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Review

From Inflamed Gingiva to Invasive Malignancy: Molecular Crosstalk in Oral Carcinogenesis: A Scoping Review

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Abstract

Oral squamous cell carcinoma (OSCC) develops within a complex inflammatory microenvironment where chronic mucosal inflammation and microbial dysbiosis may contribute to malignant transformation. Increasing evidence suggests that periodontal pathogens associated with chronic gingival inflammation can influence epithelial signaling, immune responses, and tumor progression. This scoping review aimed to map current molecular, genomic, and immunological evidence linking chronic gingival inflammation and periodontal pathogen–associated dysbiosis to OSCC. Following the Population-Concept-Context (PCC) framework, electronic searches were conducted in PubMed, Scopus, and Web of Science through February 2026. Original studies investigating mechanistic links between periodontal inflammation, microbial dysbiosis, and OSCC in human samples, *in vitro* models, or animal models were included. Data were extracted on microbial drivers, oncogenic signaling pathways, immune modulation, and genomic or epigenetic alterations. A total of 46 studies were included, suggesting that periodontal pathogens, particularly *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, may activate oncogenic signaling pathways such as NF-κB, PI3K/Akt, Wnt/β-catenin, and TGF-β. Evidence from *in vitro*, animal, and human studies indicates that these pathways may contribute to epithelial-mesenchymal transition (EMT), tumor invasion, and resistance to apoptosis. Microbial exposure has also been associated with modulation of the tumor immune microenvironment, including macrophage polarization, suppression of cytotoxic T-cell responses, and enhanced immune checkpoint signaling. In addition, genomic and transcriptomic studies have identified dysregulated genes and microRNAs associated with inflammation-driven carcinogenesis. Overall, chronic gingival inflammation and periodontal dysbiosis appear to contribute to OSCC development through interconnected mechanisms involving inflammatory and cytokine signalling, microbe sensing and innate immune activation, immune suppression and tumor immune escape, EMT, invasion and metastatic signaling, and metabolic reprogramming with regulatory networks. However, as current evidence is largely derived from *in vitro* and animal studies with limited prospective clinical data, well-designed longitudinal human studies are needed to confirm these associations and support biomarkers discovery and novel preventive or therapeutic strategies targeting early oncogenic events in inflamed oral tissues.

Keywords: oral squamous cell carcinoma; inflammation; dysbiosis; epithelial–mesenchymal transition; signaling pathway; biomarkers

1. Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity and accounts for the majority of head and neck cancers worldwide [1]. Despite continuous advances in surgical management, radiotherapy protocols, and systemic therapies, overall survival rates have improved only modestly over recent decades, largely due to late-stage diagnosis and high rates of local invasion and recurrence [2]. While tobacco use, alcohol consumption, and high-risk human papillomavirus (HPV) infection are well-established etiological factors, a growing body of evidence suggests that these classical risk factors do not fully explain the biological heterogeneity and progression patterns observed in OSCC. Increasing attention has therefore shifted toward the role of chronic inflammation as a fundamental enabling condition in oral carcinogenesis and systemic diseases such as cardiovascular disease [3,4].

Chronic inflammation is increasingly recognized as a critical factor that promotes cancer. Persistent inflammatory signalling fosters a tissue microenvironment characterized by sustained cytokine release, oxidative stress, proteolytic enzyme activation, and aberrant immune cell recruitment [5]. This promotes genomic instability, epigenetic alterations, dysregulated cell proliferation, resistance to apoptosis, angiogenesis, and extracellular matrix remodelling [6]. At the molecular level, inflammatory mediators activate cancer-related signalling cascades, including nuclear factor kappa B (NF-κB), phospho-

inositide 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), signal transducer and activator of transcription 3 (STAT3), Wingless/Integrated (Wnt)/β-catenin, and transforming growth factor-β (TGF-β) pathways [7]. Continuous activation of these pathways enhances epithelial–mesenchymal transition, cellular motility, invasion, metabolic reprogramming, immune evasion, and acquisition of stem-like phenotypes, biological processes that collectively define aggressive tumor behavior. Within the oral mucosal environment, chronic inflammatory stimuli may therefore act not merely as passive observers but as active drivers of malignant transformation and tumor progression [8,9].

Among chronic inflammatory conditions affecting the oral cavity, periodontitis represents one of the most prevalent and biologically sustained sources of local and systemic immune activation. Periodontitis is characterized by a dysbiotic microbial biofilm that disrupts host-microbe homeostasis, leading to persistent immune stimulation and progressive destruction of periodontal tissues [10]. Rather than being attributable to a single pathogen, periodontal disease emerges from complex ecological shifts in the oral microbiota, often driven by central pathogens capable of remodelling microbial communities and modulating host immune responses [11]. Microorganisms such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* have demonstrated the ability to interfere with epithelial barrier integrity, manipulate intracellular signalling networks, suppress apoptosis, and promote inflammatory cytokine production [12,13].

Beyond direct epithelial signalling, chronic periodontal inflammation reshapes the local immune microenvironment. Sustained infiltration of neutrophils, macrophages, and lymphocytes, along with elevated levels of IL-6, TNF-α, IL-1β, and matrix metalloproteinases, contributes to a pro-tumorigenic niche [13,14]. This inflammatory context may facilitate immune dysregulation, impair effective anti-tumor surveillance, and support tumor-promoting immune phenotypes. Additionally, reactive oxygen and nitrogen species generated during chronic inflammation can induce DNA damage and mutational events, further linking periodontal pathology with carcinogenic potential [15]. Importantly, the oral cavity represents a unique anatomical site in which epithelial tissues are continuously exposed to both microbial communities and inflammatory mediators, creating a dynamic interface between dysbiosis and oncogenic transformation [16].

In recent years, experimental, clinical, and omics-based investigations have increasingly explored the mechanistic intersections between periodontal dysbiosis and OSCC [17,18]. *In vitro* studies have shown that exposure of oral epithelial or cancer cell lines to periodontal pathogens induces epithelial-mesenchymal transition (EMT) markers, enhances migratory capacity, increases invasive behaviour, and modulates apoptosis-related proteins [11,19,20]. Animal models suggest that chronic microbial exposure may accelerate tumor growth and alter immune cell composition within the tumor microenvironment [21,22,23]. Preclinical studies have identified correlations between periodontal status, inflammation, and OSCC incidence, as well as associations between specific microbial signatures and tumor tissue profiles [24,25]. Transcriptomic and bioinformatic analyses, including evaluations of cancer genomic datasets, have reported enrichment of inflammatory signalling pathways and immune-related gene expression patterns in tumors harbouring microbial signatures. Emerging evidence also implicates epigenetic mechanisms, such as microRNA dysregulation and DNA methylation changes, as potential mediators bridging chronic inflammation and malignant progression [26,27].

However, despite this expanding body of research, the mechanistic landscape linking gingival inflammation to OSCC remains fragmented. Studies vary widely in design, ranging from *in vitro* experiments and animal models to clinical observational analyses and computational approaches. The specific inflammatory drivers, microbial factors, oncogenic pathways, and tumor processes investigated are often heterogeneous and reported in isolation [28]. Consequently, there is a lack of integrative mapping that systematically connects microbial dysbiosis and chronic inflammatory signalling with defined oncogenic cascades, tumor microenvironment alterations, and functional tumor behaviours such as EMT, invasion, immune evasion, and stemness acquisition [5]. Moreover, the translational implications of these mechanistic insights, whether as biomarkers for early detection, risk stratification tools, or therapeutic targets, have not been comprehensively categorized [29].

Given this complexity and heterogeneity, a scoping review methodology is particularly appropriate to explore the breadth of available evidence, identify recurring mechanistic themes, and delineate research gaps. Therefore, the aim of this scoping review is to systematically identify, categorize, and synthesize experimental, clinical, and omics-based studies investigating the molecular and immunological mechanisms linking chronic gingival inflammation and periodontal dysbiosis to oral squamous cell carcinoma progression. By mapping inflammatory drivers, oncogenic signalling pathways, tumor-associated processes, immune microenvironment modulation, and epigenetic alterations within a unified framework, this review seeks to construct a structured mechanistic continuum that may guide future translational research and precision-oriented strategies in oral oncology.

2. Materials and Methods

This scoping review was conducted following the methodological framework of the Joanna Briggs Institute (JBI) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

extension for Scoping Reviews (PRISMA-ScR) checklist (see **Supplementary Material**).

2.1 Objective and Population–Concept–Context Framework

This scoping review aimed to map existing molecular, genomic, and immunological evidence linking chronic gingival inflammation and periodontal dysbiosis to OSCC, with a primary focus on tumor-related mechanisms and translational relevance.

The review was guided by the Population–Concept–Context (PCC) framework [30]:

Population (P): Human OSCC tissues, clinical samples, OSCC cell lines, and animal models of oral carcinogenesis.

Concept (C): Chronic gingival inflammation, periodontitis, periodontal pathogens, and oral microbial dysbiosis as biological drivers of oncogenic signalling, epithelial plasticity, immune modulation, and genomic dysregulation.

Context (C): Experimental and clinical settings investigating molecular mechanisms underlying tumor initiation, progression, invasion, immune evasion, and tumor microenvironment remodelling in OSCC.

2.2 Research Question

The primary research question guiding this review was: What molecular, oncogenic, genomic, and immunological mechanisms link chronic gingival inflammation and periodontal pathogen–associated dysbiosis to tumor initiation, progression, and immune modulation in oral squamous cell carcinoma?

2.3 Eligibility Criteria

Studies were included if they: (1) investigated oral squamous cell carcinoma in human samples, *in vitro* models, or animal models; (2) examined chronic gingival inflammation, periodontitis, periodontal pathogens, or oral microbial dysbiosis as mechanistic drivers; (3) evaluated molecular, genomic, transcriptomic, or immunological pathways relevant to tumor biology; (4) reported activation of oncogenic signalling pathways (e.g., NF-κB, PI3K/Akt, MAPK, STAT3, Wnt/β-catenin, TGF-β, p53) or tumor-associated processes such as epithelial–mesenchymal transition, invasion, proliferation, stemness, apoptosis resistance, metabolic reprogramming, or immune microenvironment modulation; (5) were original research articles published in English or Chinese.

Exclusion criteria were: (1) narrative reviews, systematic reviews, or meta-analyses; (2) case reports or case series without mechanistic investigation; (3) purely epidemiological association studies lacking molecular or oncogenic analysis; (4) studies not specifically addressing OSCC; (5) articles not available in full text in English.

2.4 Information Sources and Search Strategy

An electronic literature search was conducted in PubMed, Scopus, and Web of Science databases up to and including February 2026. No time restrictions were applied. The complete search strategies for each database are provided in **Supplementary Table 1**. The search strategy combined MeSH terms and free-text keywords related to oral squamous cell carcinoma, periodontitis, gingival inflammation, periodontal pathogens (e.g., *Porphyromonas gingivalis*, *Fusobacterium nucleatum*), oral dysbiosis, and inflammation. Boolean operators (AND, OR) were applied according to each database's syntax rules. Grey literature sources were not included in the search strategy.

2.5 Article Selection

All retrieved records were exported into Mendeley Reference Manager version 2.143.0 (Elsevier, Amsterdam, the Netherlands). After removal of duplicates, titles and abstracts were independently screened by two reviewers to identify potentially eligible studies. Subsequently, full-text articles meeting the inclusion criteria were independently assessed for eligibility by the same reviewers. Any disagreements at any stage of the selection process were resolved through discussion or by consultation with a third reviewer.

2.6 Data Charting and Extraction

A standardized data charting form was developed before full extraction. Data extraction was independently performed by two reviewers using the predefined form. Any discrepancies were resolved through discussion or by consultation with a third reviewer.

2.7 Protocol Registration and Quality Appraisal

This scoping review was not prospectively registered. In accordance with Joanna Briggs Institute guidance for scoping reviews, a formal methodological quality appraisal or risk-of-bias assessment of included studies was not performed, as the primary objective was to map and synthesize the breadth of available evidence rather than to evaluate the quality of evidence or estimate effect sizes.

3. Results

3.1 Study Selection

The initial database search identified 1093 records across PubMed, Scopus, and Web of Science. After removal of 625 duplicate records, 468 studies remained for title and abstract screening. At this stage, 365 records were excluded due to irrelevance to full text not available, studies not specifically addressing OSCC, purely epidemiological association studies lacking molecular or oncogenic analysis, narrative reviews, systematic reviews, or meta-analyses.

Following full-text assessment of 103 articles for eligibility, 46 studies met the inclusion crite-

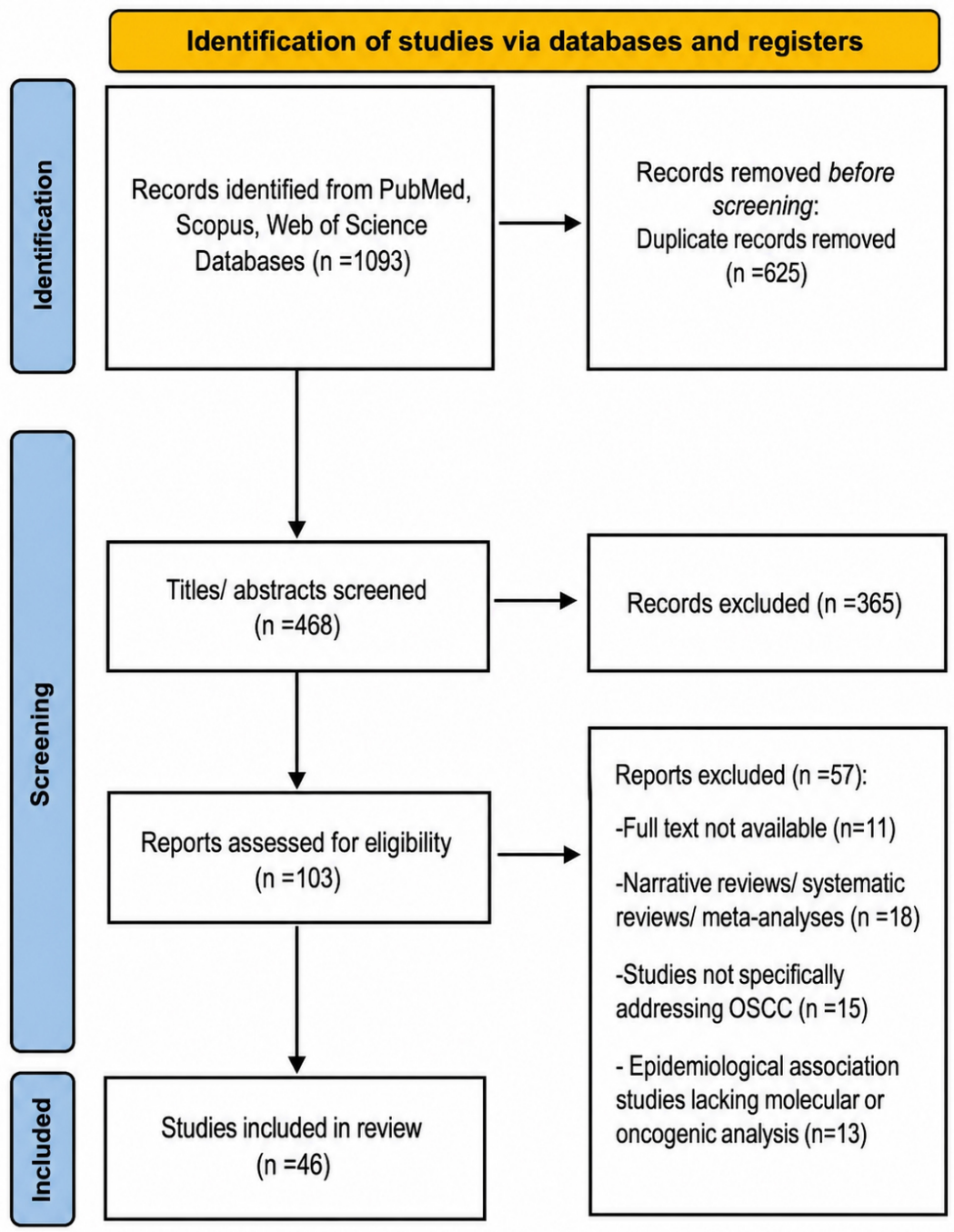

Fig. 1. PRISMA-ScR flow diagram of the articles' identification. OSCC, oral squamous cell carcinoma; PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

ria and were included in the final scoping review [3,5,8,11,16,18,21,23,24,25,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66]. The study selection process is summarized in Fig. 1 (PRISMA flow diagram).

3.2 Characteristics of the Included Studies

The 46 included studies, published between 2014 and 2026, investigated the mechanistic relationship between chronic gingival inflammation, periodontal pathogens, and OSCC. The studies employed a range of methodological designs, including clinical investigations, *in vitro*, *in vivo* models, and bioinformatic or multi-omics analyses. Experimental studies frequently utilized established OSCC cell lines and murine models to evaluate microbial interactions, oncogenic signaling pathways, and tumor microenvironment modulation. Clinical investigations commonly analyzed tumor tissues, saliva samples, or oral microbiome profiles from patients with OSCC.

Table 1. Summary of the principal mechanistic pathways linking periodontal dysbiosis and chronic gingival inflammation to oral squamous cell carcinoma.

Mechanistic theme	Representative studies
Inflammatory and cytokine signaling axis	[21,37,49,53]
Microbe sensing and innate immune activation	[21,25,31,38,41,43,55,59]
Immune suppression and tumor immune escape	[25,41,60,61]
EMT, invasion and metastatic signaling	[37,43,44,60]
Metabolic reprogramming and regulatory networks	[32,35,38]

EMT, epithelial-mesenchymal transition.

Across the included studies, particular attention was given to periodontal pathogens associated with oral microbial dysbiosis, most notably *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Prevotella intermedia*. These microorganisms were investigated for their potential roles in activating oncogenic signaling pathways, promoting epithelial–mesenchymal transition, and modulating immune responses within the tumor microenvironment. The principal mechanistic themes and representative studies are summarized in Table 1 (Ref. [21,25,31,32,35,37,38,41,43,44,49,53,55,59,60,61]), while the detailed characteristics and findings of all included studies are provided in **Supplementary Table 2**.

3.2.1 Microbial Dysbiosis as a Driver of OSCC

A large proportion of the included studies investigated periodontal pathogens and oral microbial dysbiosis as potential biological drivers of oral squamous cell carcinoma (OSCC). Several bacterial species associated with chronic periodontal inflammation were reported to be enriched in OSCC tissues, saliva samples, or tumor-associated microbial communities [24,31,32,33,34].

Among these microorganisms, *Porphyromonas gingivalis* and *Fusobacterium nucleatum* were the most frequently investigated pathogens. Multiple experimental studies demonstrated that infection with these bacteria promotes OSCC cell proliferation, migration, invasion, and epithelial plasticity [16,31,32,36]. In addition, other periodontal or oral bacteria, including *Prevotella intermedia*, *Treponema denticola*, *Capnocytophaga gingivalis*, *Streptococcus mutans*, and *Stomatobaculum longum*, were also implicated in tumor progression through diverse cellular and molecular mechanisms [23,37,38,39,40,66].

Microbiome sequencing studies reported distinct microbial signatures in OSCC tissues, characterized by enrichment of anaerobic bacteria such as *Parvimonas*, *Peptostreptococcus*, *Selenomonas*, and other dysbiosis-associated taxa. These microbial communities, which can be treated by local antiseptics in both periodontal and peri-implant microbiomes, were associated with tumor progression, altered metabolic pathways, and changes in immune cell infiltration within the tumor microenvironment [25,41,42,43].

Experimental investigations further demonstrated that bacterial extracellular vesicles, outer membrane vesicles, and microbial metabolites may directly influence tumor cell signalling and intercellular communication, contributing to carcinogenic processes in the oral epithelium [23,38,44,45,46].

An important consideration in interpreting the role of oral microbes in OSCC is the ongoing "driver versus passenger" debate. While several studies suggest that bacteria such as *Fusobacterium nucleatum* and *Porphyromonas gingivalis* may actively contribute to tumour progression through modulation of inflammation, immune responses, and oncogenic signalling, an alternative interpretation proposes that these microorganisms may also function as opportunistic colonisers of the tumour microenvironment [67,68]. OSCC tissues are characterised by hypoxia, necrosis, and metabolic reprogramming, which may create a niche that facilitates selective bacterial enrichment [69]. In particular, tumour-associated metabolic changes, including increased glycolysis and lactate production, may promote the growth and persistence of anaerobic species such as *F. nucleatum*. This supports a bidirectional model in which microbial dysbiosis may both contribute to and be shaped by tumour development, rather than acting as a unidirectional driver of carcinogenesis [70].

3.2.2 Activation of Oncogenic Signalling Pathways

Several studies examined how periodontal pathogens and inflammatory stimuli activate oncogenic signalling pathways involved in OSCC initiation and progression. Chronic exposure to microbial components and inflammatory mediators was shown to activate multiple intracellular pathways that regulate cell proliferation, survival, invasion, and epithelial plasticity [16,34,47,48].

Among the most frequently reported pathways were NF-κB, PI3K/Akt, MAPK, STAT3, Wnt/β-catenin, and TGF-β signalling. Activation of these pathways was associated with increased tumor cell proliferation, enhanced survival signalling, resistance to apoptosis, and promotion of EMT [16,34,42,49].

Multiple studies demonstrated that bacterial infection could induce EMT through upregulation of transcription factors such as Snail, Slug, and zinc finger E-box binding homeobox 1 (ZEB1), accompanied by decreased expression of epithelial markers such as E-cadherin and increased expression of mesenchymal markers and matrix metallo-

proteinases (MMPs) [3,11,36,39,50]. These molecular alterations were associated with enhanced cell migration, invasion, and metastatic potential of OSCC cells.

Additional studies reported that periodontal pathogens may influence cell cycle regulation, metabolic pathways, and oxidative stress responses, further contributing to tumor progression and epithelial transformation [23,32,35].

3.2.3 Modulation of the Tumor Immune Microenvironment

A major theme emerging from the included studies was the role of periodontal pathogens and chronic gingival inflammation in modulating the immune microenvironment of OSCC tumors. Microbial stimuli were shown to influence both innate and adaptive immune responses within the tumor microenvironment [5,51,52,53].

Several studies reported increased infiltration or activation of tumor-associated macrophages (TAMs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), neutrophils, and neutrophil extracellular traps (NETs) in response to periodontal pathogens. These immune cell populations are known to contribute to tumor-promoting inflammation and immunosuppressive conditions [42,46,51,52].

Mechanistic studies have shown that bacterial components such as lipopolysaccharide (LPS) can activate TLR4-mediated signaling, inducing PD-L1 upregulation in OSCC cells and promoting an invasive phenotype, which may contribute to tumor immune escape [50]. Bioinformatic analyses have further identified shared inflammatory and immune-related pathways between periodontitis and OSCC, supporting molecular links between periodontal inflammation and oral carcinogenesis [49,54].

Additional investigations showed that microbial infection may promote macrophage recruitment and M2 polarization, as well as $CD8^+$ T-cell exhaustion, thereby facilitating tumor progression through immune suppression and altered cytokine signalling networks [41,43].

3.2.4 Genomic and Epigenetic Regulation

Several studies explored the genomic, transcriptomic, and epigenetic mechanisms linking periodontal disease and OSCC. Bioinformatic and multi-omics analyses identified shared molecular signatures between periodontitis and oral cancer, including dysregulated genes involved in inflammatory signalling, immune responses, and extracellular matrix remodelling [38,49,54,56].

Hub genes identified in shared regulatory networks included IL-1β, CXCL8, MMP12, and MMP13, which were upregulated in both conditions and associated with immune cell infiltration and tumor prognosis [25,49,56].

In addition, multiple studies reported dysregulation of microRNAs (miRNAs) that regulate key oncogenic and inflammatory pathways. Identified miRNAs included miR-21, miR-31, miR-497, miR-224, miR-210, miR-29c, and miR-486-5p, which were implicated in the regulation of cell proliferation, apoptosis, immune responses, and epithelial plasticity [56,57,58,59].

Collectively, these genomic and epigenetic alterations suggest that periodontal inflammation and microbial dysbiosis may influence OSCC development through complex regulatory networks controlling gene expression and tumor-associated signalling pathways [38,54,56].

4. Discussion

This scoping review synthesized current molecular, microbial, genomic, and immunological evidence linking chronic gingival inflammation and periodontal pathogen–associated dysbiosis to the development and progression of OSCC. The analysis of 46 studies revealed converging evidence that periodontal pathogens and chronic inflammatory processes may contribute to oral carcinogenesis through multiple interconnected mechanisms, including inflammatory and cytokine signalling, microbe sensing and innate immune activation, immune suppression and tumor immune escape, epithelial-mesenchymal transition (EMT), invasion and metastatic signaling, and metabolic reprogramming with regulatory networks.

These findings support the concept that chronic periodontal inflammation may represent a component of a multifactorial biological framework involved in OSCC pathogenesis. Rather than acting as a single causal factor, periodontal dysbiosis appears to function as a microbial–inflammatory driver capable of reshaping epithelial signaling networks and the tumor microenvironment in ways that may support or facilitate tumor-related processes.

The current evidence is largely associative and mechanistic. While experimental *in vitro* and *in vivo* studies provide biological plausibility for these pathways, causality in humans has not been demonstrated. Accordingly, the relationship between periodontal dysbiosis and OSCC should be interpreted as mechanistically supported but not causally established.

An important consideration in interpreting the observed associations between periodontal disease, microbial dysbiosis, and OSCC is the presence of potential confounding factors. These include tobacco smoking, alcohol consumption, HPV infection, oral hygiene practices, socioeconomic status, and overall systemic health. These factors are independently associated with both periodontitis and OSCC and may therefore confound or modify the observed microbial and inflammatory signatures. Therefore, future studies should incorporate rigorous adjustment for these variables in well-designed longitudinal cohorts to better disentangle their relative contributions.

4.1 Chronic Inflammation and Carcinogenesis

Chronic periodontal inflammation emerges as a fundamental factor linking gingival pathology to oral squamous cell carcinoma [16,47,48]. Persistent inflammatory signal-

ing in the gingival tissues creates a tumor-permissive microenvironment characterized by elevated proinflammatory cytokines, chemokines, and activation of NF-κB and IL-17 pathways [49,56]. Chen et al. [49] identified overlapping inflammatory cascades between periodontitis and OSCC, including IL-17 signaling and cytokine–cytokine receptor interactions. Similarly, Yuan et al. [25] observed increased levels of IL-1β, IL-10, and IL-18 in both inflamed gingiva and tumor tissues, supporting a mechanistic continuum from chronic periodontal inflammation to tumor initiation. These findings underscore that the inflamed gingiva is not merely a passive site of infection but an active promoter of oncogenic signaling through sustained immune activation.

4.2 Epithelial–Mesenchymal Transition and Tumor Invasion

EMT is one of the most consistently reported mechanisms linking periodontal disease to OSCC invasion [32,37,60]. Periodontal pathogens serve as triggers for EMT by engaging signaling pathways that drive cytoskeletal remodeling, loss of epithelial polarity, and acquisition of migratory phenotypes [16,48]. Inaba et al. [47] demonstrated that *Porphyromonas gingivalis* infection induces proMMP9 expression through ERK1/2, p38, and NF-κB signaling, enhancing tumor invasion. Similarly, Ha et al. [48] reported that chronic exposure to *P. gingivalis* increases EMT markers and cancer stem cell traits (CD44, CD133), facilitating aggressive phenotypes. The synergistic effects of *P. gingivalis* and *Fusobacterium nucleatum* were highlighted by Lee et al. [16], showing EMT induction via GSK3β inhibition and activation of transcription factors Snail, Slug, and ZEB1. Other oral bacteria, including *Capnocytophaga gingivalis* and *Stomatobaculum longum*, also contribute to EMT and invasion, emphasizing that microbial dysbiosis broadly primes epithelial cells for malignant transformation [23,39].

4.3 Tumor Immune Microenvironment and Immune Escape

A key mechanism linking periodontal inflammation to OSCC is the modulation of the tumor immune microenvironment [46,53]. Multiple studies indicate that periodontal pathogens not only promote EMT but also reshape immune cell composition to favor tumor progression. Chen et al. [31] demonstrated that outer membrane vesicles from *P. gingivalis* suppress innate immune responses via the cGAS–STING pathway, facilitating immune evasion. Similarly, Zhang Y et al. [24] reported increased $CD4^+$ T cells and decreased $CD8^+$ cytotoxic T-cell activity in infected tumors, highlighting immune suppression. Nie et al. [53] and Sun et al. [46] observed that *F. nucleatum* triggers macrophage recruitment and M2 polarization, further establishing a pro-tumorigenic microenvironment. These alterations suggest that chronic microbial exposure during periodontitis not only initiates tumor-promoting signaling but also facilitates immune escape, a hallmark of cancer progression.

4.4 Metabolic and Genetic Reprogramming in OSCC

Emerging evidence indicates that periodontal pathogens and oral dysbiosis influence tumor metabolism and gene regulatory networks, contributing to OSCC progression [56]. Sun et al. [46] demonstrated that *F. nucleatum* promotes glycolytic reprogramming through the GalNAc–autophagy–TBC1D5 pathway, creating a metabolically favorable environment for tumor-associated macrophages. In parallel, miRNA-mediated regulation has been implicated in microbially driven oncogenic signaling, with Khoshbayan et al. [59] and Li Z et al. [56] showing that *P. gingivalis* and associated dysbiosis modulate miR-21, miR-31, and other oncogenic miRNAs, thereby controlling proliferation, apoptosis, and chemoresistance.

4.5 Integration of Microbial and Host Oncogenic Signaling

Taken together, the studies indicate that oral microbes modulate host oncogenic pathways, linking periodontal inflammation to OSCC through interconnected mechanisms [18,54,60,61]. Chronic gingival inflammation triggers cytokine cascades and NF-κB activation, periodontal pathogens induce EMT and stemness traits, immune cell populations are remodeled to favor tumor evasion, and microbial signals drive metabolic and genetic reprogramming.

Beyond the contributions of individual bacterial species, growing evidence supports the concept that oral carcinogenesis may be influenced by dysbiotic microbial communities acting through mechanisms of keystone pathogenicity and polymicrobial synergy. In this framework, *Porphyromonas gingivalis* may exert effects disproportionate to its abundance by subverting host immune responses, impairing microbial clearance, and sustaining a chronic inflammatory environment [71]. These alterations can promote ecological changes that favour the colonization and persistence of other periodontal pathogens, including *Treponema denticola*, *Prevotella intermedia*, and *Fusobacterium nucleatum*. Moreover, metabolic cooperation between community members, including cross-feeding interactions and the utilization of inflammatory tissue breakdown products, may enhance community stability and virulence. Rather than acting independently, these microorganisms appear to function within a coordinated dysbiotic network that amplifies inflammatory signalling, extracellular matrix degradation, immune modulation, and activation of oncogenic pathways. This community-based model provides a more comprehensive explanation for the complex microbial signatures observed in OSCC and suggests that tumour-associated microbial effects may emerge from collective ecosystem dynamics rather than from the actions of a single pathogen [62,72].

The findings of this review support an association between periodontal dysbiosis and OSCC, however, causality remains difficult to establish. The available evidence is consistent with a bidirectional relationship in which micro-

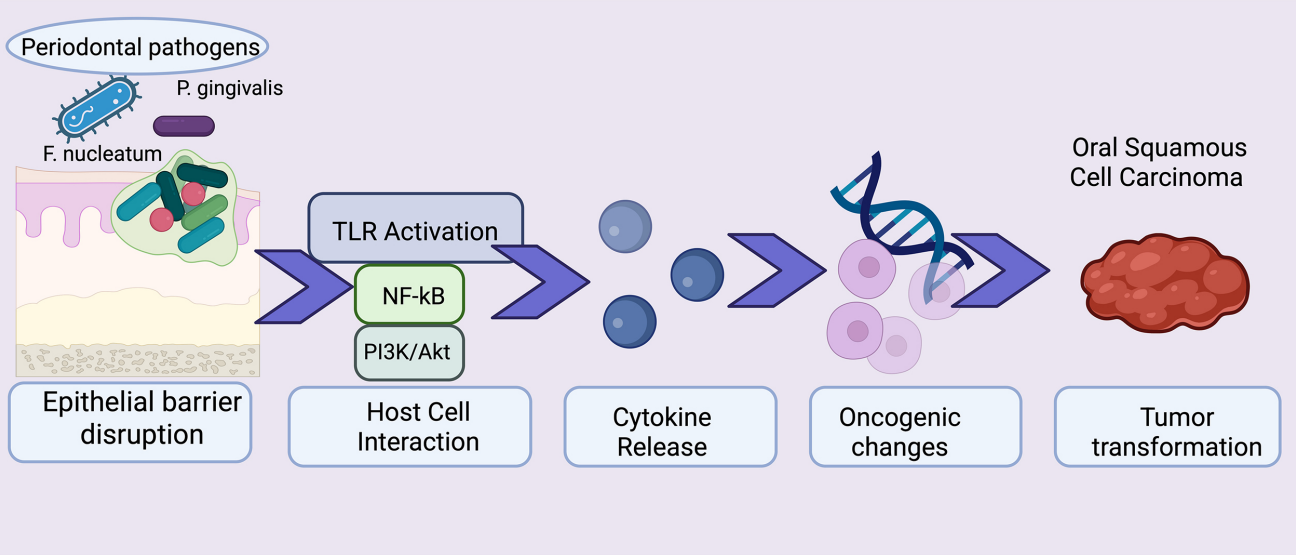

Fig. 2. Molecular mechanisms linking periodontal dysbiosis and chronic gingival inflammation to oral squamous cell carcinoma development and progression. Created in BioRender. Angjelova, A. (2026) https://BioRender.com/9tz8kla. TLR, Toll-like receptor; NF-κB, nuclear factor kappa B; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B.

bial dysbiosis may contribute to tumor initiation and progression while tumor-associated changes simultaneously promote the selective enrichment of specific microbial communities [63,64,65,66,69].

Interestingly, some context-dependent results, such as those according to Lan et al. [35], which include *P. gingivalis*-induced G2/M cell cycle arrest and tumor suppression, highlight the complexity of host-microbe interactions. Lan et al. [35] further reported downregulation of MUC1 expression and remodeling of the tumor immune microenvironment, suggesting that the biological effects of *P. gingivalis* may be highly dependent on the surrounding context. Variations in bacterial virulence characteristics, infection dynamics, and local microenvironmental conditions may influence downstream cellular responses. While chronic colonization has frequently been associated with inflammatory and pro-tumorigenic signaling, distinct host responses may emerge under different biological conditions. Furthermore, factors such as oxygen availability, metabolic status, and immune cell composition within the tumor microenvironment may modulate the impact of microbial exposure on tumor behavior. These discrepancies may reflect differences in infection duration, bacterial strains, or host immunity, emphasizing that molecular crosstalk in oral carcinogenesis is dynamic and context-specific. These interconnected pathways highlight the dynamic molecular crosstalk between microbial dysbiosis and host oncogenic signaling networks in oral carcinogenesis, as summarized in Fig. 2.

4.6 Limitations and Future Directions

Despite the mechanistic insights provided by the included studies, several limitations should be acknowledged. Many studies rely on *in vitro* models or animal experiments, which may not fully replicate the human oral tumor microenvironment. Clinical studies often involve small, heterogeneous cohorts, limiting generalizability and comparability.

In addition, methodological differences in microbial detection, experimental models, and disease definitions contribute to overall heterogeneity. Most studies are cross-sectional or experimental, and longitudinal data are lacking, limiting the ability to infer temporal or causal relationships between periodontal dysbiosis and OSCC.

It remains unclear whether microbial alterations are causal drivers of carcinogenesis or secondary changes induced by the tumor environment, highlighting an important gap in current knowledge. Future research should integrate longitudinal clinical studies, multi-omics approaches, and microbiome sequencing to clarify causal relationships and identify potential biomarkers for early detection. Moreover, targeted modulation of microbial communities or inflammatory pathways could represent promising therapeutic strategies to prevent or mitigate OSCC progression.

5. Conclusion and Translational Insights

This scoping review highlights the complex molecular crosstalk linking chronic periodontal inflammation, microbial dysbiosis, and the initiation and progression of oral squamous cell carcinoma. Across the included studies, five principal mechanistic themes consistently emerged: inflammatory and cytokine signalling, microbe sensing and innate immune activation, immune suppression and tumor immune escape, epithelial-mesenchymal transition (EMT), invasion and metastatic signaling, and metabolic reprogramming with regulatory networks. Rather than demonstrating direct causality, the available evidence suggests

that periodontal pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* may act as potential modulators of these oncogenic pathways, contributing to molecular events associated with tumor invasion, immune escape, and altered cellular metabolism.

These mechanistic insights have important translational implications. Identification of microbial and host-derived biomarkers could improve early detection of OSCC in patients with chronic periodontal inflammation, while targeted modulation of inflammatory pathways, immune checkpoints, or metabolic networks may offer novel preventive or therapeutic strategies. However, current evidence remains largely preclinical or associative, and therefore, these applications are still hypothetical and require validation.

Author Contributions

EJ: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation; AA: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation; RC: Writing – review & editing, Writing – original draft, Data curation, Validation; AP: Writing – original draft, Investigation, Data curation, Validation; AM: Data curation, Formal analysis, Validation, Writing – review & editing; GI: Conceptualization, Writing – review & editing, Writing – original draft, Funding acquisition, Project administration, Methodology, Formal analysis, Data curation. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL53502.

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