreux et al.[41]
Gastric cancer	*P. stomatis*, *D. pneumosintes*, *S. exigua*, *P. micra*, *S. anginosus*	Cross sectional	Gastric mucosal	81 Cases including superficial gastritis, atrophic gastritis, intestinal metaplasia and gastric cancer	16S rRNA sequencing	*P. stomatis*, *D. pneumosintes*, *S. exigua*, *P. micra* and *S. anginosus* play important roles in GC progression	Coker et al.[47]
	Peptostreptococcus, *Streptococcus*, *Fusobacterium*	Cross sectional	Tissue	62 Pairs of matched GC and adjacent non-cancerous	16S rRNA gene sequencing	The bacterial taxa enriched in the cancer samples were predominantly represented by oral bacteria (such as *Peptostreptococcus*, *Streptococcus*, and *Fusobacterium*), while lactic acid-producing bacteria (such as *Lactococcus lactis* and *Lactobacillus brevis*) were more abundant in adjacent non-tumor tissues	Chen et al.[46]
Pancreatic cancer	*Neisseria elongata*, *Streptococcus mitis*	Cross sectional	Saliva	Discovery phase: 10 PCs and 10 healthy controls Validation phase: 28 PCs, 28 healthy controls, and 27 CPs	qPCR	*Neisseria elongata and Streptococcus mitis* shown significant variation between patients with pancreatic cancer and controls. The combination of two bacterial biomarkers (*N. elongata* and *S. mitis*) yielded a receiver operating characteristic plot area under the curve value of 0.90 (95% CI 0.78 to 0.96, $p < 0.0001$) with a 96.4% sensitivity and 82.1% specificity in distinguishing patients with pancreatic cancer from healthy subjects	Farrell et al.[52]
	P. gingivalis	Prospective cohort	Blood samples	405 PCs and 416 matched controls	Immunoblot array	Individuals with high levels of antibodies against *Porphyromonas gingivalis* ATTC 53978 had a twofold higher risk of PC than individuals with lower levels of these antibodies	Michaud et al.[49]
	P. gingivalis, *A. actinomycetemcomitans*	Prospective cohort	Pre-diagnostic oral wash samples	361 PCs and 371 matched controls	16S rRNA gene sequencing	*P.gingivalis* and *A.actinomycetemcomitans* were associated with higher risk of PC. Phylum *Fusobacteria* and its genus *Leptotrichia* were associated with decreased pancreatic cancer risk	Fan et al.[50]
	Haemophilus, *Enterobacteriaceae*, *Lachnospiraceae G7*, *Bacteroidaceae*, *Staphylococcaceae*	Case–control	Saliva	273 PCs and 285 controls	16S rRNA gene sequencing	Increasing relative levels of *Haemophilus* were associated with decreased odds of pancreatic cancer, while the presence of *Enterobacteriaceae*, *Lachnospiraceae G7*, *Bacteroidaceae*, or *Staphylococcaceae* were associated with increased odds of pancreatic cancer	Vogtmann et al.[51]
Liver cancer	*Oribacterium*, *Fusobacterium*	Cross sectional	Tongue coat	35 Liver cancers, 25 healthy controls	16S rRNA gene sequencing	*Oribacterium* and *Fusobacterium* could distinguish liver cancer patients from healthy subjects	Lu et al.[53]

TABLE 1 (Continued)

Cancer type	Oral microbiome	Study design	Sample type	Numbers of samples	Microbial assessment platform	Major findings	References
Lung cancer	*Capnocytophaga*, *Veillonella*	Cross sectional	Saliva	Discovery phase: 20 lung cancer and 10 controls Validation phase: 41 lung cancer and 15 controls	16S rRNA gene sequencing, qPCR	The levels of *Capnocytophaga* and *Veillonella* were significantly higher in the saliva from lung cancer patients, which may serve as potential biomarkers for the disease detection/classification	Yan et al.[54]
	Streptococcus, *Veillonella*	Cross sectional	Airway brushings	39 Lung cancer, 36 non-cancer, and 10 healthy controls	16S rRNA gene sequencing	A higher abundance of *Streptococcus* and *Veillonella* was enriched in the lower airways of lung cancer patients	Tsay et al.[55]
	Veillonella, *Streptococcus*, *Lautropia*, *Leptotrichia*, *Rothia*, *Aggregatibacter*, *Fusobacterium*, *Prevotella*, *Bacteroides*, *Faecalibacterium*	Cross sectional	Saliva, blood	39 NSCLCs and 20 healthy controls	16S rRNA gene sequencing, ELISA	The relative abundance of *Veillonella*, *Streptococcus*, *Lautropia*, *Leptotrichia*, *Rothia*, and *Aggregatibacter* was significantly higher in the NSCLC group compared with the healthy control group. Additionally, the relative abundances of *Fusobacterium*, *Prevotella*, *Bacteroides*, and *Faecalibacterium* in NSCLC group were generally decreased	Zhang et al.[56]
	P. gingivalis	Prospective cohort	Tissue	100 Patients with small cell lung cancer, 119 patients with lung adenocarcinoma and 100 patients with lung squamous cell carcinoma	Immunohistochemistry	The colonization rate of *P.gingivalis* in carcinoma tissues was significantly higher than that in adjacent lung tissues. And the survival rate and median survival time of patients with *P.gingivalis* infection were significantly shortened	Liu et al.[57]
Head and neck squamous cell carcinomas	*Capnocytophaga gingivalis*, *Prevotella melaninogenica*, *Streptococcus mitis*	Cross sectional	Saliva	229 OSCC-free and 45 OSCC subjects	Checkerboard DNA–DNA hybridization	*Capnocytophaga gingivalis*, *Prevotella melaninogenica* and *Streptococcus mitis*, were elevated in the saliva of individuals with OSCC	Mager et al.[61]
	P. gingivalis	Cross sectional	Tissue	10 Gingival squamous cell carcinoma, 5 normal gingiva	Immunohistochemical staining	*P. gingivalis* is abundantly present in malignant oral epithelium suggesting a potential association of the bacteria with gingival squamous cell carcinoma	Katz et al.[62]
	Campylobacter, *Eikenella*, *Alloprevotella*, *Fusobacterium*, *Selenomonas*, *Dialister*, *Peptostreptococcus*, *Filifactor*, *Peptococcus*, *Catonella*, *Parvimonas*, *Capnocytophaga*, *Peptostreptococcaceae*	Cross sectional	Oral swab	40 OSCC lesion and 40 anatomically matched normal sites	16S rRNA gene sequencing	*Campylobacter*, *Eikenella*, *Alloprevotella*, *Fusobacterium*, *Selenomonas*, *Dialister*, *Peptostreptococcus*, *Filifactor*, *Peptococcus*, *Catonella*, *Parvimonas*, *Capnocytophaga*, and *Peptostreptococcaceae* was significantly enriched in OSCC samples. Additionally, several operational taxonomic units (OTUs) associated with Fusobacterium were highly involved in OSCC and demonstrated good diagnostic power	Zhao et al.[60]

(Continues)

TABLE 1 (Continued)

Cancer type	Oral microbiome	Study design	Sample type	Numbers of samples	Microbial assessment platform	Major findings	References
	F. nucleatum subsp. Polymorphum, *P. aeruginosa*, *Campylobacter sp.oral taxon 44*	Cross sectional	Tissue and swabs	20 Fresh OSCC and 20 deep-epithelium swabs matched control subjects	16S rRNA gene sequencing	*F. nucleatum* subsp. polymorphum was the most significantly overrepresented species in the tumors followed by *P. aeruginosa* and *Campylobacter sp.* oral taxon 44, while *Streptococcus mitis*, *Rothia mucilaginosa*, and Haemophilus parainfluenzae were the most significantly abundant in the controls. Functional prediction showed that genes involved in bacterial mobility, flagellar assembly, bacterial chemotaxis, and LPS synthesis were enriched in the tumors while those responsible for DNA repair and combination, purine metabolism, phenylalanine, tyrosine and tryptophan biosynthesis, ribosome biogenesis, and glycolysis/gluconeogenesis were significantly associated with the controls	Al-Hebshi et al.[63]
	Acinetobacter, *Fusobacterium*, *Streptococcus*, *Prevotella*	Cross sectional	Tissue, saliva, mouthwash	30 OSCC	16S rRNA gene sequencing	*Proteobacteria* were most enriched in the tissue group at the phylum level, while *Firmicutes* were predominant in the groups saliva and mouthwash. At the genus level, the predominant taxa of group tissue were *Acinetobacter* and *Fusobacterium*, and for group saliva and mouthwash, the predominant taxa were *Streptococcus* and *Prevotella*. The genera related to late stage tumors were *Acinetobacter* and *Fusobacterium*, suggesting microbiota may be implicated in OSCC developing	Zhang et al.[59]
	F. nucleatum, *Prevotella intermedia*, *Aggregatibacter segnis*, *Capnocytophaga leadbetteri*, *Peptostreptococcus stomatis*, *Catonella morbi*, *Porphyromonas catoniae*, *Campylobacter rectus*, *Gemella morbillorum*, *Peptococcus* sp.	Cross sectional	Tissue	50 OSCC	16S rDNA sequencing	At the species level, the abundances of *F. nucleatum*, *Prevotella intermedia*, *Aggregatibacter segnis*, *Capnocytophaga leadbetteri*, *Peptostreptococcus stomatis*, and another five species were significantly increased, suggesting a potential association between these bacteria and OSCC	Zhang et al.[64]

Abbreviations: BC, breast cancer; CCL, chemokine (C-C motif) ligand; CP, chronic pancreatitis; CRC, colorectal cancer; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ELISA, enzyme-linked immunosorbent assay; ESCC, esophageal squamous cell carcinoma; FFPE, formalin-fixed, paraffin-embedded; FISH, fluorescence in situ hybridization; GC, gastric cancer; HNSCC, head and neck squamous cell carcinomas; LPS, lipopolysaccharide; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; PC, pancreatic cancer; PDAC, pancreatic adenocarcinoma; qRT-PCR, quantitative real time polymerase chain reaction.

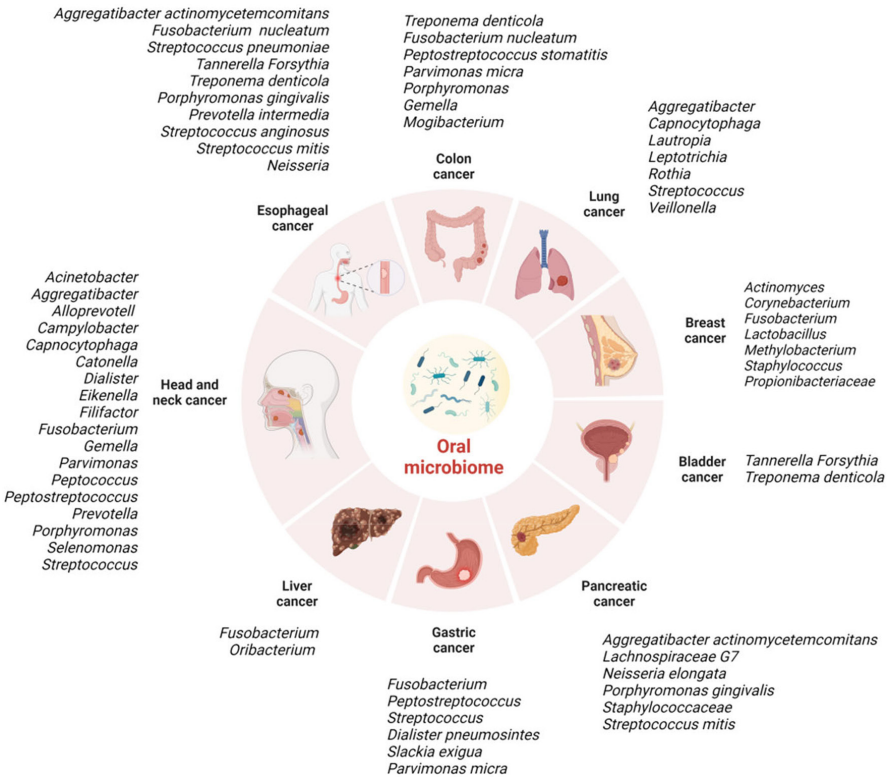

FIGURE 3 Oral microbiota associations with common cancers. A schematic representation illustrating the correlation between oral microbiota and various cancer types, including head and neck, colorectal, lung, breast, bladder, pancreatic, gastric, liver, and esophageal cancers.

HNSCCs originate from the mucosal epithelium in the oral cavity, pharynx, and larynx, representing the most prevalent malignancies occurring in the head and neck region.[58] At the genus level, the predominant taxa of OSCC tissue and saliva were: *Acinetobacter*, *Fusobacterium*, *Streptococcus*, *Prevotella Dialister*, *Peptococcus*, *Catonella* and *Parvimonas*.[59,60] *Capnocytophaga gingivalis*, *Prevotella melaninogenica* and *Streptococcus mitis* were enriched in the saliva of patients with OSCC and they can predict 80% of cancer cases while excluding 83% of controls in the non-matched group.[61] Additionally, the most common bacteria associated with periodontitis, *P. gingivalis*, were abundantly present in malignant oral epithelium.[62] The first epidemiological evidence linking *F. nucleatum* and *Pseudomonas aeruginosa* to OSCC was reported by Al-Hebshi et al.[63] Another cross sectional study involving 50 patients with OSCC using the 16S rDNA sequencing, reported significantly increased abundances of various bacteria, including *F. nucleatum*, *Prevotella intermedia*, *Aggregatibacter segnis*, and others. These findings suggest a potential association between these bacteria and OSCC.[64]

4 | MECHANISTIC ROLES OF PERIODONTAL PATHOGENS IN VARIOUS CANCERS

This segment of the review provides an in-depth analysis of the multifaceted roles played by periodontal pathogens, including *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans*, *T. denticola*, and *T. forsythia*, in the pathogenesis of various cancers. Table 2 displays their respective roles in tumor proliferation, invasion, metastasis, and modulation of the tumor microenvironment.

4.1 | *Porphyromonas gingivalis*

4.1.1 | Characteristics of *P. gingivalis*

P. gingivalis, a gram-negative bacterium, is considered a primary etiologic factor in the pathogenesis of periodontal disease.[66] Furthermore, this bacterium has been linked to several extraoral infection-related diseases, including cardiovascular disease, diabetes, pulmonary disease, and rheumatoid arthritis.[67] Increasing evidence suggests the involvement of *P. gingivalis* in the etiology of oral, gastrointestinal, and pancreatic cancers.[49,68] The investigation of gut microbiota, comparing cancer cases and control subjects for the presence and relative abundance of taxa, also identified an association between an elevated risk of CRC and increased presence of proinflammatory genera *Fusobacterium* and *Porphyromonas*.[40]

P. gingivalis possesses diverse virulence factors that facilitate its reproduction within the host's reservoir. The most significant virulence factors of *P. gingivalis* include fimbriae, lipopolysaccharide (LPS), outer membrane vesicles (OMV), and gingipains.[69] Fundamental pathogenic mechanisms involve generating dysregulated microbiota and impairing immune defenses. Among these virulence factors, fimbriae play a pivotal role in bacterial colonization. Two distinct types of fimbriae exist, with the significant type encoded by the FimA gene and the minor type encoded by the mfa1 gene.[70,71] Six FimA

TABLE 2 Peiodontal pathogens and cancer: Summary of mechanistic evidence.

Periondontal pathogens	Associated cancer	Study design	Sample type	Effect	References
Porphyromonas gingivalis	CRC	In vitro	Human CRC cell line S1 and murine colon cancer MC38 cells	*P. gingivalis* can invade cells and promote the proliferation of colorectal cancer cells by activating the MAPK/ERK signaling pathway	Mu et al.[108]
	CRC	In vitro	CL-11	Peptidoglycans of *P.gingivalis* plays a major role in PD-L1 up-regulation in colon cancer cells. In addition, the mechanism of PD-L1 up-regulation depends on NOD 1 and NOD 2 and involves activation of RIP2 and MAPK signaling pathways	Adel-Khattab et al.[107]
	CRC	In vitro, animal model, clinical	CRC tissue samples and feces; colorectal adenoma mouse model, orthotopic and subcutaneous colorectal xenograft mouse model	*P.gingivalis* is associated with a poor prognosis in human colorectal cancer because this bacterium colonizes and becomes enriched in tumor tissue, resulting in activation of the NLRP3 inflammasome in the immune microenvironment, which ultimately promotes colorectal carcinoma progression	Wang et al.[109]
	EC	In vitro, animal model, clinical	ESCC samples; human ESCC cell lines Kyse-410, Kyse-150, Kyse-180, and Yes-2; humanized mouse model for ESCC	Highlighted the importance of reciprocal regulation of B7-H4– and KDM5B-related pathways involved at different stages in the lymphocyte compartment during *P. gingivalis* infection	Yuan et al.[100]
	EC	In vitro, clinical	ESCC saliva samples; ESCC cell lines Eca109 and KYSE-150	*P.gingivalis* triggered NF-κB signaling and promoted the proliferation and metastasis of ESCC cells	Meng et al.[103]
	EC	In vitro, animal model	Human embryonic kidney 293T (HEK293T) cell line and the human ESCC cell lines KYSE-30 and KYSE-150; xenograft models in nude mice	*P.gingivalis* could promote the proliferation and migration of ESCC cells through the miR-194/GRHL3/PTEN/Akt negative feedback signaling pathway mediated by miR-194	Liang et al.[104]
	EC	In vitro, animal model, clinical	ESCC samples; human ESCC cell lines CE81T and TE2; 4NQO-induced ESCC model in mice	*P.gingivalis* may promote esophageal cancer development and progression. Direct targeting of *P.gingivalis* or concomitant IL-6 signaling may be a promising strategy to prevent and/or treat ESCC associated with *P.gingivalis* infection	Chen et al.[102]
	EC	In vitro, clinical	ESCC samples; ESCC cell lines KYSE-30, KYSE-70, KYSE-140, and KYSE-150	*P.gingivalis* infection reduces the sensitivity of ESCC cells to chemotherapy drugs through activation of the STAT3 signaling pathway both in vivo and in vitro	Gao et al.[105]
	EC	In vitro, animal model, clinical	ESCC samples; Human ESCC cell lines NE6-T and KYSE30; mouse xenograft tumor model	*P.gingivalis* activates the TGF-β signaling pathway through GARP via upregulation of TLR4/MyD88, at least partially, in ESCC cells. FimA contributed partly to the tumor-promoting role of *P.gingivalis* through TGF-β/Smad signaling. The clinical data showed that *P.gingivalis* infection and the phosphorylation of Smad2/3 were significantly associated with the overall survival of patients with ESCC. Inhibiting TGF-β signaling or eliminating *P.gingivalis* suppresses tumor growth and metastasis, suggesting the potential clinical application of targeting the *P.gingivalis*-related signaling network for treating ESCC patients	Gao et al.[106]

TABLE 2 (Continued)

Periondontal pathogens	Associated cancer	Study design	Sample type	Effect	References
	HNC	In vitro	SCC-25 and BHY cells	After infection with *P. gingivalis*, both B7-H1 and B7-DC receptors were up-regulated, which might facilitate immune evasion by oral cancers	Groeger et al.[86]
	HNC	In vitro	SAS and Ca9-22 cells	*P.gingivalis* activates theERK1/2-Ets1, p38/HSP27, and PAR2/NF-κB pathways to induce proMMP-9 expression and to promote cellular invasion of OSCC cell lines	Inaba et al.[94]
	HNC	In vitro, animal model	SCC-25 and CAL 27;4NQO-induced OSCC model in mice	Chronic bacterial infection has been observed to promote OSCC, with enhanced signaling along the IL-6-STAT3 axis believed to be responsible for this effect. Both *P.gingivalis* and *F. nucleatum* have been shown to stimulate tumorigenesis through direct interaction with oral epithelial cells via TLR. Additionally, these oral pathogens have been found to stimulate proliferation of human OSCC cells and induce expression of key molecules associated with tumorigenesis	Gallimidi et al.[93]
	HNC	In vitro	SAS cells	*P.gingivalis* activates PAR4 signaling pathways, leading proMMP-9 over-expression and cellular invasion in OSCC cells	Inaba et al.[95]
	HNC	In vitro, animal model	4NQO-induced OSCC model in mice, SCC-25 and CAL 27 human tongue SCC cell lines	*P.gingivalis* stimulate tumorigenesis via direct interaction with oral epithelial cells through Toll-like receptors and stimulate human OSCC proliferation and induce expression of key molecules implicated in tumorigenesis	Binder et al.[93]
	HNC	In vitro	Ca9-22 OSCC cells	OSCC cells infected with *P.gingivalis* exhibited elevated MMP-1 and MMP-10 expression, a response triggered by the release of IL-8, consequently amplifying the aggressiveness of OSCC cells	Ha et al.[97]
	HNC	In vitro	Tissue biopsies of healthy gingiva and HNC tumors, Human bone invasive oral squamous cell carcinoma BHY cells	*P.gingivalis* and human α-defensins could led to an increase in oral tumor cell proliferation	Hoppe et al.[90]
	HNC	In vitro	SCC-25 cells	*P.gingivalis* membrane up-regulates the expression of genes of TLR, NF-κB, and MAPK signaling pathways which inducting pro-inflammatory cytokines and inducing cancer proliferation	Groeger et al.[91]
	HNC	In vitro	H400 cells	Heat-killed *P.gingivalis* triggered EMT-signaling pathways and up-regulated the expression of MMP-2, -3 and -9	Abdulkareem et al.[96]
	HNC	In vitro	Tca8113 cells	*P.gingivalis* could promotes OSCC proliferation by inducing cyclin D1 expression via the miR-21/PDCD4/AP-1 signaling pathway	Chang et al.[92]

(Continues)

TABLE 2 (Continued)

Periondontal pathogens	Associated cancer	Study design	Sample type	Effect	References
	HNC	In vitro, animal model	Cal-27 cells, s.c. transplantation model of OSCC in mice	*P.gingivalis* possessed the capability to hinder macrophage-mediated phagocytosis of Cal-27 cells, with membrane-component molecules speculated, such as proteins, that can act as the effector. Furthermore, persistent exposure to antibiotics-inactivated *P.gingivalis* fostered OSCC progression in mice and prompted the polarization of macrophages toward M2 tumor-associated macrophages, primarily exhibiting pro-tumor characteristics	Liu et al.[87]
	HNC	In vitro, animal model, clinical	OSCC samples, 4NQO-induced OSCC model in mice	The cohort study showed that the localization of *P.gingivalis* in tumor tissues was related to poor survival of patients with OSCC. The promotion of tumor progression by *P.gingivalis* involves the recruitment of MDSCs via increasing secretion of IL-6, IL-8, CCL2, and CXCL2 from infected oral dysplastic keratinocytes	Wen et al.[88]
	HNC	In vitro, animal model	The human OSCC cell lines, UM-SCC-14A and HSC-3; nude mice	*P.gingivalis* enhance the migration, invasion, tumorsphere formation, and tumorigenesis of OSCC cells in vivo. Pathogen-induced OSCC cell migration occurred through the activation of integrin alpha V and FAK. These effects were abolished by stably inhibiting the expression of alpha V or FAK. Moreover, the process was inhibited by nisin	Kamarajan et al.[134]
	HNC	In vitro	H400 cells	*P.gingivalis* increased IL-1β by upregulating AIM2, NLRP3 and downregulating POP1	Aral et al.[89]
	HNC	In vitro, animal model, clinical	OSCC samples; human OSCC cell line TSCCa; OSCC mouse model created with SCC7 cell lines	*P.gingivalis* promotes OSCC progression by recruiting tumor-associated neutrophils (TANs) through activation of the CXCL2/CXCR2 axis in the TME of OSCC	Guo et al.[99]
	PC	In vitro, animal model	Human pancreatic carcinoma cell lines MIA PaCa-2 and PANC1; injected severe combined immunodeficient mice with PANC1 cells	Live *P.gingivalis* prompted the proliferation of pancreatic cancer cells and augmented tumor growth in murine models	Gnanasekaran et al.[111]
	PC	Animal model	PG-LPS (lipopolysaccharide from *P.gingivalis* ATCC 33277) was prepared in physiological saline and intraperitoneally administered to C57BL/J mice	The upregulated expression levels of *Reg3A* and *G* might play a key role in PG-LPS-related pancreatic cancer in mouse	Hiraki et al.[110]
	PC	In vitro, animal model, clinical	Murine pancreatic cancer cell line Pan02; orthotopic and subcutaneous PC mouse model; PC samples	*P.gingivalis* promoted PC progression via elevating the secretion of neutrophilic chemokines and neutrophil elastase (NE)	Tan et al.[112]
	PC	In vitro, animal model, clinical	PDAC mouse model; human PDAC cell lines, Panc-1, MIA-PaCa-2, AsPC-1, BxPC-3 and murine PDAC cell line Panc02; pancreatic tissue	Viable *P. gingivalis* was recovered from the pancreas of healthy mice after application of the bacteria to the oral mucosa, and chronic application of the bacteria to the oral cavity induced acinar cell-to-ductal metaplasia in the pancreas, and led to a shift in the pancreatic microbiome. Oral cavity application of *P.gingivalis* accelerated progression of pancreatic intraepithelial neoplasia to PDAC in mice expressing inducible acinar cell oncogenic KRAS. Oncogenic KRAS enabled intracellular survival of *P. gingivalis*, and intracellular bacteria promoted PDAC cell survival in hypoxic and nutrient-depleted conditions	Saba et al.[113]

TABLE 2 (Continued)

Periondontal pathogens	Associated cancer	Study design	Sample type	Effect	References
Fusobacterium nucleatum	BC	In vitro, animal model, clinical	Human breast cancer cell line MCF-7 and MDA-MB-231, mouse BALB/c breast cancer model cell line 4T1, mouse C57BL/6 breast cancer model cell line AT3, and mouse C57BL/6 melanoma model cell line B16; Balb/C, C57BL/c, and SCID-beige mice; BC samples	This study provide strong evidence for a model whereby *F. nucleatum* generally reaches tumors via the hematogenous route and specifically attaches to them via a bacterial lectin-host sugar (Fap2-Gal-GalNAc) interaction	Parhi et al.[31]
	BC	In vitro, animal model, clinical	BC cell lines MDA-MB-231 and MCF-7; BC tissues; BALB/c nude mice	*F. nucleatum* plays an important role in BC tumor growth and metastasis by regulating TLR4 through Fn-EVs	Li et al.[152]
	CRC	In vitro, clinical	HCT116; CRC tissues	*F. nucleatum* adhesin FadA binds E-cadherin and promotes CRC cell proliferation. FadA promotes inflammation and E-cadherin-mediated CRC tumor growth in xenograft mice	Rubinstein et al.[140]
	CRC	In vitro, animal model, clinical	C57BL/6J–Apc^{Min}/J, BALB/c *Il-10*$^{-/-}$ and BALB/c *T-bet*$^{-/-}$ *Rag2*$^{-/-}$; CD3ε+ CD4+ T cells fromApc^{Min} mice; colonic adenocarcinoma, adenomas and stool samples	*Fusobacteria* recruit tumor-infiltrating immune cells, fostering a pro-inflammatory microenvironment that supports the progression of colorectal neoplasia	Kostic et al.[146]
	CRC	In vitro, animal model, clinical	CT26-luc, human colon adenocarcinoma cell line HT29, RKO, and HCT116; murine CRC model; CRC samples; NSG mice	Gal-GalNAc is highly expressed in human CRC, metastases, and a preclinical CRC model. Fap2 is a fusobacterial Gal-GalNAc-binding lectin. Fap2 mediates *F. nucleatum* binding to Gal-GalNAc overexpressed in CRC. Blood-borne Fap2-expressing *F. nucleatum* localizes to orthotopic mouse colon tumors	Abed et al.[142]
	CRC	In vitro, clinical	CRC tissues; human colon cancer cell lines SW480 and Caco-2	Invasive *F. nucleatum* activates β-catenin signaling via a TLR4/P-PAK1/P-β-catenin S675 cascade in the carcinogenesis of CRC; TLR4 and PAK1 could be potential pharmaceutical targets for the treatment of *F. nucleatum*-related CRCs	Chen et al.[143]
	CRC	In vitro, animal model, clinical	CRC tissues; The CRC cell lines (HCT116, SW480, HT29, Caco2, LoVo, SW620, DLD1, RKO, Colo205) and IEC; C57BL/6J-Adenomatous polyposis coli $(APC)^{min}$/J mice	CRC cells infected with *F. nucleatum* increased cells proliferation, invasive activity, and ability to form xenograft tumors in mice. The activation of TLR4 signaling by *F. nucleatum* leads to MYD88 activation, subsequently triggering the nuclear factor NF-κB and upregulating miR21 expression. Patients exhibiting both high levels of tissue *F. nucleatum* DNA and miR21 expression showed a heightened risk for poor outcomes	Yang et al.[144]

(Continues)

TABLE 2 (Continued)

Periondontal pathogens	Associated cancer	Study design	Sample type	Effect	References
	CRC	In vitro, animal model, clinical	CRC tissues; male C57BL/6-$Apc^{Min}/^{+}$ mice; mouse macrophage cell line RAW 264.7	*F. nucleatum* infection increased M2 macrophage polarization in vitro and in vivo, enhanced colorectal tumor growth, which is likely TLR4-dependent involving the IL-6/p-STAT3/c-Myc signaling pathway	Chen et al.[145]
	CRC	In vitro, animal model	C1, SB, 10C, HCT116, DLD1, SW480, HT29, RKO, PC-9, 22RV1, UMUC3, and MCF-7; nude mice	The FadA adhesin from *F.nucleatum* up-regulates Annexin A1 expression through E-cadherin	Rubinstein et al.[141]
	EC	Clinical	EC samples	*F. nucleatum* was detected in esophageal cancer tissues and was associated with shorter survival, suggesting that it may serve as a useful prognostic biomarker. *F. nucleatum* might also contribute to the acquisition of aggressive tumor behavior through the activation of chemokines, such as CCL20	Yamamura et al.[34]
	EC	In vitro, animal model, clinical	ESCC samples; Human esophageal cancer cell lines TE-8 and TE-10; TE-8 cells was injected subcutaneously and bilaterally into BALB/c mice	*F. nucleatum* invaded ESCC cells and induced the NF-κB pathway through the NOD1/RIPK2 pathway, leading to tumor progression	Nomoto et al.[136]
	EC	In vitro, animal model, clinical	The human ESCC KYSE150 cell line and 293 T cell line; ESCC tissues; NSG mice	*F. nucleatum* could induce the enrichment of MDSCs in the tumor microenvironment by activating NLRP3 in ESCC cells. *F. nucleatum* infection could cause CDDP resistance in ESCC	Liang et al.[137]
	EC	In vitro, animal model, clinical	ESCC tissues; CD8+ T cells, KYSE150; NSG mice	*F. nucleatum* may induce high expression of KIR2DL1 on the surface of $CD8^{+}$ T cells in ESCC tissues to provide a favorable microenvironment for self-sustaining infection, thus promoting tumor progression	Wang et al.[138]
	GC	In vitro, clinical	GC tissues and peripheral blood; human erythroleukemia cell K562 and promyelocytic cell HL-60	*F. nucleatum* infection promotes NET formation, which releases EVs containing 14-3-3ε. These EVs could deliver 14-3-3ε to HPCs and promote their differentiation into MKs via activation of PI3K-Akt signaling	Liu et al.[153]
	GC	In vitro, animal model, clinical	GC tissues; BGC-823 (C6123) and SGC-7901 (C6795) cell lines; BALB/c nude mice	Fn-EVs facilitated GC tumor proliferation, DNA damage repair, stemness and metastasis in vitro and in vivo. Fn-EVs also conferred GC cells resistance to oxaliplatin, which might rely on its regulation on DNA damage repair and stemness	Meng et al.[154]
	HNC	In vitro, animal model	4NQO-induced OSCC model in mice, SCC-25 and CAL 27 human tongue SCC cell lines	*F. nucleatum* stimulate tumorigenesis via direct interaction with oral epithelial cells through Toll-like receptors and stimulate human OSCC proliferation and induce expression of key molecules implicated in tumorigenesis	Binder et al.[93]

TABLE 2 (Continued)

Periodontal pathogens	Associated cancer	Study design	Sample type	Effect	References
	HNC	In vitro, animal model	SCC-25 and CAL 27;4NQO-induced OSCC model in mice	Chronic bacterial infection has been observed to promote OSCC, with enhanced signaling along the IL-6-STAT3 axis believed to be responsible for this effect. Both *P.gingivalis* and *F. nucleatum* have been shown to stimulate tumorigenesis through direct interaction with oral epithelial cells via TLR. Additionally, these oral pathogens have been found to stimulate proliferation of human OSCC cells and induce expression of key molecules associated with tumorigenesis	Gallimidi et al.[93]
	HNC	In vitro	H400 cells	Heat-killed *F. nucleatum* triggered EMT-signaling pathways and increased MMP-2, -3, and -9 expression	Abdulkareem et al.[96]
	HNC	In vitro, clinical	OSCC tissues; human squamous cell carcinoma cell lines SCC-9 and HSC-4	*F. nucleatum* infection could initiate EMT via the lncRNA MIR4435-2HG/miR-296-5p/Akt2/SNAI1 signaling pathway, potentially linking *F. nucleatum* infection to the onset of oral epithelial carcinomas	Zhang et al.[130]
	HNC	In vitro, animal model	The human OSCC cell lines, UM-SCC-14A and HSC-3; nude mice	*F. nucleatum* enhance the migration, invasion, tumorsphere formation, and tumorigenesis of OSCC cells in vivo. Pathogen-induced OSCC cell migration occurred through the activation of integrin alpha V and FAK. These effects were abolished by stably inhibiting the expression of alpha V or FAK. Moreover, the process was inhibited by nisin	Kamarajan et al.[134]
	HNC	In vitro, animal model	HN and BHY cells; 4NQO-induced OSCC model in mice	*Fusobacteria* could potentially enhance cancer cell invasiveness, survival, and EMT when presented in the oral tumor microenvironment	Harrandah et al.[131]
	HNC	In vitro	Tca8113 tongue squamous cell carcinoma cell	*F. nucleatum* infection promoted the proliferation ability of Tca8113 by causing DNA damage via the Ku70/p53 pathway	Geng et al.[132]
	HNC	In vitro	H400 cells	*F. nucleatum* promoted IL-1β by increasing AIM2 and downregulating POP1	Aral et al.[89]
	HNC	In vitro	Human oral squamous cell carcinoma lines Cal-27 and HSC-3	*F. nucleatum* promotes cisplatin resistance and migration in oral squamous cell carcinoma cells through the Wnt/NFAT pathway	Da et al.[133]
	HNC	In vitro, animal model, clinical	OSCC tissues; C3H mice; human primary oral keratinocytes, human OSCC cell lines CAL27, SCC15, and SCC25, human monocyte cell line THP-1	*F. nucleatum*-induced acidification renders a protumorigenic immune microenvironment, which in turn causes cell malignant transformation. *F. nucleatum* colonized in OSCC tissues could induce cancer cells to produce much more lactate via the GalNAc-Autophagy-TBC1D5-GLUT1 signaling axis	Sun et al.[129]
Aggregatibacter actinomycetemcomitans	HNC	In vitro	Human gingival squamous carcinoma cell line Ca9-22	Delivering the CdtB protein and transfecting the *cdtB* gene could induce cell cycle arrest and apoptosis in Ca9-22 cells in vitro	Yamamoto et al.[176]
	HNC	In vitro	Tissue biopsies of healthy gingiva and HNC tumors, Human bone invasive oral squamous cell carcinoma BHY cells	*A. actinomycetemcomitans* enhanced oral tumor cell death	Hoppe et al.[90]

(Continues)

TABLE 2 (Continued)

Periondontal pathogens	Associated cancer	Study design	Sample type	Effect	References
Treponema denticola	HNC	In vitro	Tumor tissues	In addition, *Td*-CTLP positivity was significantly associated with invasion depth, tumor diameter and the expression of TLR-7, TLR-9 and c-Myc in early-stage mobile tongue squamous cell carcinoma	Listyarifah et al.[177]
	HNC	In vitro, animal model	The human OSCC cell lines, UM-SCC-14A and HSC-3; nude mice	*T. denticola* enhance the migration, invasion, tumorsphere formation, and tumorigenesis of OSCC cells in vivo. Pathogen-induced OSCC cell migration occurred through the activation of integrin alpha V and FAK. These effects were abolished by stably inhibiting the expression of alpha V or FAK. Moreover, the process was inhibited by nisin. *T. denticola* induced the expression of TLR2, TLR4, and MyD88. Stable suppression of MyD88 significantly inhibited FAK activation induced by *Treponema denticola* and abolished the pathogen-induced migration	Kamarajan et al.[134]
	HNC	In vitro, animal model	The OSCC cell line Cal-27; female BALB/c-nu nude mice	*T. denticola* could promote OSCC cell proliferation directly, and the mechanism was associated with intracellular TGF-β pathway activation	Peng et al.[184]
	Orodigestive carcinogenesis	In vitro, animal model, clinical	Orodigestive tumor tissue (squamous cell carcinomas of tongue, tonsil, esophagus, and adenocarcinoma of stomach, pancreas, and colon); New Zealand White rabbit	*Td*-CTLP could activate pro MMP-8 and -9 into their active forms and degrade proteinase inhibitors such as TIMP-1, TIMP-2, and α-1-antichymotrypsin, along with complement C1q	Nieminen et al.[185]

Abbreviations: 4NQO, 4-nitroquinoline 1-oxide; AIM2, absent in melanoma 2; AP-1, activator protein-1; BC, breast cancer; CCL, chemokine (C-C motif) ligand; CRC, colorectal cancer; CXCL, chemokine (C-X-C motif) ligand; CXCR, C-X-C chemokine receptor; EC, eosphageal cancer; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; ESCC, esophageal squamous cell carcinoma; EVs, extracellular vesicles; FAK, focal adhesion kinase; GC, gastric cancer; GLUT, glucose transporter; HNC, head and neck cancer; HPCs, hematopoietic progenitor cells; HSP27, heat shock protein 27; IL, interleukin; lncRNA, long non-coding RNA; MAPK, Mitogen-activated protein kinase; MDSCs, myeloid-derived suppressor cells; miR, microRNA; MMP, matrix metalloproteinase; MyD88, myeloid differentiation primary response 88; NFAT, nuclear factor of activated T cells; NF-κB, nuclear Factor-kappa B; NLRP, nucleotide-binding oligomerization domain, leucine-rich repeat-containing receptor (NLR) family pyrin domain-containing; NOD, nucleotide-binding oligomerization domain; OSCC, oral squamous cell carcinoma; PAR, protease-activated receptor; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PDCD4, programmed cell death protein 4; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RIPK, receptor-interacting protein kinase; STAT3, signal transducer and activator of transcription 3; TGF-β, Transforming Growth Factor β; TIMP, tissue inhibitor of metalloproteinases; TLR, toll like receptor; TME, tumor microenvironment.

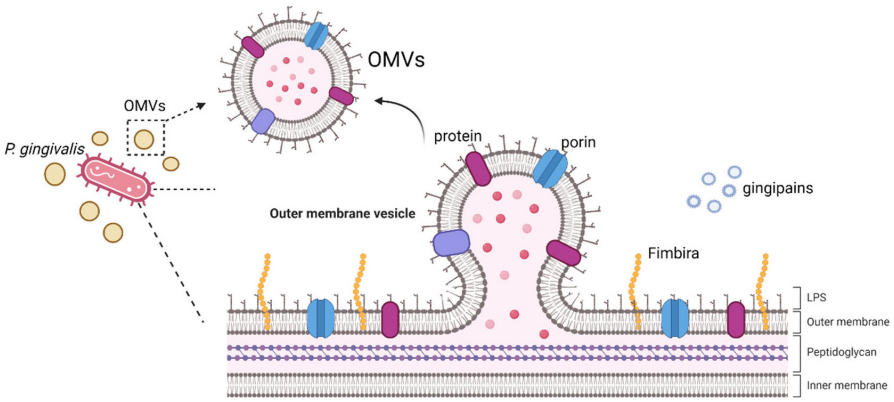

FIGURE 4 Characteristics of *Porphyromonas gingivalis* (*P. gingivalis*) and its outer membrane vesicles (OMVs). *P. gingivalis* consists of cell membrane and genetic material. The outer layer of *P. gingivalis*' cell membrane encompasses fimbriae, proteins, and channels. The primary virulence factors of *P. gingivalis* primarily stem from both its structural components, such as lipopolysaccharide (LPS) and fimbriae, and its secretory components, including gingipains and outer membrane vesicles (OMVs). *Adapted from* Ref. [85].

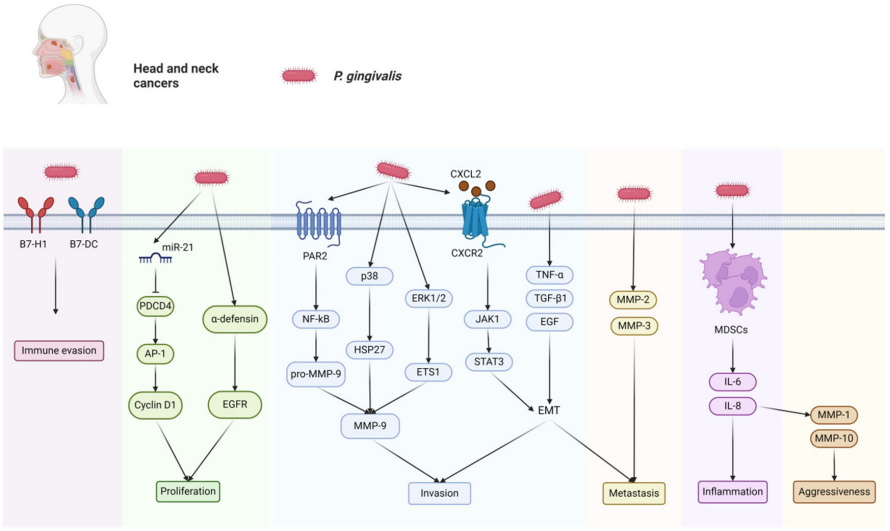

FIGURE 5 Mechanisms by which *Porphyromonas gingivalis* may contribute to head and neck cancers. This figure illustrates the potential mechanisms by which the periodontal pathogen *Porphyromonas gingivalis* (*P. gingivalis*) contributes to the development and progression of head and neck cancers. It depicts a series of signaling pathways and molecular interactions initiated by *P. gingivalis*, leading to immune evasion, proliferation, invasion, metastasis, inflammation, and increased aggressiveness of cancer cells. *P. gingivalis* induces the expression of B7-H1 and B7-DC receptors on host cells, leading to immune evasion. It also promotes OSCC proliferation by inducing epidermal growth factor receptor (EGFR) and cyclin D1 expression via the miR-21/PDCD4/AP-1 signaling pathway. *P. gingivalis* induces the expression of MMP-9 through activate the protease-activated receptor (PAR) 2/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), p38/heat shock protein27 (HSP27), and ERK1/2-Ets1 pathway, ultimately promoting invasion. The activation of the Chemokine (C-X-C motif) ligand 2 (CXCL2)/C-X-C chemokine receptor 2 (CXCR2) axis by *P. gingivalis* triggers the epithelial-mesenchymal transition (EMT) phenotype through the JAK1/signal transducer and activator of transcription 3 (STAT3) signaling pathway. *P. gingivalis* elevates TGF-β1, TNF-α, and epidermal growth factor (EGF) levels, associated with EMT signaling pathways, closely linked to invasion and metastasis. The activation of MMP-2, matrix metalloproteinase (MMP)-3 by *P. gingivalis* is shown to facilitate metastasis. Additionally, the bacteria induce the production of IL-6 and IL-8, leading to inflammation, which further enhances the aggressiveness of cancer cells through MMP-1 activation.

genotypes have been identified, with FimA II and FimA IV genotypes predominating in patients with periodontitis. In contrast, the FimA I genotype is most frequently observed in healthy patients.[70,71] These findings suggest that microbial danger may be discerned at the subspecies level, and the outcome could contribute to varying degrees of predispositions.[72]

The LPS, present on the outer membrane of *P. gingivalis*, consists of lipid A, core oligosaccharide, and O-antigen, serving as another virulence factor capable of activating macrophages through toll-like receptors (TLRs).[73,74] It suppresses alkaline phosphatase, α1 collagen, and osteocalcin differentiation and mineralization in periodontal ligament stem cells.[70] Lipid A, in particular, can stimulate TLR4 on host cells, initiating signaling cascades that result in the production of pro-inflammatory cytokines. The enzymes generated by *P. gingivalis* represent an additional virulence factor. The key enzymes facilitating the growth of this bacterium are known as proteases,

specifically referred to as gingipains. These enzymes play a crucial role in degrading extracellular matrix proteins, including fibronectin and collagen.[75] To evade the host's defense mechanism, they dismantle immunoglobulins, complement factors, T cell receptors, and the α-defensins mechanism expressed by neutrophils.[76] For example, these enzymes can cleave surface proteins of T cells, such as CD4 and CD8, thereby influencing T cells functionality.[77] Gingipains induce the secretion of interleukin-6 (IL-6) by oral epithelial cells[78] and the expression of IL-8 by gingival fibroblasts.[79] Additionally, they can hydrolyze and deactivate both anti-inflammatory cytokines (IL-4, IL-5) and pro-inflammatory cytokines (IL-12, IFN-γ).[80,81]

Biofilms and OMVs are two crucial structures produced by microorganisms, playing pivotal roles in the survival, dissemination, and pathogenicity of microbes.[82] Biofilms consist of water, bacterial cells, and extracellular polymeric substances, and serve as protective layers, making them resistant to clinical interventions, including antibiotics.[82] OMVs, spherical membrane-enclosed nanostructures released from the outer membrane of gram-negative bacteria, play a crucial role in bacterial survival, virulence, and pathogenicity.[83] OMVs from *P. gingivalis* contribute to biofilm development by interacting with other periodontopathogens. They foster bacterial adhesion and invasion into host cells, adaptation to stress, and evasion of immune defense mechanisms.[82–84] Figure 4 summarizes the structure and representative components of *P. gingivalis*.

4.1.2 | Proposed carcinogenic mechanisms

Head and neck cancer

P. gingivalis strains have been shown to induce the expression of B7-H1 and B7-DC receptors in squamous cell carcinoma cells, potentially aiding in immune evasion in oral cancer.[86] Liu et al.[87] investigated the impact of *P. gingivalis* on the phagocytosis of Cal-27 cells (OSCC cell line) by bone marrow-derived macrophages and its effects on OSCC growth in vivo. They found that *P. gingivalis* had the capability to hinder macrophage-mediated phagocytosis of Cal-27 cells, with membrane-component molecules, such as proteins, speculated to act as the effector. Furthermore, persistent exposure to antibiotics-inactivated *P. gingivalis* fostered OSCC progression in mice and prompted the polarization of macrophages toward M2 tumor-associated macrophages, primarily exhibiting pro-tumor characteristics.[87] These results suggest that *P. gingivalis* may enhance immune evasion in oral cancer by protecting cancer cells from macrophage attack. Moreover, *P. gingivalis* promotes tumor progression by generating a cancer-promoting microenvironment. In a mouse model of carcinogenesis induced by 4-nitroquinoline-1 oxide (4NQO), *P. gingivalis* infection exacerbates oral lesions and promotes tumor progression through invasion of oral lesions. Increased infiltration of CD11b+myeloid cells and myeloid-derived suppressor cells (MDSCs) is observed in these lesions. In vitro experiments reveal that exposure of human-derived dysplastic oral keratinocytes (DOKs) to *P. gingivalis* leads to the accumulation of MDSCs. Chemokines such as Chemokine (C-X-C motif) ligand 2 (CXCL2), chemokine (C-C motif) ligand 2 (CCL2), IL-6, and IL-8 are implicated in facilitating the recruitment of MDSCs, suggesting their potential role in tumor progression.[88] Moreover, *P. gingivalis* upregulates IL-1β by upregulating the inflammasome complexes nucleotide-binding oligomerization domain, leucine-rich repeat-containing receptor (NLR) family pyrin domain-containing 3 (NLRP3) and absent in melanoma 2 (AIM2), while downregulats pyrin domain (PYD)-only protein 1 (POP1).[89]

P. gingivalis and human α-defensins could lead to an increase in oral tumor cell proliferation.[90] Groeger et al.[91] utilized a profiler PCR array and found that *P. gingivalis* membrane upregulates the expression of genes of TLR, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and mitogen-activated protein kinases (MAPK) signaling pathways, leading to the induction of pro-inflammatory cytokines and promoting cancer proliferation. Moreover, *P. gingivalis* promotes OSCC proliferation by inducing cyclin D1 expression via the miR-21/programmed cell death protein 4 (PDCD4)/activator protein-1 (AP-1) signaling pathway.[92] Furthermore, another study observed that certain activators of TLR2/1 and TLR4, or when exposed to *P. gingivalis*, trigger essential molecular components intricately associated with the progression and virulence of oral tumors, such as IL-6, cyclin D1, TNF-α, and heparanase.[93] Matrix metalloproteinase 9 (MMP-9) is implicated in the invasion and metastasis of cancer cells. Inaba et al.[94,95] demonstrated that *P. gingivalis* activates the extracellular signal-regulated kinase (ERK)1/2-Ets1, p38/heat shock protein27 (HSP27), protease-activated receptor (PAR) 4, and PAR2/NF-κB pathways to induce proMMP-9 expression and to promote cellular invasion of OSCC cell lines. Additionally, heat-killed *P. gingivalis* upregulates the expression of MMP-2, MMP-3, and MMP-9 in OSCCs. Epithelial-mesenchymal transition (EMT) is closely associated with invasion and metastasis. Heat-killed *P. gingivalis* increased the levels of TGF-β1, TNF-α, and epidermal growth factor (EGF), which are involved in EMT-signaling pathways, in OCSS cell lines. Furthermore, exposure to heat-killed *P. gingivalis* enhances migration and the rate of wound closure.[96] OSCC cells infected with *P. gingivalis* also exhibit elevated MMP-1 and MMP-10 expression, triggered by the release of IL-8, thereby amplifying the aggressiveness of OSCC cells.[97] Physiologically, bacteria and other microorganisms in the oral cavity are recognized by TLR2. Ikehata et al.[98] reported that the progression of OSCC can be accelerated by the activation of TLR2 through bacterial components. This activation potentially contributes to acquired resistance against cisplatin-induced apoptosis via modulation of the miR-146a pathway.

In tumor-bearing animal experiments, tumor samples with *P. gingivalis* infection in the tumor microenvironment (TME) of OSCC displayed enhanced cell invasion and proliferation, along with larger tumor volumes. Additionally, the expression of *P. gingivalis*, CXCL2, and tumor-associated neutrophils (TANs) serve as independent risk factors for poor prognosis in OSCC patients. Treatment with a CXCL2/CXCR2 signaling axis inhibitor significantly attenuated cell invasion and proliferation and reduced tumor volume in mice.

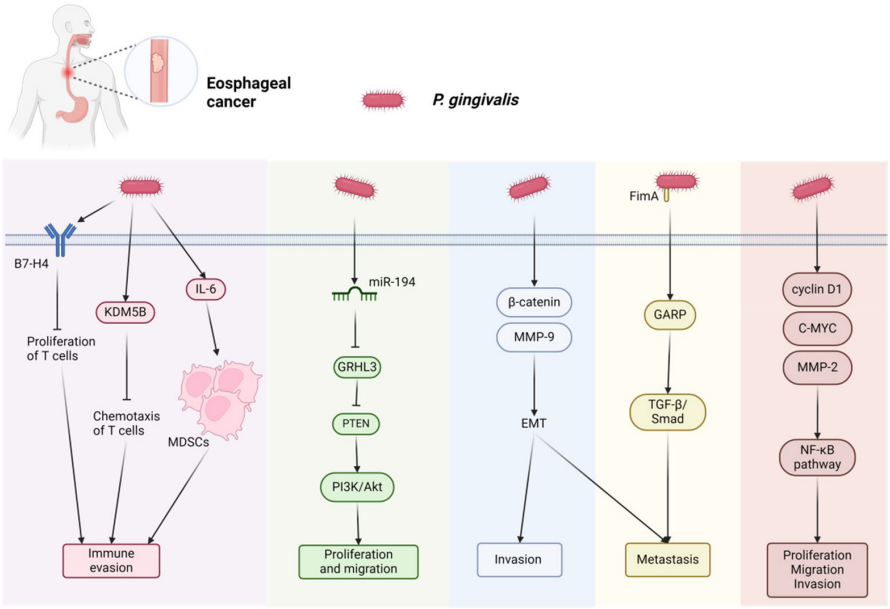

FIGURE 6 Mechanisms by which *Porphyromonas gingivalis* may contribute to esophageal cancer. *Porphyromonas gingivalis* (*P. gingivalis*) up-regulates B7-H4 and KDM5B in esophageal squamous cell carcinoma, contributing to immune evasion. Additionally, *P. gingivalis* infection also promotes IL-6 production and MDSCs recruitment. Furthermore, it upregulates miR-194 while inhibiting GRHL3 and PTEN. This, in turn, activates the phosphoinositide 3-kinase (PI3K)/Akt pathway, promoting cell proliferation and migration. By inducing the epithelial-to-mesenchymal transition (EMT) process, *P. gingivalis* enhances the invasiveness and metastasis of cancer cells through the upregulation of molecules such as β-catenin and matrix metalloproteinase 9 (MMP-9). It enhances the expression of glycoprotein A repetitions predominant (GARP), thus activating transforming growth factor-β (TGF-β)/Smad signaling pathway. This effect is partially dependent on *P. gingivalis* fimbriae (FimA), thereby promoting tumor growth and lung metastasis. *P. gingivalis* upregulates the expression of cyclin D1, c-Myc, and MMP-2, as well as activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which collectively promote cell proliferation, migration, and invasion.

Lentivirus-mediated blockade of the CXCL2/CXCR2 signaling axis results in decreased activity of the JAK1/signal transducer and activator of transcription (STAT) signaling pathway and reversal of the EMT phenotype[99] (Figure 5).

Eosphageal cancer

P. gingivalis isolated from esophageal squamous cell carcinoma (ESCC) lesions is recognized as a major pathogen associated with this fatal disease. Yuan et al.[100] investigated host immune responses during *P. gingivalis* infection, revealing increased expression of B7-H4 and lysine demethylase 5B (KDM5B) in experimentally infected ESCC. B7-H4, also known as B7S1, B7x, or VTCN1, plays a negative regulatory role in T cell activation.[101] Anti-B7-H4 and histone demethylase inhibitors were investigated for their immunotherapeutic effects against chronic infection and xenografted human tumors. Through combined therapy in three distinct preclinical mouse models, enhanced resistance against *P. gingivalis* infection and tumor challenge was observed, possibly attributed to T cell-mediated responses and immune memory formation. The coexpression of B7-H4 and KDM5B correlated significantly with bacterial load in ESCC subjects, suggesting potential therapeutic targets for improving control of *P. gingivalis* infection and associated neoplasia.[100] Additionally, another study found that *P. gingivalis* was associated with elevated EC incidence in a 4-nitroquinoline 1-oxide-induced mouse model and increased xenograft tumor growth. *P. gingivalis* infection promoted IL-6 production and MDSCs recruitment. Inhibition of IL-6 signaling attenuated the tumor-promoting effects of *P. gingivalis* in both mouse models. Moreover, ESCC cells infected with *P. gingivalis* exhibited enhanced characteristics associated with EMT, including increased expression levels of β-catenin and MMP-9, while simultaneously showing decreased expression levels of E-cadherin.[102]

In vitro studies revealed that *P. gingivalis* enhances the proliferation and motility of ESCC cells, upregulating key molecules such as cyclin D1, MMP-2, c-Myc, and BCL-XL, associated with the NF-κB signaling pathway.[103] Gao et al. examined the impact of *P. gingivalis* infection on ESCC and found that it significantly enhanced cellular proliferation, invasion, and migration in the ESCC cell lines KYSE-30 and KYSE-150. High-throughput sequencing identified upregulation of miR-194 in these infected cells, with miR-194 modulation affecting cell migration and invasion. Bioinformatics analysis identified GRHL3 as a direct target of miR-194, with decreased expression of GRHL3 observed in *P. gingivalis*-infected ESCC cells and patients. Downregulation of both GRHL3 and PTEN, along with upregulation of p-Akt, suggests a potential signaling pathway involving miR-194/GRHL3/PTEN/Akt in ESCC progression promoted by *P. gingivalis*.[104]

Gao et al.[105] have found that *P. gingivalis* infection is associated with a worse prognosis in patients with ESCC, reduced efficacy of neoadjuvant chemotherapy (NACT), and promotion of apoptosis resistance and proliferation in ESCC cells. Furthermore, it has been reported that TGF-β/Smad signaling mediates the oncogenic function

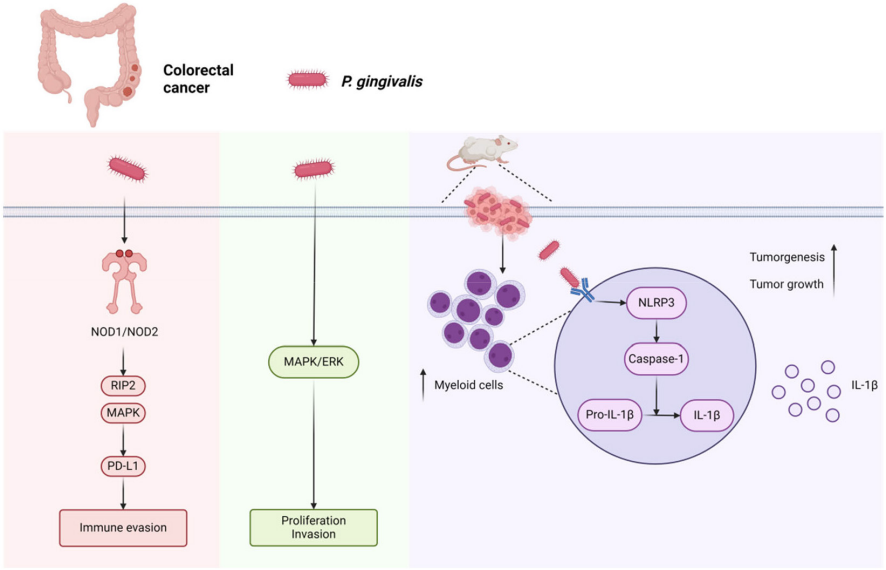

FIGURE 7 Mechanisms by which *Porphyromonas gingivalis* may contribute to colorectal cancer. *Porphyromonas gingivalis* (*P. gingivalis*) has been demonstrated to induce programmed cell death 1 (PD-L1) expression through the regulation of molecules such as non-occlusive disease (NOD)1/NOD2, receptor-interacting protein 2 (RIP2), and mitogen-activated protein kinases (MAPK). This process serves to mediate the immune evasion of tumor cells. In vivo, *P. gingivalis* has been observed to stimulate the secretion of pro-inflammatory factors by myeloid cells, including nucleotide-binding oligomerization domain, leucine-rich repeat-containing receptor (NLR) family pyrin domain-containing 3 (NLRP3), Caspase-1, and interleukin (IL)-1β. This leads to the promotion of inflammation and the acceleration of tumor growth. Activation of the MAPK/ERK signaling pathway by *P. gingivalis* has been demonstrated to accelerate cell proliferation and invasive behavior.

of *P. gingivalis* in ESCC.[106] Global transcriptomic analysis revealed that *P. gingivalis* infection induces elevated secretion of TGF-β and activates TGF-β/Smad signaling in both cultured cells and clinical ESCC samples. Moreover, this study demonstrated that *P. gingivalis* enhances the expression of Glycoprotein A repetitions predominant (GARP), thus activating TGF-β/Smad signaling, with this effect partially dependent on *P. gingivalis* fimbriae (FimA). Xenograft models further demonstrated that *P. gingivalis* infection activated TGF-β signaling, thereby promoting tumor growth and lung metastasis.[106] (Figure 6).

Colorectal cancer

Adel-Khattab et al.[107] investigated the impact of *P. gingivalis* on colon cancer cells (CL-11). They stimulated the cells with *P. gingivalis* total membrane (TM) fractions and peptidoglycans (PDG), as well as viable *P. gingivalis* bacteria. Their findings revealed that both the TM fraction and PDG induced an upregulation of PD-L1 in colon cancer cells, with PDG having a significant influence. The mechanism involved the activation of NOD 1 and NOD 2, along with the RIP2 and MAPK signaling pathways. Mu et al.[108] observed that *P. gingivalis* can adhere to and invade host cells, promoting cell proliferation. They found an increase in the percentage of S phase cells in the cell cycle assay. Through qPCR and western blot analyses, they suggested that the MAPK/ERK signaling pathway is significantly activated by *P. gingivalis*. Wang et al.[109] found that *P. gingivalis* enhanced tumor counts and volumes in the $Apc^{Min/+}$ mouse model and boosts tumor growth in orthotopic rectal and subcutaneous carcinoma models. It also modulates the tumor immune microenvironment by selectively expanding myeloid-derived immune cells and fostering a proinflammatory milieu. Furthermore, *P. gingivalis* contributes to the progression of colorectal cancer neoplasia by activating the hematopoietic NLRP3 inflammasome (Figure 7).

Pancreatic cancer

Hiraki et al.[110] estabilished a mouse model that is not affected by acute indlammation in various organs by intraperitoneally administering *P. gingivalis*-LPS to mice. They analyzed pancreatic gene expression and observed elevated expression of *Reg3A* and *G*, which are previously associated with PC. Gnanasekaran et al.[111] discovered that live *P. gingivalis* prompted the proliferation of pancreatic cancer cells. Interestingly, this impact was not contingent upon TLR2. Furthermore, *P. gingivalis* augmented tumor growth in murine models, with the pro-tumorigenic effects potentially attributable, at least in part, to the activation of the Akt signaling cascade. Tan et al.[112] confirmed the presence of a rich intratumor microbiota in human PC tissue, with the oral cavity bacterium *P. gingivalis* identified as colonizing and proliferating within the tumor microenvironment. Exposure to *P. gingivalis* accelerated tumor growth in both orthotopic and subcutaneous PC mouse models. Mechanistically, intratumoral *P. gingivalis* accelerated PC progression by enhancing the secretion of neutrophilic chemokines and neutrophil elastase (NE). Saba et al.[113] illustrated the migration of *P. gingivalis* from the oral cavity to the pancreas in a genetically engineered mouse model of pancreatic ductal adenocarcinoma (PDAC). Repetitive administration of *P. gingivalis* to wild-type mice induced pancreatic acinar-to-ductal metaplasia (ADM) and altered the composition of

the intrapancreatic microbiome. In iKC mice, *P. gingivalis* expedited the progression from pancreatic intraepithelial neoplasia (PanIN) to PDAC. In vitro, *P. gingivalis* infection induced the expression of acinar cell ADM markers SOX9 and CK19, while intracellular bacteria shielded PDAC cells from reactive oxygen species-mediated cell death induced by nutrient stress.

4.2 | *Fusobacterium nucleatum*

4.2.1 | Characteristics of *F. nucleatum*

Fusobacterium nucleatum (*F. nucleatum*) is an obligate anaerobic gram-negative bacterium commonly found in both healthy and diseased individuals within the oral cavity.[114] It is associated with periodontal diseases and has been isolated from clinical specimens of many diseases, such as appendicitis, brain abscesses, osteomyelitis, pericarditis, and chorioamnionitis.[114,115] There are reports indicating that *F. nucleatum* is also likely involved in the onset of gastrointestinal and oral cancer.[116]

F. nucleatum has the ability to co-aggregate with almost all bacterial species involved in oral plaque formation.[117] In addition, it can bind to and facilitate the transport of non-invasive bacterial species into host cells, functioning as a shuttle during this process.[118] *F. nucleatum* also mediates essential biofilm organization and engages in interactions with host cells by expressing multiple adhesins, such as adhesion inducing determinant 1 (Aid1), coaggregation-mediated protein A (CmpA), fibroblast activation protein 2 (Fap2), FomA, fusobacterial adhesin (FadA), and RadD.[119] Aid1, likely unique to Fusobacteria, can facilitate RadD-mediated interaction with oral *streptococci*.[120] The interplay between *F. nucleatum* and *Streptococcus gordonii* is facilitated through CmpA.[121] FadA, the significant adhesin identified to bind host cells, stands out as the most extensively characterized virulence factor of *F. nucleatum*.[122] It plays a critical role in the tumorigenic response as well as in the binding and invasion of host cells by the organism.[119]

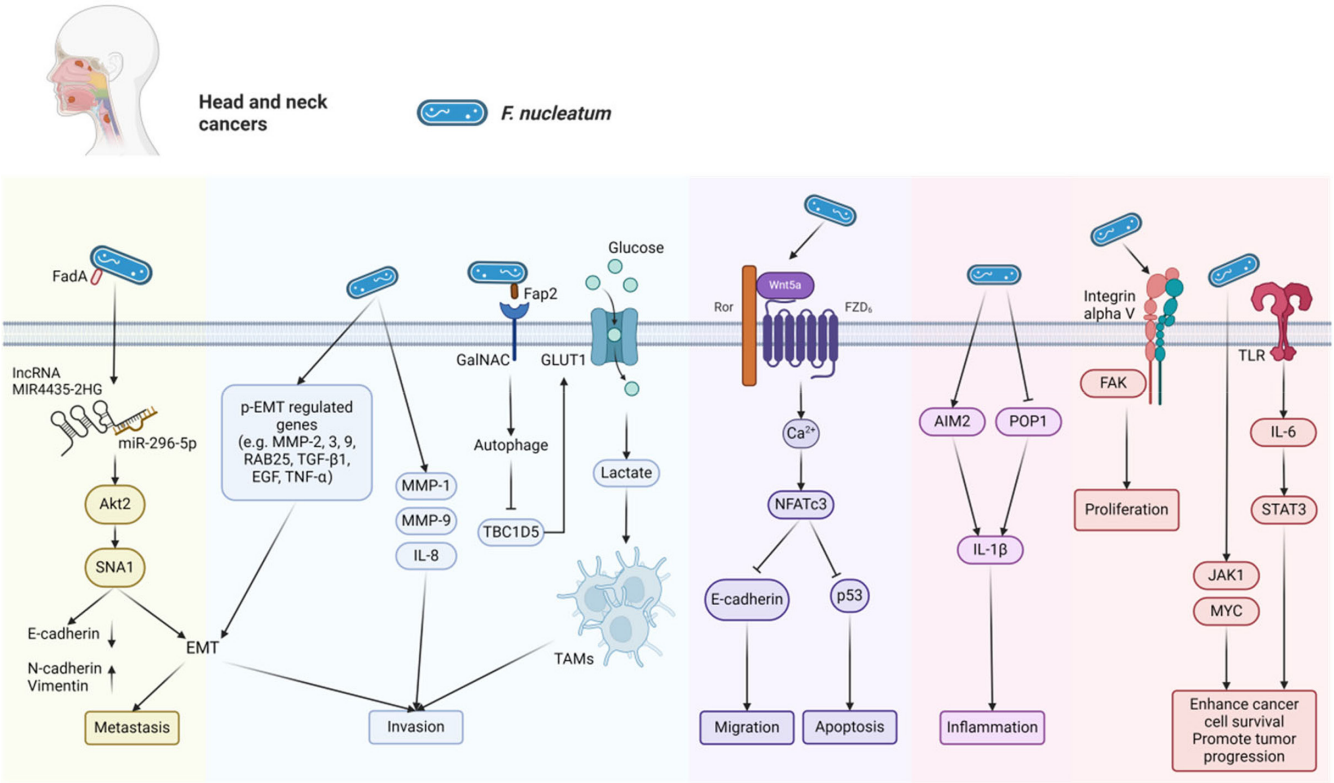

FIGURE 8 Mechanisms by which *Fusobacterium nucleatum* may contribute to head and neck cancer. *Fusobacterium nucleatum* (*F. nucleatum*) infection initiates the epithelial-to-mesenchymal transition (EMT) through the lncRNA MIR4435-2HG/miR-296-5p/Akt2/SNAI1 signaling pathway. The infection with *F. nucleatum* also increased cytokine expression, contributing to EMT induction and increased cancer cell invasiveness. Moreover, *F. nucleatum* triggered GalNAc-Autophagy-TBC1D5 signaling, leading to GLUT1 aggregation on the plasma membrane and extracellular lactate deposition. *F. nucleatum* promotes migration and apoptosis in oral squamous cell carcinoma (OSCC) cells via the Wnt/nuclear factor of activated T cells (NFAT) pathway. Additionally, *F. nucleatum* induces absent in melanoma 2 (AIM2) expression and downregulated pyrin domain (PYD)-only protein 1 (POP1), promoting interleukin-1β (IL-1β) production and inflammation. It also triggers integrin alpha V and focal adhesion kinase (FAK), inducing OSCC cell proliferation. Furthermore, *F. nucleatum* activates toll like receptor (TLR) signaling, resulting in IL-6 production that activates signal transducer and activator of transcription 3 (STAT3), thereby regulating squamous cell carcinoma growth. *F. nucleatum* induces the expression of janus kinase 1 (JAK1) and MYC in oral cancer cells, highlighting its role in promoting tumorigenesis.

By binding to E-cadherin, FadA triggers the activation of β-catenin signaling, influencing both inflammatory and oncogenic responses.[12] Fap2, a galactose-sensitive hemagglutinin and adhesion, can bind with acetylgalactosamine (Gal-GalNAc) to mediate CRC development.[123] The study showed that Fap2 could also bind to human inhibitory receptor T cell immunoglobulin and ITIM domain (TIGIT), including T cells and natural killing (NK) cells.[124] This Fap2-TIGIT interaction shields both *F. nucleatum* and adjacent tumor cells from immune cell-mediated killing.[124] In addition to TIGIT, *F. nucleatum* employs its surface protein CbpF to hinder T and NK cells function through the activation of carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1).[125,126] FomA exhibits the ability to attach to *F. nucleatum*-specific IgA. Additionally, FomA can stimulate intestinal immunity, leading to increased secretion of IgA, which serves as a deterrent to its colonization.[127] These adhesins are also considered to potentially contribute to the carcinogenesis process.[128]

4.2.2 | Proposed carcinogenic mechanisms

Head and neck cancer

Sun et al.[129] observed the accumulation of *F. nucleatum* in the invasive margins of OSCC tissues, correlating with the formation of tumor-associated macrophages (TAMs). They identified that *F. nucleatum* triggered GalNAc-Autophagy-TBC1D5 signaling, resulting in glucose transporter 1 (GLUT1) aggregation on the plasma membrane and extracellular lactate deposition. Concurrent functional inhibition of GalNAc and GLUT1 effectively suppressed TAMs formation and restrained OSCC progression.[129]

Zhang et al.[130] found that *F. nucleatum* infection induces cell migration in both noncancerous human immortalized oral epithelial cells and OSCC cells, without affecting cell proliferation or cell cycle progression. They noted upregulation of mesenchymal markers such as N-cadherin, Vimentin, and snail family transcriptional repressor 1 (SNAI1), along with decreased E-cadherin expression, which translocated to the cytoplasm. Moreover, both FadA adhesin and heat-inactivated *F. nucleatum* showed similar effects to viable bacterial cells. High-throughput sequencing identified upregulated lncRNA *MIR4435-2HG*, which negatively regulated miR-296-5p expression, reduced in *F. nucleatum*-infected human immortalized oral epithelial cells (HIOECs) and SCC-9 cells. Knockdown of *MIR4435-2HG* with siRNA decreased SNAI1 expression, while miR-296-5p indirectly regulated SNAI1 expression via Akt2. Thus, their study suggested that *F. nucleatum* infection can initiate EMT via the lncRNA *MIR4435-2HG*/miR-296-5p/Akt2/SNAI1 signaling pathway, potentially linking *F. nucleatum* infection to the onset of oral epithelial carcinomas. Harrandah et al.[131] demonstrated in vitro that *F. nucleatum* induces the expression of STAT3, janus kinase 1 (JAK1), MYC, and EMT markers in oral cancer cells. Additionally, it enhances the expression of MMP-1, MMP-9, and IL-8, leading to increased cancer cell invasiveness. This in vivo study revealed that both *P. gingivalis* and *F. nucleatum* promote tumor progression. *F. nucleatum* was also observed to trigger TLR signaling, resulting in IL-6 production that activates STAT3, which regulate SCC growth.[93] In HNCSS cell line (H400), *F. nucleatum* increased AIM2 and downregulated POP1, promoting IL-1β.[89] The heat-killed *F. nucleatum* increased cytokines expression which invoveld in EMT-induction, such as TGF-β1, EGF, and TNF-α, and increased MMP-2, -3, and -9 expression in OSCC cell line H400.[96] Geng et al.[132] found that the infection with *F. nucleatum* led to increased expression of γH2AX, a marker for DNA double-strand break, in Tca8113 tongue squamous cell carcinoma cells. This infection promoted cell proliferation and altered the cell cycle, downregulated p27 expression, and decreased the levels of Ku70 and wild-type p53. Overexpression of Ku70 reversed these effects, leading to the upregulation of wild-type p53 and inhibition of cell proliferation. These findings suggest that *F. nucleatum* infection promotes OSCC proliferation via the Ku70/p53 pathway by inducing DNA damage. Another study demonstrated that *F. nucleatum* enhances cisplatin resistance and migration in oral squamous carcinoma cells by downregulating p53 and E-cadherin via the Wnt/nuclear factor of activated T cells (NFAT) pathway. Pretreatment of Cal-27 and HSC-3 cells with *F. nucleatum* significantly increased survival rates against cisplatin. Western blot analysis revealed decreased expression of migration and apoptosis-related proteins E-cadherin and p53. *F. nucleatum* activation of the Wnt/NFAT pathway was observed, with elevated expression levels of wnt5a and Nuclear factors of activated T cells 3 (NFATc3). These findings suggest that *F. nucleatum* promotes cisplatin resistance and migration in oral squamous cell carcinoma cells through the Wnt/NFAT pathway.[133]

P. gingivalis, *T. denticola*, and *F. nucleatum* were observed to enhance the migration, invasion, tumorsphere formation, and tumorigenesis of OSCC cells in vivo. However, they did not significantly impact cell proliferation or apoptosis. Pathogen-induced OSCC cell migration occurred through the activation of integrin alpha V and focal adhesion kinase (FAK). These effects were abolished by stably inhibiting the expression of alpha V or FAK. Moreover, the process was inhibited by nisin, a 34-amino acid polycyclic antimicrobial peptide produced by Gram-positive *Lactococcus* and *Streptococcus* species.[134,135] (Figure 8).

Esophageal cancer

The presence of *F. nucleatum* in EC tissues correlated with shorter survival, suggesting its potential utility as a prognostic biomarker. Through microarray data enrichment analyses of kyoto encyclopedia of genes and genomes (KEGG) pathways, it was identified that *F. nucleatum* may promote aggressive tumor behavior by activating chemokines such aschemokine (C-C motif) ligand 20 (CCL20), a finding confirmed by immunohistochemistry.[34] Nomoto et al.[136] found that *F. nucleatum* invades ESCC cells and triggers the NF-κB pathway, thereby promoting tumor progression both in vivo and in vitro. Moreover, *F. nucleatum* enhances the growth, migration, and invasion capabilities of ESCC cells. The activation of NF-κB by *F. nucleatum* is facilitated through nucleotide oligomerization domain 1 (NOD1) and receptor-interacting protein kinase 2 (RIPK2).

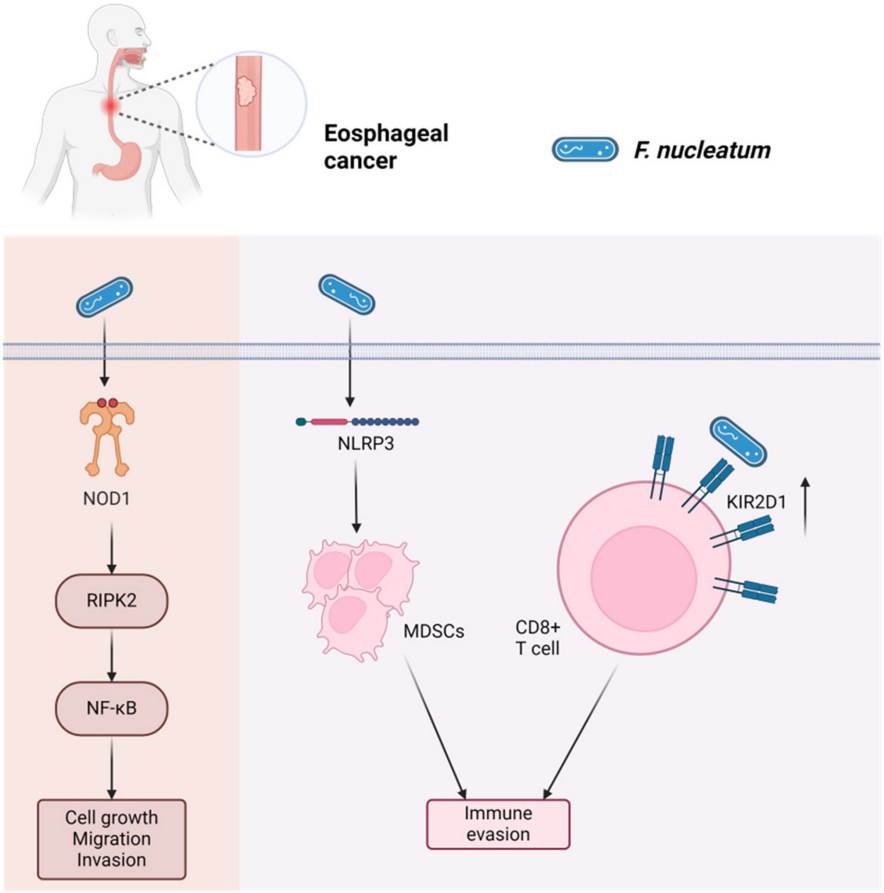

FIGURE 9 Mechanisms by which *Fusobacterium nucleatum* may contribute to esophageal cancer. *Fusobacterium nucleatum* (*F. nucleatum*) activates the nucleotide oligomerization domain 1 (NOD1)/receptor-interacting protein kinase 2 (RIPK2)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, leading to cell growth, migration, and invasion in esophageal cancer. *F. nucleatum* interacts with myeloid-derived suppressor cells (MDSCs) and CD8+ T cells through the nucleotide-binding oligomerization domain, leucine-rich repeat-containing receptor (NLR) family pyrin domain-containing 3 (NLRP3) and KIR2D1 receptors, respectively, resulting in immune evasion.

Liang et al.[137] observed a correlation between *F. nucleatum* infection in ESCC tissues, heightened NLRP3 expression, and an increase in myeloid-derived suppressor cells (MDSC). Both in vitro and in vivo models demonstrated that *F. nucleatum* prompts a significant accumulation of MDSCs by upregulating NLRP3 expression in ESCC cells and reducing their susceptibility to cisplatin (CDDP) therapy. Wang et al.[138] noted that *F. nucleatum* induced the expression of KIR2DL1, a significant inhibitory molecule, on the surface of $CD8^+$ T cells, consequently attenuating their cytotoxic activity. This phenomenon facilitates tumor cell evasion from immune surveillance and diminishes the effectiveness of CDDP therapy. By examining the correlations between the elevated expression of KIR2DL1 on $CD8^+$ T cell surfaces induced by *F. nucleatum* and the clinicopathological characteristics of ESCC patients, they observed that tumors with increased malignancy exhibited a microenvironment conducive to *F. nucleatum* survival and the induction of KIR2DL1 expression on $CD8^+$ T cells (Figure 9).

Colorectal cancer

Fusobacteria from the oral cavity could potentially migrate to CRC sites either through the digestive tract's descent or via the bloodstream during intermittent bacteremia triggered by routine oral activities like chewing, hygiene practices, or dental treatments. In a study by Abed et al.,[139] CRC colonization by *F. nucleatum* was compared between mice inoculated through gavage and intravenous injection in the MC38 and CT26 orthotopic CRC models. The findings indicated that fusobacterial colonization of CRC tumors was more successful through hematogenous dissemination compared to oral administration. These results suggest that the bloodstream may serve as the primary route for oral fusobacteria to reach and colonize colon tumors.

Rubinstein et al.[140] unveiled the mechanism by which *F. nucleatum* adheres to and invades CRC cells, stimulating oncogenic cell proliferation and inflammatory responses both in vivo and in vitro through its distinct FadA adhesin. This adhesin binds specifically to E-cadherin, activating β-catenin signaling and modulating inflammatory and oncogenic pathways. An unrecognized modulator of Wnt/β-catenin signaling, annexin A1, plays a key role in *F. nucleatum*'s stimulatory effect by promoting Cyclin D1 activation in proliferating colorectal cancer cells. Subsequent work by Rubinstein et al.[141] further demonstrated that the FadA adhesin from *F. nucleatum* increased annexin A1 expression via E-cadherin. Interestingly, this positive feedback loop between FadA and annexin A1 was exclusively detected in cancerous cells, while it was absent in non-cancerous cells. Based on these findings, they proposed a "two-hit" hypothesis for colorectal carcinogenesis, wherein the initial "hit" involves the accumulation of host driver mutations, such as increased annexin A1 expression. Subsequently, microbes like *F. nucleatum* represent the second "hit," exacerbating the progression of cancer.[141] Abed et al.[142] identified a host polysaccharide and fusobacterial lectin responsible for the abundance of *fusobacteria* in CRC. *Fusobacterial* Fap2 recognizes Gal-GalNAc, highly expressed in CRC, acting as a Gal-GalNAc lectin. Strains lacking Fap2 or with inactivated

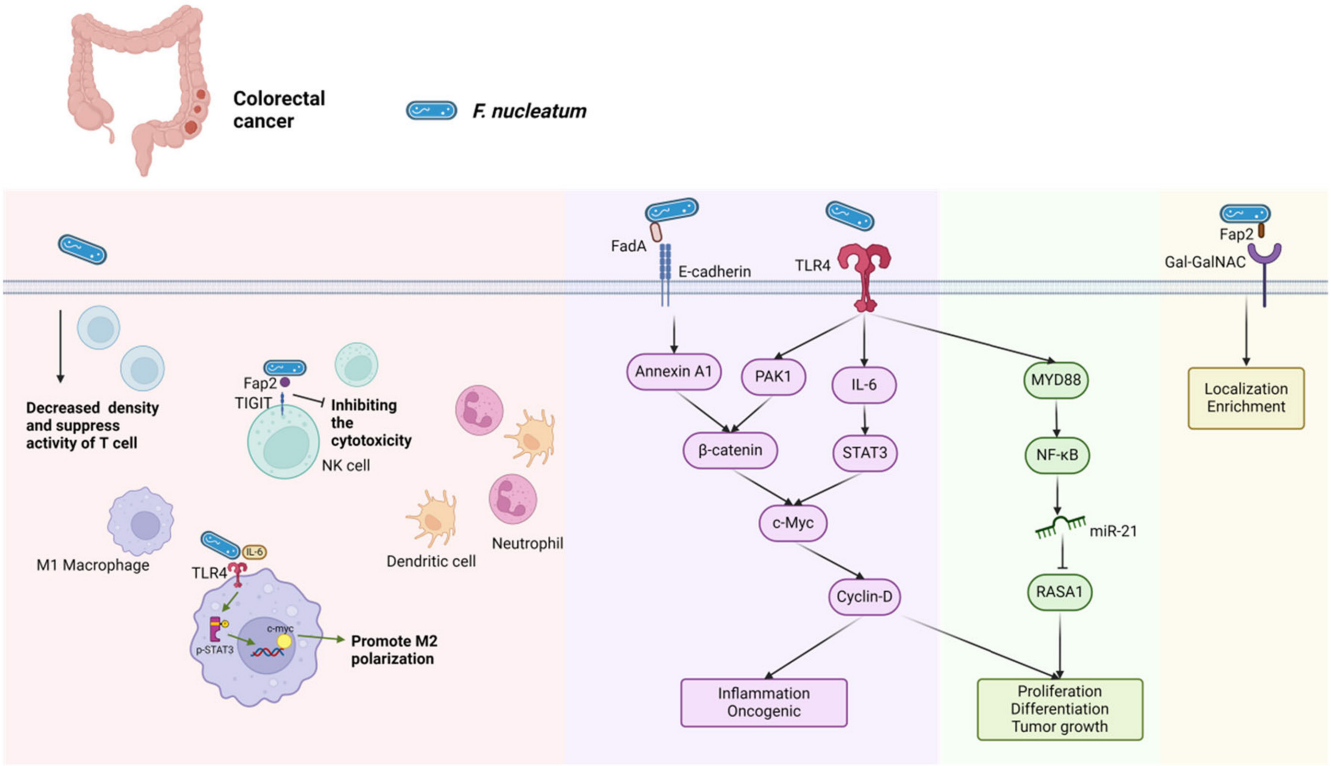

FIGURE 10 Mechanisms by which *Fusobacterium nucleatum* may contribute to colorectal cancer. The invasion of *Fusobacterium nucleatum* (*F. nucleatum*) selectively recruits myeloid cells into the tumor microenvironment. Upon interaction with immune cells, *F. nucleatum* leads to reduced T cell density, heightened M2 macrophage polarization, suppression of natural killer (NK) cell activity, and increased dendritic cells and tumor-associated neutrophils, collectively dampening anti-tumor immunity. The adhesin FadA of *F. nucleatum* interacts with E-cadherin on host cells, leading to the activation of annexin A1. This activation regulates β-catenin and subsequent downstream signaling pathways in proliferating colorectal cancer cells. Exposure to *F. nucleatum* increases the protein abundance of toll like receptor (TLR) 4/P-PAK1/P-β-catenin S675/c-Myc/CyclinD1, promoting inflammation, and oncogenic transformation. *F. nucleatum* also activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, upregulating miR-21, which in turn decrease RASA1. This cascade ultimately increases proliferation, differentiation, and tumor growth. Additionally, *F. nucleatum* interacts with the Gal-GalNAc pathway, contributing to its localization and enrichment within the tumor microenvironment. *Adapted from* Ref. [276].

Fap2 mutants exhibit reduced binding to Gal-GalNAc-expressing CRC cells and established CRCs in murine models. Moreover, intravenously administered *F. nucleatum* localizes to mouse tumor tissues in a Fap2-dependent manner, suggesting *fusobacteria* utilize a hematogenous route to colon adenocarcinomas. Chen et al.[143] observed elevated levels of TLR4, p21-activated kinase 1 (PAK1), and nuclear β-catenin proteins in *F. nucleatum*-positive CRCs. Exposure to *F. nucleatum* or its lipopolysaccharide resulted in increased protein abundance of TLR4/P-PAK1/P-β-catenin S675/c-Myc/CyclinD1, along with enhanced nuclear translocation of β-catenin. Pre-treatment with TLR4 or PAK1 inhibitors reduced the protein abundance of P-β-catenin S675, c-Myc, and Cyclin D1, and nuclear β-catenin accumulation. Inhibition of TLR4 also reduced P-PAK1 protein abundance, suggesting invasive *F. nucleatum* activates β-catenin signaling through a TLR4/P-PAK1/P-β-catenin S675 cascade in CRC. TLR4 and PAK1 may serve as potential therapeutic targets for the treatment of *F. nucleatum*-related CRCs. Besides, Yang et al.[144] discovered that activation of TLR4 signaling by *F. nucleatum* leads to MYD88 activation, subsequently triggering NF-κB and upregulating miR21 expression. This miRNA decreases RAS GTPase RASA1 levels, which plays a crucial role in regulating cell proliferation, differentiation, and apoptosis. Patients exhibiting both high levels of tissue *F. nucleatum* DNA and miR21 expression showed a heightened risk for poor outcomes. Furthermore, *F. nucleatum* also plays a regulatory role in immune responses. Chen et al.[145] observed an increase in M2 polarization of macrophages upon *F. nucleatum* infection both in vitro and in vivo. Moreover, *F. nucleatum* infection augmented colorectal tumor growth through a TLR4-dependent mechanism, involving the activation of the IL-6/p-STAT3/c-Myc signaling. *F. nucleatum* also plays a selective role in recruiting tumor-infiltrating myeloid cells, particularly CD11b+ cells such as dendritic cells (DCs), macrophages, and granulocytes, thereby promoting tumor progression in CRC mouse models.[146] These $CD11b^+$ myeloid cells play a pivotal role in enhancing tumor development and angiogenesis.[147] Toor et al.[148] observed increased levels of granulocytic myeloid cells, including myeloid-derived suppressor cells (MDSCs), in both the tumor microenvironment and peripheral blood of CRC patients. MDCSs, known for their potent immune suppressive activity, exhibit significant T cell suppressive capabilities. This aligns with findings that *F. nucleatum* impedes the accumulation of tumor-infiltrating T cells in breast and colorectal cancer tissues[31,146,149–151] (Figure 10).

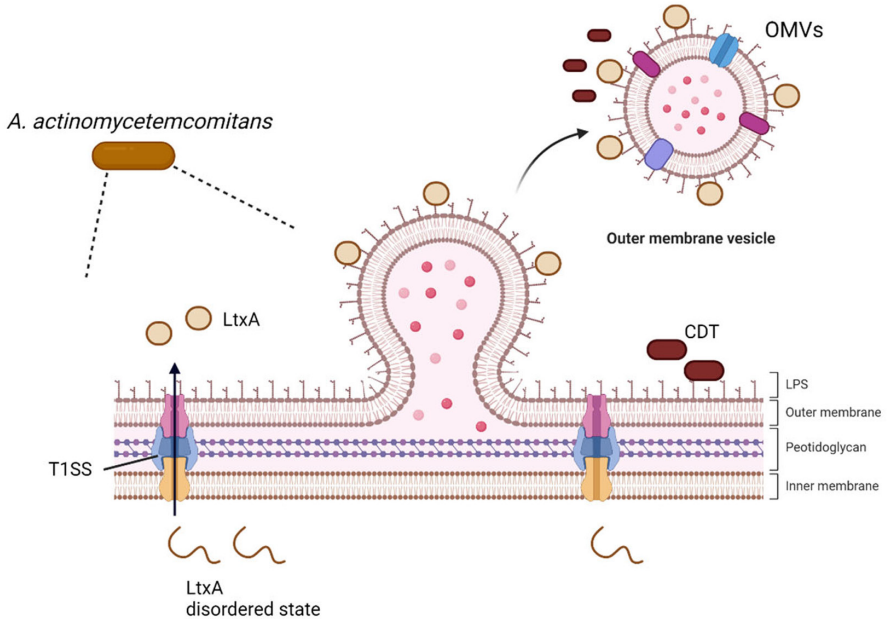

FIGURE 11 Characteristics of *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*). *A. actinomycetemcomitans* possesses several virulence factors, including the potent leukotoxin (LtxA), lipopolysaccharide (LPS), cytolethal distending toxin (CDT), cell surface-associated materials, enzymes, and less well-defined virulence factors capable of influencing the host's defense mechanisms. Additionally, *A. actinomycetemcomitans* OMVs have been observed to transport these virulence factors, ultimately impacting the immune response.

Breast cancer

Parhi et al.[31] observed an increase in Gal-GalNAc levels during the progression of human breast cancer. They found a correlation between the presence of *F. nucleatum* gDNA in breast cancer samples and elevated Gal-GalNAc levels. The study demonstrated Fap2-dependent binding of *F. nucleatum* to breast cancer samples, a process inhibited by GalNAc. Intravascular inoculation of Fap2-expressing *F. nucleatum* ATCC 23726 specifically colonized mammary tumors in mice, while Fap2-deficient bacteria exhibited impaired tumor colonization. Inoculation with *F. nucleatum* suppressed the accumulation of tumor-infiltrating T cells and promoted tumor growth and metastatic progression. In a recent study, Li et al.[152] investigated the impact of extracellular vesicles (EVs) derived from *F. nucleatum* (Fn-EVs) on BC cells. They observed a significant increase in cell viability, proliferation, migration, and invasion in BC cells upon administration of Fn-EVs. Notably, knockdown of TLR4 in BC cells blocked these effects. Furthermore, in vivo experiments confirmed the contributory role of Fn-EVs in promoting tumor growth and metastasis in BC, potentially through their modulation of TLR4 signaling.

Gastric cancer

Liu et al.[153] observed increased counts of neutrophil extracellular traps (NETs) and platelets in *F. nucleatum*-positive GC patients. Extracellular vesicles (EVs) derived from *F. nucleatum*-positive patients were found to promote the differentiation and maturation of megakaryocytes (MKs) and exhibited increased levels of 14-3-3 proteins, particularly 14-3-3ε. In vitro experiments demonstrated that the upregulation of 14-3-3ε promoted MK differentiation and maturation. Additionally, hematopoietic progenitor cells (HPCs) and K562 cells were capable of receiving 14-3-3ε from the EVs, which interacted with GP1BA and 14-3-3ζ to initiate phosphoinositide 3-kinase (PI3K)-Akt signaling. Meng et al.[154] discovered that Fn-EVs significantly enhanced resistance to oxaliplatin and promoted cell proliferation, migration, invasion, and stemness in GC cells. Moreover, Fn-EVs enhanced the stemness and DNA repair capabilities of GC cells. In vivo experiments revealed that administration of Fn-EVs not only promoted the growth of GC tumors and liver metastasis but also conferred resistance to oxaliplatin treatment in GC tumors.

4.3 | *Aggregatibacter actinomycetemcomitans*

4.3.1 | Characteristics of *A. actinomycetemcomitans*

A. actinomycetemcomitans, a gram-negative bacterium, is linked to periodontitis and other systemic diseases, like infective endocarditis and rheumatoid arthritis.[155,156] It generates many virulence factors capable of inducing cell death and either triggering or evading inflammation.[157] The virulence factors of the organism include the potent leukotoxin (LtxA), LPS, cell surface-associated materials, enzymes, and less clearly defined virulence factors that modulate the host defense activity.[158] (Figure 11) LtxA plays a significant role in *A. actinomycetemcomitans* pathogenicity, specifically targeting human immune cells.[159–163] Monocytes/macrophages exhibit high susceptibility to LtxA, resulting in their lysis through the activation of caspase 1 and the secretion of IL-1β.[158,164,165] *A. actinomycetemcomitans* is the only known oral species identified to express cytolethal distending toxin (CDT). CDT primarily induces DNA damage, cell cycle arrest, and eventual apoptosis in the affected host cells.[163,166] Additionally, it is able to impair macrophage function by inhibiting phagocytic activity and altering cytokine balance.[167] CDT can potentially activate another pathogenic mechanism by stimulating the production of pro-inflammatory and osteolytic cytokines in the intoxicated host cells, leading to periodontal breakdown.[168,169] The LPS of *A. actinomycetemcomitans* triggers the production of

proinflammatory mediators, including IL-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α).[170] It also influences nitric oxide production in macrophages, contributing to pathophysiological changes during both acute and chronic inflammation, ultimately leading to tissue damage.[158,171] Experiments have revealed that *A. actinomycetemcomitans* OMVs can transport virulence factors, including LtxA, LPS, CDT, and microRNA-size small RNAs, to host cells, thereby influencing the immune response.[172,173] Investigations indicate that *A. actinomycetemcomitans* infection induces the formation of DNA double-strand breaks in host cells, potentially elevating the risk of carcinogenesis.[174] Analysis of gingival crevicular samples showed a robust association between the pathogen *A. actinomycetemcomitans* and malignancy in 32 out of 99 patients.[175]

4.3.2 | Proposed carcinogenic mechanisms

Stimulation of oral tumor cells with *P. gingivalis* resulted in increased cell proliferation, interestingly, *A. actinomycetemcomitans* enhanced oral tumor cell death. Both bacteria and antimicrobial peptides exerted diverse effects on the transcription levels of oncogenic defensin genes and epidermal growth factor receptor (EGFR) signaling. The primary impact of the two oral pathogens on the proliferation behavior of oral tumor cells was opposite. However, they both induced similar secondary effects on the proliferation rate by modulating the extent of oncogenic important α-defensin gene expression.[90] *A. actinomycetemcomitans* produces the cytolethal distending toxin (Cdt), consisting three proteins: CdtA, CdtB, and CdtC, which induce cell cycle arrest and apoptosis. In a study by Yamamoto et al.,[176] it was demonstrated that delivering the CdtB protein and transfecting the *cdtB* gene could lead to cell cycle arrest and apoptosis in Ca9-22 cells in vitro. They proposed the potential use of electroporation to induce apoptosis in human gingival squamous cell carcinoma by introducing the *cdtB* gene.

4.4 | *Tannerella forsythia* and *Treponema denticola*

Tannerella forsythia (*T. forsythia*) and *Treponema denticola* (*T. denticola*) are anaerobic gram-negative bacteria that are associated with the risk of periodontitis and gingivitis.[177–179] *T. forsythia* expresses many virulence factors, including trypsin-like and PrtH proteases, sialidases like SiaH and NanH, Bacteroides surface protein A (BspA), apoptosis-inducing activity, α-D-glucosidase and *N*-acetyl-β-glucosaminidase, a hemagglutinin, components of the bacterial surface layer, and methylglyoxal.[180] Studies demonstrated that *T. forsythia* and other pathogens could enhance bone loss and the formation of abscesses in animals.[181,182] *T. forsythia* has the capability to stimulate pro-inflammatory cytokines, including IL-1ß and IL-6, through $CD4^+$ T helper cells and TNF-α.[180] Research has indicated an upregulation of *Treponema* in saliva and tissue samples of patients with oral or esophageal cancer.[33,183] However, the precise impact of *T. denticola* on OSCC cells remains unclear.

4.4.1 | Proposed carcinogenic mechanisms

T. denticola was found to induce the expression of TLR2, TLR4, and MyD88. Stable suppression of MyD88 significantly inhibited FAK activation induced by *T. denticola* and abolished the pathogen-induced migration. These findings highlight the contribution of periodontal pathogens to a highly aggressive cancer phenotype through the interplay between TLR/MyD88 and integrin/FAK signaling pathways.[134] Peng et al.[184] found that *T. denticola* could invade Cal-27 cells and directly promote cell proliferation, regulate the cell cycle, and inhibit apoptosis. *T. denticola* also promoted the growth of OSCC tumors in mice, and it upregulated Ki67 expression. Mechanistically, *T. denticola* was found to promote the development of OSCC by activating the TGF-β pathway. Researchers have taken interest in *T. denticola* chymotrypsin-like proteinase (*Td*-CTLP) as a significant virulence factor of *T. denticola*. Nieminen et al.[185] observed the

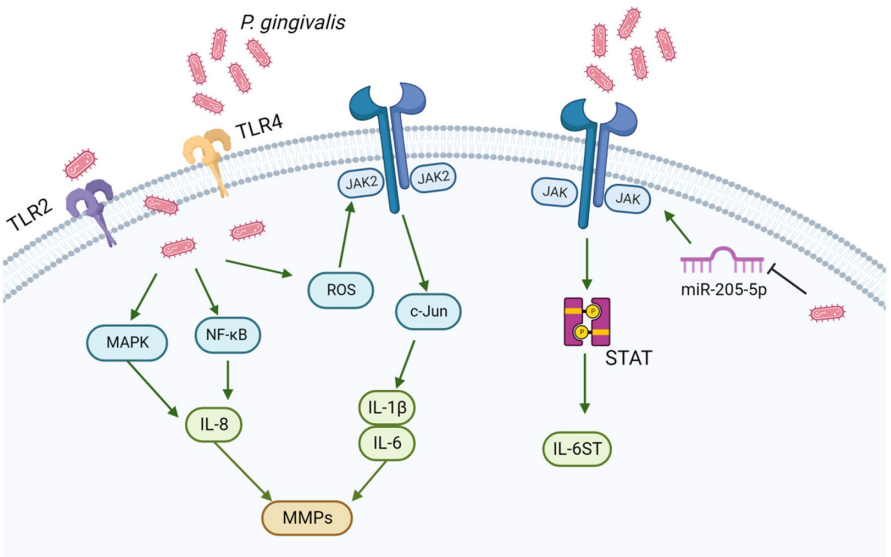

FIGURE 12 Mechanisms linking *P. gingivalis* and inflammation. *P. gingivalis* can promote inflammatory responses via toll like receptor (TLR) 4/TLR2. It can activate mitogen-activated protein kinases (MAPK) and kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways to express interleukin-8 (IL-8) and activate the janus kinase (JAK)/c-Jun signaling axis to elevate IL-1β and IL-6. It also can inhibit miR-205-5p expression from activating JAK/signal transducer and activator of transcription (STAT) by upregulating IL6ST.

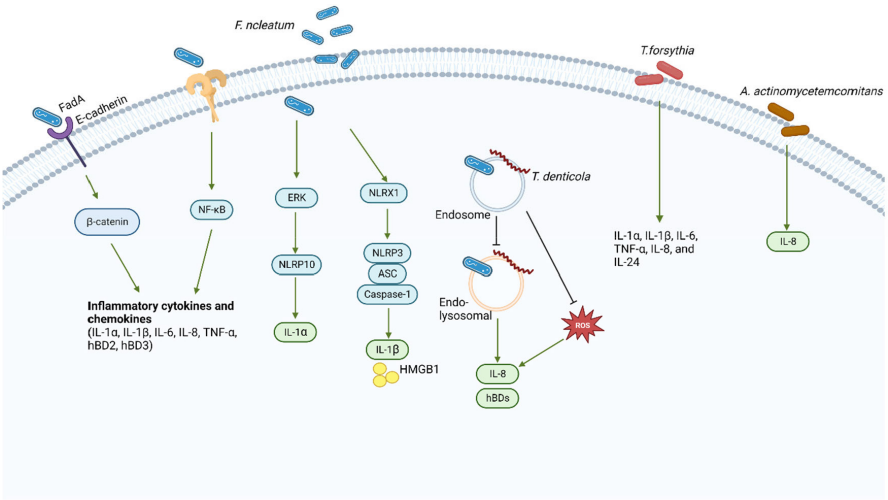

FIGURE 13 Mechanisms that link inflammation and *F. nucleatum*, *T. denticola*, *T. forsythia* and *A. actinomycetemcomitans*. The interaction between fusobacterial adhesin (FadA) and E-cadherin triggers the activation of the β-catenin. *F. nucleatum* initiates the toll like receptor (TLR) pathway, activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), leading to an increase in inflammatory cytokine (interleukin-6 (IL-6), IL-8, IL-10, IL-18, tumor necrosis factor-α (TNF-α), and human β-defensins (hBDs)). Additionally, *F. nucleatum* can elevate IL-1α level by modulating the extracellular regulated protein kinases (ERK) signaling pathway. Furthermore, *F. nucleatum* infection triggers the activation of the nucleotide-binding domain and leucine-rich-repeat-containing family member X1 (NLRX1), which further promotes the formation of NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome, leading to the stimulation of IL-1ß. Co-infection with *T. denticola* and *F. nucleatum* induced expression of hBDs and IL-8 by inhibiting endo-lysosomal maturation and reactive oxygen species (ROS). *T. forsythia* induces various proinflammatory cytokines, including IL-1α, IL-1β, IL-6, TNF-α, IL-8, and IL-24 in different cell types. Clinical isolates of *A. actinomycetemcomitans* may interfere with neutrophil function by immunosuppressing IL-8 responses.

presence of *Td*-CTLP in the majority of orodigestive tumor samples. They found that *Td*-CTLP could activate pro MMP-8 and -9 into their active forms and degrade proteinase inhibitors such as TIMP-1, TIMP-2, and α-1-antichymotrypsin, along with complement C1q. Furthermore, the presence of *Td*-CTLP correlated significantly with the depth of invasion, tumor diameter, and the expression levels of TLR-7, TLR-9, and c-Myc. Additionally, *Td*-CTLP positivity was significantly associated with invasion depth, tumor diameter and the expression of TLR-7, TLR-9 and c-Myc in early-stage mobile tongue squamous cell carcinoma.[177] Overall, *T. denticola* and *Td*-CTLP contribute to creating a tumor tissue microenvironment favorable for invasion and metastasis.

5 | MECHANISMS RELATED TO PERIODONTAL PATHOGENS-LINKED CARCINOGENESIS

In addition to their direct impact on cancer cells, periodontal pathogens have been found to exert various effects on other cell types. These pathogens have been associated with carcinogenesis through various potential mechanisms of action, including the induction of chronic inflammation, suppression of the host's immune system, facilitation of cell invasion and proliferation, anti-apoptotic activity, and the presence of carcinogenic substances. Understanding these diverse effects is essential for unraveling the comprehensive mechanisms underlying cancer development. In this section, we delve into the multifaceted impact of periodontal pathogens on different cell types and potential contributions to carcinogenesis to provide a holistic understanding of how periodontal pathogens contribute to cancer progression.

5.1 | Induction of chronic inflammation

It has become increasingly clear that chronic inflammation significantly increases the risk of carcinogenesis. Uncontrolled inflammation may disrupt stromal integrity, which can promote cancer progression and accelerate the processes of invasion and metastasis.[17,93,186] Periodontal pathogens induce chronic inflammation, especially *Fusobacterium*, *Porphyromonas*, and *Prevotella*.[187,188] These germs have been linked to the up-regulation of various cytokines, including IL-1β, IL-6, IL-17, IL-23, TNF-α, and other inflammatory mediators such as the CXC family, MMP-8, and MMP-9, which may play a role in carcinogenesis.[189–191] Serum IL-6 concentrations are elevated in patients with OSCC and are correlated with a worse prognosis.[192] Additionally, there is an increase in IL-8 levels in the saliva of OSCC patients.[193] The activation of NF-κB is a prominent characteristic in the development of bacteria-associated tumor. During infection, LPS has been known to trigger a robust immune response in human with gram-negative bacteria. Pattern recognition receptors (PRRs) like TLRs, triggering the NF-κB signaling pathway and inducing the production of inflammatory-associated cytokine. This activation plays a pivotal role in the inflammation induced by bacteria and contributes to the carcinogenesis process.[12,194,195]

P. gingivalis activated MAPK and NF-κB signaling pathways, leading to the production of IL-8. Additionally, it stimulates the JAK/c-Jun signaling axis, resulting in elevated levels of IL-1β and IL-6.[196,197] Furthermore, it promotes inflammatory responses through TLR4/TLR2 pathways in host cells.[198–200] In response to infective agents, the host's natural defense mechanism activates inflammatory signaling cascades, utilizing miRNA species as alternative genetic inhibitory transcriptional endpoints.[201] *P. gingivalis* has the capability to suppress the expression of miR-205-5p, leading to the activation of JAK/STAT by upregulating IL6ST[202] (Figure 12).

F. nucleatum is a robust inducer of inflammatory cytokines. *F. nucleatum* infection in gingival epithelial cells (GECs) triggers the activation of NF-κB, which translocates to the nucleus and enhances the expression of pro-inflammatory genes, including those responsible for pro-IL-1β.[93,203] LPS derived from *F. nucleatum* is responsible for cellular-inflammatory response and immune system activation in periodontal diseases.[12,204] This leads to the production of inflammatory cytokines such as IL-1α, IL-1β, IL-6, IL-8, and MMPs through the activation and translocation of NF-κB into the nucleus.[12,205–207] *F. nuleatum* also intensifies TNF-α production from GECs and macrophages, contributing to free radical generation during sepsis.[206,208] NLRP10, the smallest human NLRP, exhibits both anti- and pro-inflammatory functions.[209] It activates the extracellular regulated protein kinases (ERK) signaling pathway in human epithelial cells infected with *F. nuleatum*, leading to an elevation in the levels of the pro-inflammatory cytokine IL-1α.[209] Krisanaprakornkit et al.[210] demonstrated that LPS extracted from *F. nucleatum*'s cell wall, along with TNF-α, induces human β-defensin 2 (hBD2) and IL-8. Another study demonstrated that the infection of gingival squamous cells with *F. nucleatum* induces the expression of hBD2 and hBD3.[211] As an adhesive bacterium, *F. nuleatum* engages in co-aggregates with various microbial species in the oral cavity.[114] FadA assumes a pivotal role in inducing of tumorigenic responses by binding to E-cadherin and activating β-catenin signaling. This activation leads to a differential regulation of inflammatory and oncogenic responses.[140]

In addition, *F. nucleatum* infection activates the nucleotide-binding domain and leucine-rich-repeat-containing family member X1 (NLRX1). This stimulation additionally boosts the NLRP3 inflammasome, initiating caspase-1 activation, culminating in the processing and liberation of IL-1β in GECs.[203,212] The inflammation is amplified through the release of the danger signals apoptosis-associated speck-like protein containing a carboxy-terminal CARD (ASC) and caspase-1, resulting in the secretion of high mobility group box-1 (HMGB1).[203] HMGB1, a DNA-binding nuclear protein, is implicated in various inflammatory disorders, cell adhesion, and migration.[213] The interaction between HMGB1 and advanced glycation end-product (RAGE) may contribute to oral inflammation and the development of oral cancer[204] (Figure 13).

T. denticola fails to stimulate the generation of innate immune mediators, such as IL-6, IL-8, and hBDs from epithelial cells.[214] Conversely, co-infection with *T. denticola* disrupts endo-lysosomal maturation of *F. nucleatum*-containing endosomes, causing a buildup of intracellular reactive oxygen species (ROS). This accumulation leads to inhibition of hBDs and IL-8 expression in GECs.[215] Upon colonization, *T. denticola* can establish its niche, creating a conducive environment for other plaque bacteria.[214] Pahumunto et al.[216] analysis of 50 clinical strains and 7 reference strains of *A. actinomycetemcomitans* revealed that JP2-like leukotoxin promoter gene, NS1, and NS2 from clinical isolates may interfere with neutrophil function by inducing minimal and immunosuppressing IL-8 responses, thereby enhancing bacteria survival and virulence. *T. forsythia* is recognized for inducing various proinflammatory cytokines, including IL-1α, IL-1β, IL-6, TNF-α, IL-8, and IL-24 in different cell types[217] (Figure 13).

5.2 | Inhibition of the host's immune system

The interaction between the host immune system and microbiota may contribute to the progression of cancer.[187] Periodontal pathogens, such as *P. gingivalis* and *F. nucleatum*, not only initiate proinflammatory immune responses but also trigger or induce immunosuppressive reactions, undermining the anti-tumor immunity.[218,219] Bacterial toxins, like CDT secreted by *A. actinomycetemcomitans*, disrupt the host response by influencing phagocytic activity and altering the balance of cytokines.[167] *A. actinomycetemcomitans*' outer membrane protein 29 (OMP29) and OMP29^{par} can subvert the host immune response by suppressing C-X-C Motif Chemokine Ligand 8 (CXCL-8), crucial in tumor angiogenesis, and modulating genes related to apoptosis and inflammatory response in GECs.[220] The tumor microenvironment, characterized by immunosuppression, plays a pivotal role in tumor immune escape mechanisms.[221] PD-L1 is associated with cell-mediated immune responses, exerting crucial immune-regulatory functions during infection and self-recognition.[222] High PD-L1 expression levels were observed in tissue samples from OSCC.[223] Groeger et al.[224] illustrated that the membrane fraction of *P. gingivalis* stimulates the expression of the PD-L1 in squamous carcinoma cells and gingival keratinocytes. Peptidoglycan (PDG) from *P. gingivalis* was found to induce PD-L1 expression in various cancer cells, including OSCCs and colon cancer cells, dependent on NOD1 and NOD2, and the activation of RIP2 and MAPK signaling pathways.[107] While upregulation of the PD-1/PD-L1 pathway may be necessary to limit host damage, inhibiting T cell responses undoubtedly benefits invading pathogens.[225]

P. gingivalis has been demonstrated to dampen the IFN-γ-stimulated release of CXCL9, CXCL10, and CXCL11 from epithelial cells. The inhibition of chemokine expression operates at the gene transcription level and correlates with the down-regulation of IRF-1 and a decrease in STAT1 levels.[226] The nucleoside diphosphate kinase (NDK) secreted by *P. gingivalis* has been implicated in promoting tumorigenesis. NDK inhibits ATP activation of purinergic receptor (P2X7), subsequently suppressing the production of IL-1ß in the epithelium.[227,228] Arjunan et al.[229] demonstrated that *P. gingivalis*, through Mfa1 and FimA fimbriae, fosters immunosuppression and oncogenic cell proliferation in myeloid-derived dendritic suppressor cells.

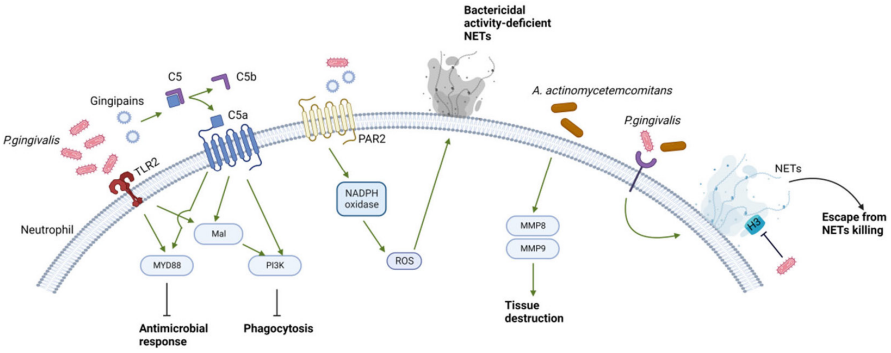

FIGURE 14 *P. gingivalis* and *A. actinomycetemcomitans* escape the killing by neutrophils. *P. gingivalis* triggers a crosstalk between toll like receptor 2 (TLR2) and C5aR, modulating the signaling pathways of myeloid differentiation primary response 88 (MyD88) and phosphatidylinositol 3-kinase (PI3K). Furthermore, *P. gingivalis* employs histone H3 citrullination, facilitated by PPAD, to evade neutrophil extracellular traps (NETs). Additionally, gingipains from *P. gingivalis* activate protease-activated receptor 2 (PAR-2) and Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, resulting in the formation of NETs lacking bactericidal activity. *A. actinomycetemcomitans* similarly induces NETs formation and the secretion of matrix metalloprotease (MMP)-8 and MMP-9 in neutrophils, potentially contributing to tissue destruction and disease progression. *Adapted from* Ref. [232].

Neutrophils play a vital role in defending periodontal tissues through the innate immune system, engaging in phagocytosis, bacterial killing, and digestion.[230,231] *P. gingivalis* disrupts the antimicrobial response of macrophages, hindering antigen presentation and T-cell activation by manipulating the C5aR/TLR2 crosstalk. This modulation involves the regulation of MyD88 and PI3K signaling pathways. The downstream molecule MyD88 undergoes degradation via ubiquitination, inhibiting the host-protective antimicrobial response.[232] The crosstalk between C5aR and TLR2, triggered by *P. gingivalis*, also activates PI3K, leading to reduced phagocytosis of *P. gingivalis* by neutrophils.[232–234] Additionally, *P. gingivalis* citrullinates histone H3, impairing the bactericidal components in neutrophil extracellular traps (NETs) and thereby weakening their effectiveness.[87,232] NETs, web-like structures released by neutrophils during infection, aid in capturing and killing pathogens.[232] Gingipains activate protease-activated receptor 2 (PAR-2), triggering Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, increasing ROS levels, and promoting NETs formation.[232,235] However, NETs induced by *P. gingivalis* lack bactericidal activity.[235] *A. actinomycetemcomitans* can also induce NETs formation and the release of MMP-8 and -9 in neutrophils alone, potentially contributing to tissue destruction and disease progression[236] (Figure 14).

P. gingivalis employs various strategies to evade immune detection and manipulate host responses. The utilization of lipid A structures enables evasion from immune detection via TLR4.[237] Additionally, gingipains produced by *P. gingivalis* degrade CD14 on macrophage surfaces, hindering the phagocytosis of infected apoptotic cells.[232,238,239] Furthermore, the fimbria and sialidase of *P. gingivalis* contribute to immune evasion through the exploitation of CXCR4 and CR3. The binding to CXCR4 activates cAMP-dependent protein kinase A (PKA) signaling, which inhibits TLR2-mediated proinflammatory and antimicrobial responses.[240–242] During the inflammatory process, *P. gingivalis* triggers IL-12 secretion, playing a crucial role in macrophage clearance of bacteria and stimulating T cells to produce IFN-γ.[241,243] The release of sialidase enhances *P. gingivalis* virulence, reducing IL-12 production and influencing T-cell responses.[241] Moreover, *P. gingivalis* inhibits T-cell antimicrobial responses by down-regulating IL-2 expression, achieved through the prevention of protein kinase C and p38 phosphorylation and AP-1.[244] Additionally, the up-regulation of IL-10 by *P. gingivalis* in macrophages inhibits antigen presentation and T-cell activation.[232] The increased IL-10 production induced by *P. gingivalis* activates PD-L1 on macrophages and PD-1 on $CD4^+$T cell surfaces, indicating multiple inhibitory mechanisms employed by *P. gingivalis* to evade the host's immune response.[245]

5.3 | Cell invasion and proliferation

In addition to prolonged cellular survival, *P. gingivalis* induces heightened proliferation in infected epithelial cells.[246] The FimA fimbriae of *P. gingivalis* elevate the proliferation rate of GECs, accelerating progression through the S-phase. This effect is associated with a reduction in p53 levels and activation of the PI3K pathway.[247] *P. ginglivalis* LPS enhanced the proliferation of gingival stem/progenitor cells without compromising their regenerative capacity through NF-κB.[248] Exposure of immortalized OKF6 cells to *P. gingivalis* resulted in changes in the molecular profile of proteins associated with cell proliferation, EMT, stem cell generation, migration, invasion, and resistance to anoikis. This alteration was accompanied by increased rates of proliferation, which correlated with the activation of the PI3K/Akt signaling pathway and the mTOR pathway.[249] *F. nucleatum* enhances cell proliferation by activating p38, followed by HSP27, which plays a significant role in cell proliferation, differentiation, and oncogenesis.[250] This activation is associated with the secretion of MMP-9 and MMP-13, both contributing to the invasion and metastasis phenotype.[251] Moreover, *F. nucleatum* stimulation promotes cellular migration

through the activation of epithelial and endothelial tyrosine kinase/bone marrow X kinase (Etk/BMX), S6 kinase p70, and RhoA kinase.[251] This interaction with human epithelial cells during *F. nucleatum* infection results in the up-regulation of 12 kinases, as evaluated by the Kinetworks immunoblotting system, which are involved in cell migration, proliferation, and cell survival signaling.[251,252] The interaction of *F. nucleatum* with the epithelial cell surface CD46, as observed by Mahtout et al.,[253] may contribute to the elevation of proinflammatory mediators and MMPs in periodontal sites, subsequently modulating tissue destruction. Jia et al.[254] reported that the cultured media derived from *P. gingivalis* can lead to the malignant transformation of normal esophageal epithelial cells. This transformation is characterized by increased proliferation and migration of the cells, as well as the appearance of aneuploid cells. In addition, mouse esophageal epithelial cells exposed to *P. gingivalis* cultured media exhibited disordered arrangement, increased proliferation, and weakened expression of Claudin 1 and Claudin 4, both associated with dysplasia. Furthermore, the expression of cancer-related genes was upregulated, while tight junction-related genes were downregulated. Notably, aberrant activation of the sonic hedgehog pathway was observed, and its inhibition attenuated the pathogenic effect of *P. gingivalis* cultured media in normal esophageal epithelium (Figure 15).

5.4 | Anti-apoptotic activity

Apoptosis plays a crucial role in various biological processes, including normal cell turnover, immune system development and function, embryological development, and responses to viral and bacterial infections. Dysregulation of apoptosis, either insufficient or excessive, contributes to the pathogenesis of many cancer types.[255] *P. gingivalis* exerts an anti-apoptotic effect by influencing multiple pathways. The suppression of apoptosis is facilitated by the degradation of ATP mediated by NDK, an enzyme released by *P. gingivalis*, specifically inhibiting apoptosis dependent on ATP activation of P2X7 receptors.[256] Additionally, the phosphorylation of HSP27 by *P. gingivalis*-derived NDK imparts an anti-apoptotic phenotype to primary GECs, underscoring the significance of HSP27 in mitigating host cell apoptosis induced by *P. gingivalis*.[228,257] Another mechanism by which *P. gingivalis* can block the apoptotic pathway in GECs is through modulating the JAK/STAT pathway, leading to the blockade of caspase-3 activation and subsequent control of the intrinsic mitochondrial cell death pathways.[258] Furthermore, *P. gingivalis* inhibits apoptosis and enhances the survival of GECs by activating Akt via PI3K, potentially through the inhibition of mitochondrial permeability alterations.[259] Jewett et al.[260] illustrated that *F. nucleatum*'s immunosuppressive role primarily stems from its ability to trigger apoptotic cell death in peripheral blood mononuclear cells (PBMCs) and polymorphonuclear cells (PMNs).

5.5 | Carcinogenic substances

Metabolic derivatives from certain periodontal pathogens, such as organic acids, volatile sulfur compounds (VSC), and ROS, possess the potential to induce DNA damage, mutagenesis, secondary hyperproliferation of the cells, metastasis, and cancer progression.[187,218,261] Microorganisms involved in alcohol metabolism to acetaldehyde can impact cancer development.[187] VSC-producing periodontal pathogens like *P. gingivalis*, *Prevotella intermedia*, *A. actinomycetemcomitans*, and *F. nucleatum* generate VSCs like hydrogen sulfide, methyl mercaptan, dimethyl sulfide, and dimethyl disulfide.[188] Research indicates that these VSCs influence epithelial cell proliferation and induce apoptosis through the activation of the mitochondrial pathway.[262,263] Notably, VSCs, including methyl mercaptan, contribute to connective tissue breakdown and inflammation by stimulating the release of IL-1ß from mononuclear cells.[264,265]

ROS typically function as signals to regulate cell proliferation and survival, playing a pivotal role in biological processes and host innate immune responses when induced by pathogens. Both a lower and a higher percentage of ROS can have adverse effects. When ROS levels are low, they fail to support proper cellular functioning by regulating numerous biochemical reactions.[266] However, an excessive amount of ROS can damage cellular components, disrupt normal cellular processes, and lead to cell death.[267–269] Interestingly, ROS dynamically influences the tumor microenvironment, initiating cancer angiogenesis, metastasis, and survival at different concentrations.[270] *P. gingivalis* exhibits the capacity to stimulate ROS production, leading to JAK2 phosphorylation and the upregulation of proinflammatory cytokines such as IL-6 and IL-1ß.[196] The secretion of *P. gingivalis* NDK may modulate eATP-induced cytosolic and mitochondrial ROS, and the antioxidant glutathione response (AGR) generated via the P2X7/NADPH-oxidase interactome.[271] Additionally, *P. gingivalis*-triggered ferritinophagy induces ROS production and inflammatory responses in periodontal ligament fibroblasts.[272] *F. nucleatum* has the ability to induce ROS in colon lining epithelial cells, OSCCs, and human gingival fibroblasts.[72,273,274] Previous study shows that *F. nuleatum* can inhibit human gingival fibroblast proliferation and promote cell apoptosis, ROS production, and inflammatory cytokine production, partly through the activation of the AKT/MAPK and NF-κB signaling pathways.[273] Okinaga et al.[275] demonstrated that *A. actinomycetemcomitans* induces IL-1β production in RAW 264 cells by generating ROS and cathepsin B. *T. forsythia* can stimulate ROS, subsequently inducing the expression of IL-24[217] (Figure 16).

6 | CONCLUSIONS

Cancer, characterized by its multi-step and generally slowly progressing, involves a complex interplay of genetic and environmental factors.[246] Periodontal pathogens exert direct or indirect effects on chronic inflammation, the human immune response, cell invasion and proliferation, anti-apoptotic activity, and the presence

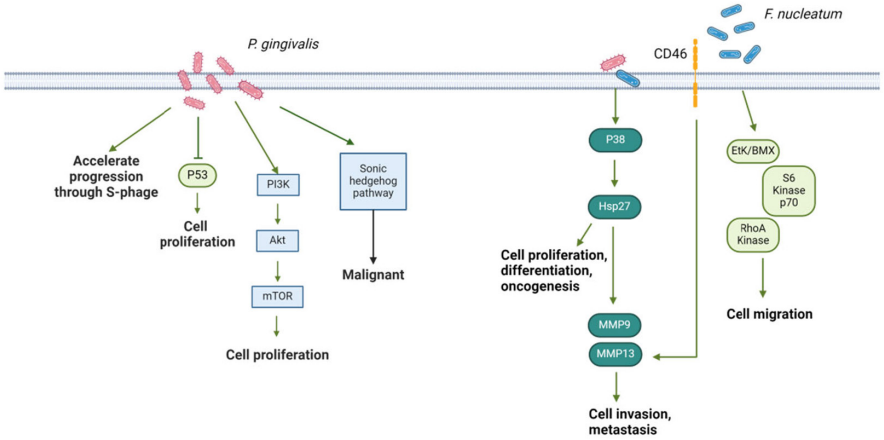

FIGURE 15 Mechanisms related to periodontal pathogens and cell invasion and proliferation. *P. gingivalis* induces cell proliferation by reducing p53 levels and activating the PI3K pathway, while *F. nucleatum* enhances proliferation through p38 activation and MMP secretion. Both bacteria promote migration via various kinase pathways. *P. gingivalis* cultured media lead to malignant transformation of esophageal cells by cancer-related genes, involving aberrant sonic hedgehog pathway activation.

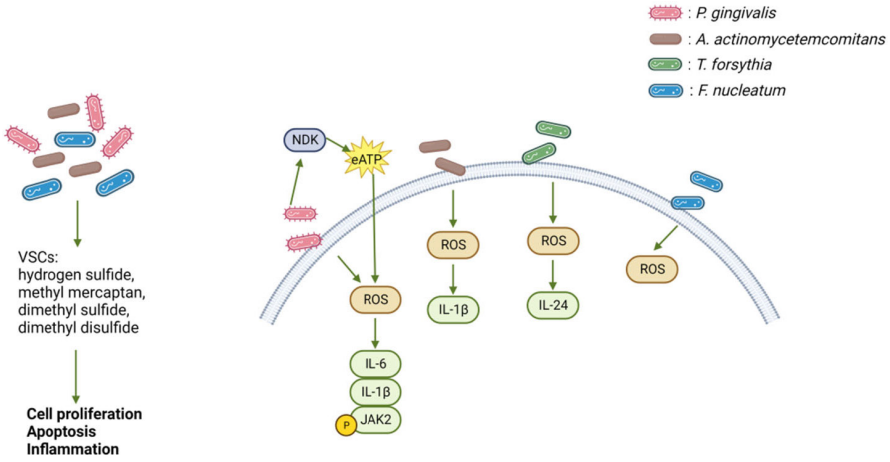

FIGURE 16 Periodontal pathogen's metabolic derivatives affect cancer development. Periodontal pathogens (e.g., *P. gingivalis*, *A. actinomycetemcomitans*, and *F. nucleatum*) produce volatile sulfur compounds (VSCs) impact cell proliferation, induce apoptosis, and trigger the release of inflammatory cytokines. Additionally, *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythia* and *F. nucleatum* can stimulate the production of reactive oxygen species (ROS), exerting a dynamic influence on the tumor microenvironment.

of carcinogenic substances, all of which precede cancer development. Although establishing a clear link between periodontal pathogens and carcinoma development poses a challenge, specific pathogens such as *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans*, *T. forsythia*, and *T. denticola* have been identified to promote diverse signaling pathways that may contribute to carcinoma development. Further exploration of the pathogenic mechanisms employed by periodontal pathogens is essential, holding the potential to unveil various pathways crucial for diagnostic, preventive, and therapeutic strategies. These insights will not only enhance the efficacy of treatment but also contribute to advancements in survival outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in the current study.

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