Review Article

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Periodontal inflammation as a negative stimulus for oral cancerization: the hidden role of periodontitis in oral cancerization

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Abstract: Periodontal inflammation, a hallmark of periodontitis, has well-known detrimental effects on oral health. Emerging evidence suggests it may also contribute to the development of oral squamous cell carcinoma (OSCC) as well as the progression of oral potentially malignant disorders (OPMDs). Chronic periodontal inflammation may contribute to oncogenesis through multiple mechanisms. The underlying biology involves the inflammatory cytokines production, immune cell infiltration, oxidative stress, and their impact on cellular behavior. Furthermore, low-grade systemic inflammation emerging from microbial dysbiosis may promote cancer cell survival, proliferation, and immune evasion – key processes in carcinogenesis. The interaction between periodontal pathogens and host tissues is closely intertwined with the progression toward epithelial dysplasia, epithelial–mesenchymal transition (EMT), and neoangiogenesis. While most of the evidence supports the association between OSCC and periodontitis, the limitations of these studies, the presence of confounding factors, and conflicting findings call this relationship into question. In this context, this review aims to discuss the most recent evidence regarding the link between periodontitis and oral carcinogenesis, with a particular focus on the ecological and molecular mechanisms underlying epithelial dysplasia, tumor initiation, progression and metastasis, while also providing new perspectives for its prevention and treatment.

Keywords: periodontitis; oral potentially malignant disorders; oral squamous cell carcinoma; chronic inflammation; oral dysbiosis

Introduction

Periodontitis is a chronic inflammatory condition of multifactorial etiology associated with dysbiotic biofilm and characterized by the progressive destruction of the supporting tissues of the teeth [1]. Its global impact is significant: between 2011 and 2020, it was among the most prevalent conditions worldwide, with an overall prevalence of 62 and 23.6 % for severe forms [2, 3].

Several studies have demonstrated that the factors involved in periodontal inflammation are not confined to the oral cavity but can disseminate throughout the entire organism, with a range of consequences for overall health [4]. An increasing body of evidence indicates an association between periodontitis and other non-communicable diseases (such as cardiovascular diseases, rheumatoid arthritis, diabetes mellitus, respiratory diseases and cancer), all of which are marked by a chronic pro-inflammatory state [5]. This close bidirectional relationship has been linked to an increased risk of all-cause mortality [5] and underscores that periodontitis extends beyond the oral cavity, qualifying it as a systemic condition [6, 7].

Recent studies have demonstrated that chronic inflammation, oxidative stress, dysbiosis, and specific periodontal pathogens may either trigger the onset of oral squamous cell

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carcinoma (OSCC) or facilitate the progression of potentially malignant disorders (OPMDs) into oral cancer [4, 8–10].

OSCC is a malignant neoplasm derived from an abnormal proliferation of the squamous cells of the oral mucosa with a high rate of mortality, recurrence, and metastasis [11]. It represents more than 90 % of all oral malignancies and is the eighth most common cancer worldwide [12], with some variations between different geographic areas.

In clinical practice, certain mucosal abnormalities can be identified before the development of OSCC. At the 2007 workshop, the World Health Organization (WHO) classified these lesions as oral potentially malignant disorders (OPMDs) [13]. Although the presence of OPMDs does not invariably lead to malignant transformation, it is associated with a higher risk compared to normal mucosal tissue. Recent studies underscore the role of less studied and "non-canonical" risk factors in the malignant progression of OPMDs, such as oxidative stress and in particular oral dysbiosis, such in cases of oral lichen planus [14, 15]. Indeed, the onset of an alteration in the oral microbiota, a phenomenon that occurs, for example, in the case of periodontitis, is a key pathophysiological mechanism in the development of OSCC through a chronic inflammation process [16].

In the dysbiotic periodontal environment, several highly pathogenic microorganisms implicated in OSCC pathogenesis can be identified, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. Periodontitis, through the establishment of a dysbiotic state and chronic low-grade inflammation, significantly influences systemic inflammation and shares fundamental mechanisms involved in oncogenesis [8].

The correlation between periodontitis and both oral and extra-oral cancers is a widely debated topic in the literature, as studies often report conflicting data. The study by Chen et al. demonstrated a significant association between periodontitis and both prostate and thyroid cancers, and further highlighted the benefits of periodontal therapy in reducing overall cancer risk [17]. A systematic review also reported a strong association between periodontitis and gastrointestinal, colorectal, pulmonary, pancreatic, and oral cancers, although the correlation appeared weaker for hematological, breast, and prostate cancers [18]. In an analysis by Xiong et al., periodontitis was found to significantly contribute only to the onset of oropharyngeal cancer [19].

However, according to Chen et al., patients with periodontitis who exhibit lower levels of systemic inflammation, in comparison to individuals with a healthy oral microbiota (eubiotic flora), appear to be at a reduced risk of developing cancer overall [17].

Furthermore, existing evidence also suggests that periodontitis may potentially play a key role in the pathogenesis of oral cancer. The strength of this association has been confirmed by several studies. A meta-analysis [9] involving nine studies reported a strong correlation, with an odds ratio (OR) of 2.94. Moreover, other systematic reviews and meta-analyses in the literature support this association, indicating a 2- to 5-fold increased risk of oral cancer in patients with periodontitis compared to healthy individuals [9]. Additional research has shown that the risk of tongue cancer increases approximately five-fold for every millimeter of alveolar bone loss due to periodontitis [20]. However, the study by Villar et al., conducted through a Systematic Literature Network Analysis (SLNA), identified several publications in which the association between periodontitis and OSCC was not statistically significant. Similarly, another investigation based on Mendelian randomization concluded that periodontitis does not exert a significant causal impact on OSCC risk [19]. In this context, the aim of this review is to examine recent evidence on the role of periodontitis as a risk factor in the onset and progression of OSCC, while proposing novel perspectives for its prevention and treatment.

Materials and Methods

Search strategy

The critical review was carried out by two reviewers in order to identify articles investigating the relationship between periodontitis and cancer, with a particular focus on the oral cavity. Search engines such as PubMed and Google Scholar were used for the search, employing specific keywords for a targeted approach and thereby facilitating the selection of articles relevant to the scope of the review. The search strategy incorporated both MeSH (Medical Subject Headings) and free terms to maximize the breadth of results. The search combined the following sets of keywords: "risk factors", "oral cancer", "cancer", "OSCC", "OPMDs", "oral squamous cell carcinoma", "oral premalignant lesions", "potentially malignant disorders", "malignant transformation", "epithelial dysplasia", "microbiota", "microbial community", "microbiome", "bacteria", "microflora", "cancerization", "tumorigenesis", "oral cancerization", "chronic inflammation", "inflammation", "periodontitis", "periodontal disease", "immunotherapy", "periodontal therapy", "tumor progression", "tumor invasion", "metastasis", "EMT", "epithelial-mesenchymal transition", "*P. gingivalis*", "*T. denticola*", "*T. forsythia*", "*Fusobacterium nucleatum*" and "*Aggregatibacter actinomycetemcomitans*." Relevant articles were subsequently selected through screening of titles, abstracts, and full texts according to predefined inclusion and exclusion criteria.

Study selection

The search included articles published from 2023 to 2025, reflecting the most recent developments in the field and offering updated perspectives. English-language articles were included, and the study designs considered were prospective and retrospective studies, cross-sectional studies, narrative reviews, systematic reviews, and meta-analyses. Articles were excluded if they (i) were not available in English, (ii) were available with abstract only, (iii) were not related to the correlation between periodontitis, dysplasia, and tumor progression and their therapeutic implications, or (iv) were opinion articles or conference reports.

The initial search yielded a total of 207 articles, which were then screened by title and abstract, resulting in 152 articles. Of these, 87 were excluded after full-text screening for not meeting the inclusion criteria, leading to a final inclusion of 65 articles.

Oral potentially malignant disorders (OPMDs) and related risk factors

The most common OPMDs are leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus. These conditions have multifactorial etiologies, including smoking, alcohol abuse, and betel quid (BQ) chewing [21]. Globally, it is estimated that around 4.47 % of the population is affected by OPMDs, with prevalence rates in Asia being notably higher, reaching up to 10.54 % [22], but the focus is on the risk of malignant transformation (MT), in fact, the rates of progression to malignancy of these lesions are about 7.9 % [23]. It is important to recognize that OPMDs encompass heterogeneous conditions, so each disorder has its own risk of malignant transformation [22].

Analyzing individually some OPMDs, it appears that oral leukoplakia (OL) is a frequent disorder with a worldwide prevalence ranging from 1.36 to 2.60 % [24] but there are higher rates in India, which could be linked to cultural, ethnic, and geographic factors [25]. OL MT proportion is 6.64 %, and the risk of malignant transformation is due to all forms of tobacco use, including reverse smoking, which increases the risk 19-fold; moreover, increased MT is found in large OL lesions, non-homogeneous lesions, located on the lateral border of the tongue, and presenting epithelial dysplasia [24] (Table 1). Other risk factors include alcohol consumption, chronic irritation, fungal infections such as candidiasis, leading to endogenous nitrosamine production [25] while in South and Southeast Asia, another important risk factor is the use of areca (betel) nut preparations.

Table 1: The different types of oral potentially malignant disorders (OPMDs) and their respective prevalence and malignant transformation (MT) rates.

Type of OPMD	Worldwide prevalence	MT rate
Oral leucoplakia	1.36–2.60 % [24]	6.64 % [24]
Oral submucous fibrosis	3.0 % [26]	4.2 % [27]
Oral erythroplakia	0.17 % [28]	19.9–45 % [28]
Oral lichen planus	1.27 % [29]	1.4 % [22]

According to studies, the most frequent disorder is oral submucous fibrosis (OSF); in fact, its global prevalence is about 3.0 %, even in this case, resulting in a higher presence in India, with rates about 4.0 % and major involvement in people aged 50 and males [26]. The malignant transformation in OSF is at 4.2 % [27] and the factors that induce the progression to OSCC are comparable with OL's factors (Table 1). Among them, we can find betel quid chewing, smoking, drinking, and microbial infection, and MT increases when there are other OPMDs, such as leukoplakia, erythroplakia, and lichen planus. As regards the mechanisms of transformation of OSF, epigenetic reprogramming, epithelial-mesenchymal transition, hypoxia, cell cycle changes, immune regulation disturbances, and oxidative damage [27].

Other conditions like oral erythroplakia and oral lichen planus are less common, but although the prevalence of oral erythroplakia (OE) is low, about 0.17 %, it is a high-risk potentially malignant condition for OSCC. In fact, its malignant conversion ranges from 19.9 to 45 % [28] (Table 1). Also, for OE, the risk factors of MT are tobacco, betel quid (areca nut), and alcohol use [28].

Concerning oral lichen planus (OLP), its prevalence is approximately 1.27 %, with slightly higher rates in women and the middle age group, but sporadic cases are also reported in very young patients or children [29], whereas its MT rate is 1.4 % [22] and the erosive type of OLP, female gender, and tongue site are risk factors for malignancy [29] (Table 1).

Since the oral mucosal immunity is compromised in OLP, it becomes more sensitive to exogenous mutagens associated with tobacco, alcohol, betel quid, and *Candida albicans*; for this reason, MT is promoted by these factors. Additionally, the erosive type of OLP, female gender, and tongue site are risk factors for malignancy [29].

The same factors cause damage more easily in atrophic and ulcerative forms of OLP, but studies suggest malignant transformation may be part of the natural course of OLP. These considerations are due to the development of cancer in patients who have not used alcohol or cigarettes [29].

Also, angiogenesis has an important role in carcinogenesis, since it allows an autonomous supply of blood, nutrients, and oxygen to the tumor microenvironment, recruiting new blood vessels through the expression of various growth factors like vascular endothelial growth factor (VEGF) [30]. Angiogenesis is therefore a useful factor for early diagnosis in malignant transformation of OPMDs; for this reason, the IPCL (intrapapillary capillary loop) classification that uses narrow-band imaging (NBI), assesses the morphology of capillaries and identifies patterns associated with malignant transformation of OPMDs [31]. The IPCL classification is based on three fundamental characteristics of capillaries: dilatation, irregularity, and tortuosity. There are, consequently, four types of morphology abnormalities of capillaries: normal, dilated, irregular, and chaotic. High-risk lesions are mostly associated with irregular and chaotic types [31].

As we said, there are a lot of risk factors for malignant transformations of OPMDs like site, size, age of onset, sex, and lifestyle habits as the use of tobacco, but the oral microbiome can affect the progression of OPMDs independently of other factors [13]; indeed, in recent years, the oral microbiome and periodontitis have been associated with the initiation and progression of neoplasm [8]. The presence of specific oral bacteria has been identified as a risk factor for the dysplastic transformation of OMPDs. Indeed, studies have highlighted notable shifts in the composition of the oral microbiota from healthy individuals to patients with potentially malignant and variously graded dysplastic lesions. While healthy individuals typically exhibit a diverse microbial community dominated by commensal bacteria, patients with dysplastic lesions show a higher concentration of pathogenic species, such as Gammaproteobacteria (including *A. actinomycetemcomitans*), Fusobacteria, *Porphyromonas*, and *Candida* [32]. The degree of microbial diversity in patients with dysplastic lesions and OSCC remains a subject of considerable debate. Some studies report a reduction in microbial diversity – both alpha and beta diversity – in OSCC and dysplastic lesions compared to healthy controls [33, 34]. Conversely, emerging evidence from literature, such as the study by Radaic et al. – demonstrates that dysplastic and neoplastic lesions are characterized by greater diversity in bacterial composition [32]. Moreover, the literature indicates that the progression from oral health to dysplasia and carcinoma is accompanied by significant alterations in the oral microbiome, notably including an increase in periodontopathogenic bacterial species at the expense of commensals [32].

Periodontitis induces local detrimental effects on the levels of teeth and gums because of dysbiosis [8]. This last induces pathogenic microorganisms to secrete bacterial toxins, which can damage cellular DNA, with abnormal cell proliferation and apoptosis. At the same time, bacterial toxins lead to local chronic inflammation of the tissue [27].

Studies show how, in some OPMDs, periodontopathogens play a key role in MT, actually, OLP mucosa is rich *in F. nucleatum*, *Eikenella corrodens* (*E. corrodens*), *T. denticola* [13] and the progression of OSF to OSCC is influenced by microbial infection [27].

Periodontal bacteria infiltrate the epithelium and block natural killer and cytotoxic cells, contributing to carcinogenesis. They also induce inflammation, favoring the proliferation of pathogenic bacteria, directly helping the progression of pathogenic processes [13]. In more detail, *P. gingivalis* and *F. nucleatum* can upregulate the genes involved in downstream TLR, NFκB, and MAPK signaling pathways in both normal and malignant oral epithelial cells [8]. In addition, *P. gingivalis*-induced autophagy suppresses cell proliferation through G1 arrest in oral cancer cells [27]. At last, *A. actinomycetemcomitans* secretes toxins and other byproducts, such as ROS, nitrogen reactive species, sulfides, nitrosamines, and acetaldehyde, that have shown a potential malignant transformation through DNA alkylation, mutations, and impaired repair [8].

As regards to role of chronic inflammation and mediators of inflammation such as interleukin 4 (IL-4) and IL-6, studies show that they increase the sensitivity of oral keratinocytes to exogenous agents [35]. Chronic inflammation coupled with a dysbiotic environment is a known risk factor for oncogenesis; several studies demonstrate a role of periodontitis in the development of oral cancer through oxidative stress, DNA damage, and alteration of the immune response [36].

Oral biofilm dysbiosis and related periodontal chronic inflammation

The oral cavity is a complex ecosystem characterized by the presence of approximately 2,000 species, including fungi, viruses, and notably, bacteria [8]. According to the Human Microbiome Project (HMP), more than 700 microorganisms coexist within the oral cavity, aggregated together within EPM, forming biofilm communities [37]. Under physiological conditions, the diverse microbial species in the oral cavity engage in interactions among themselves and with the host, collectively forming what is known as the oralome [38]. Resident bacteria in the oral cavity (defined as symbionts) coexist with other species in a symbiotic relationship that involves metabolic interactions and intercellular communication mechanisms such as quorum-sensing [39]. This polymicrobial synergy permits the regulation of colonization, growth, and even pathogenicity [40].

This steady state can be disrupted by various endogenous and exogenous stressors, such as tobacco smoking and alcohol consumption. Such changes lead to the establishment of a state of dysbiosis, in which pathobionts prevail over commensal bacteria [39], thereby contributing to the development of various pathologies through the activation of the immune system [38]. The interplay between inflammation and dysbiosis has been extensively discussed; however, it is evident that these two processes are interdependent, as inflammation can precipitate a shift toward dysbiosis, while pathobionts, through their toxins, can induce an inflammatory response and consequently cause tissue damage [39]. The periodontal inflammatory process is initiated by the recognition of pathogen-associated molecular patterns (PAMPs) through Toll-like receptors (TLRs) [8]. This recognition triggers the activation of the innate immune system and the subsequent release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8) [39]. These mediators induce neutrophil chemotaxis, with neutrophils engaging in phagocytosis, production of matrix metalloproteinases (MMPs) and ROS, activation of the RANKL receptor on osteoclasts, and stimulation of Th17 responses [41]. Following this initial immune response, both the complement system and adaptive immunity are activated. T lymphocytes – particularly TH1, TH2, and TH17 – further contribute to the production of additional mediators and to tissue destruction [39].

In witness thereof, recent evidences have demonstrated that patients with OSCC exhibit poor plaque control and a higher quantity of periodontal pathogens (1.9 times higher) compared to healthy subjects [42–44]. In a study by Isono et al., patients with OPMDs and OSCC present a higher bleeding on probing (BOP) and more advanced periodontitis compared to control groups, suggesting that the promotion of oral hygiene and plaque control are essential tools in the prevention of OSCC [44].

A substantial number of studies have highlighted the diversity of the oral microbiome among healthy individuals, patients with periodontitis, and those affected by OMPDs and OSCC at both early and advanced stages. Amplicon-based 16S rRNA sequencing has enabled comparative analyses of bacterial DNA isolated from different patient groups [45].

In healthy individuals, a wide range of bacterial populations is observed, primarily belonging to the phyla *Firmicutes* (36.7 %), *Bacteroidetes* (17.1 %), *Proteobacteria* (17.1 %), *Actinobacteria* (11.6 %), *Spirochaetes* (7.9 %), *Fusobacteria* (5.2 %) [33]. The predominant genera include Gram-positive cocci and bacilli (*Streptococcus*, *Peptostreptococcus*, *Actinomyces*, *Staphylococcus*) as well as Gram-negative organisms (*Leptotrichia*, *Neisseria*, *Fusobacterium*, *Kingella*, *Haemophilus*, *Porphyromonas*, *Prevotella*, *Propionibacterium*, *Veillonella*, and the *spirochete Treponema*) [46, 47].

In patients with periodontal inflammation, a dysbiotic microbial profile is observed, with a predominance of Gram-negative obligate anaerobes and an enrichment of periodontal pathogens, notably those belonging to Socransky's red complex (*P. gingivalis*, *T. denticola*, *T. forsythia*) and orange complex (*Prevotella*, *Fusobacterium*, *Parvimonas*) [33]. In individuals with OPMDs, microbiota is characterized by an abundance of Gram-negative bacteria and an increased presence of Firmicutes and Actinobacteria. Non-advanced OSCC cases exhibit a dysbiotic state marked by the dominance of Gram-negative bacteria and a significant reduction in Firmicutes compared to healthy subjects [48].

The predominant microorganisms in the OSCC group include well-established periodontopathogenic species: *Fusobacterium*, *Prevotella*, *Peptostreptococcus*, *P. gingivalis*, *Capnocytophaga gingivalis*, and *T. denticola* [33, 49, 50].

Cancer progression is also associated with further shifts in the oral microbiota, including a reduction in *Actinomyces*, *Haemophilus*, *Porphyromonas*, *Streptococcus*, and *Tannerella*, alongside an increase in *Bifidobacterium*, *Parvimonas micra*, *Peptostreptococcaceae*, and *Prevotella* [33].

Among various periodontal pathogens, several species have been implicated in the oncogenesis of multiple cancers, including OSCC. In particular, *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans*, *T. forsythia*, and *T. denticola* have been recognized for their potential oncopathogenic roles [4]. These bacterial species are involved in immunoinflammatory mechanisms, cellular survival and replication, cellular invasion and immune evasion [43].

Porphyromonas gingivalis

Porphyromonas gingivalis is a Gram-negative, highly virulent bacterium implicated in the pathogenesis of both periodontitis and OSCC, capable of invading epithelial cells, altering immune responses, and modifying gene expression [10, 51]. One study demonstrated a 6.5-fold increase in *P. gingivalis* in patients with OSCC compared to healthy subjects [42]. The presence of *P. gingivalis* has been associated with a 1.36-fold increase in OSCC incidence [51]. Its virulence is associated with several factors that ensure replication, survival within the host, and evasion of the immune system. These include fimbriae, lipopolysaccharide (LPS), outer membrane vesicles (OMV), and gingipains [43]. Fimbriae are involved in adhesion, colonization of host cells, and aggregation with other bacterial species. In particular, these structures mediate aggregation with *T. denticola*, thereby facilitating its invasion [39]. LPS produced by *Porphyromonas* triggers the activation of macrophages through Toll-like receptors (especially TLR4), initiating signaling

pathways that culminate in the production of pro-inflammatory cytokines [43] (Figure 1). *Porphyromonas* induces a functional polarization of macrophages toward the M2 phenotype, which is implicated in angiogenesis, tissue remodeling, and suppression of adaptive immunity. This alteration in macrophage activity facilitates the formation of a pro-tumoral microenvironment [9, 43]. Furthermore, modulation of autophagy in macrophages reduces the inflammatory response and inhibits tumor cell apoptosis, thereby promoting cancer progression [51, 52]. This bacterium inhibits apoptosis while promoting autophagy and activates the JAK/STAT and PI3K/Akt signaling pathways, thereby enhancing tumor cell survival [4]. Moreover, it induces the release of inflammatory mediators such as IL-6 and IL-8, leading to epigenetic changes, extracellular matrix degradation, and metastasis formation [37]. Furthermore, *P. gingivalis* facilitates the proliferation of other pathogens, including *T. forsythia and Spirochetes*, leading to increased inflammation and consequent tissue destruction [37].

Fusobacterium nucleatum

Fusobacterium nucleatum is an obligatory anaerobic bacterium present in elevated quantities in patients with oral cancer (2.7 times higher than in controls) [42]. It plays a crucial role in the maturation of dental plaque, acting as a bridge between various bacterial species and interacting with host cells through its adhesins [43]. Its role in oncopathogenesis depends on its ability to induce inflammation, cellular proliferation, and cellular invasion through several virulence factors, including lipopolysaccharide (LPS), fibroblast activation protein 2 (Fap2), and fusobacterial adhesin (FadA) [43]. Similar to *P. gingivalis*, LPS of *F. nucleatum* interacts with

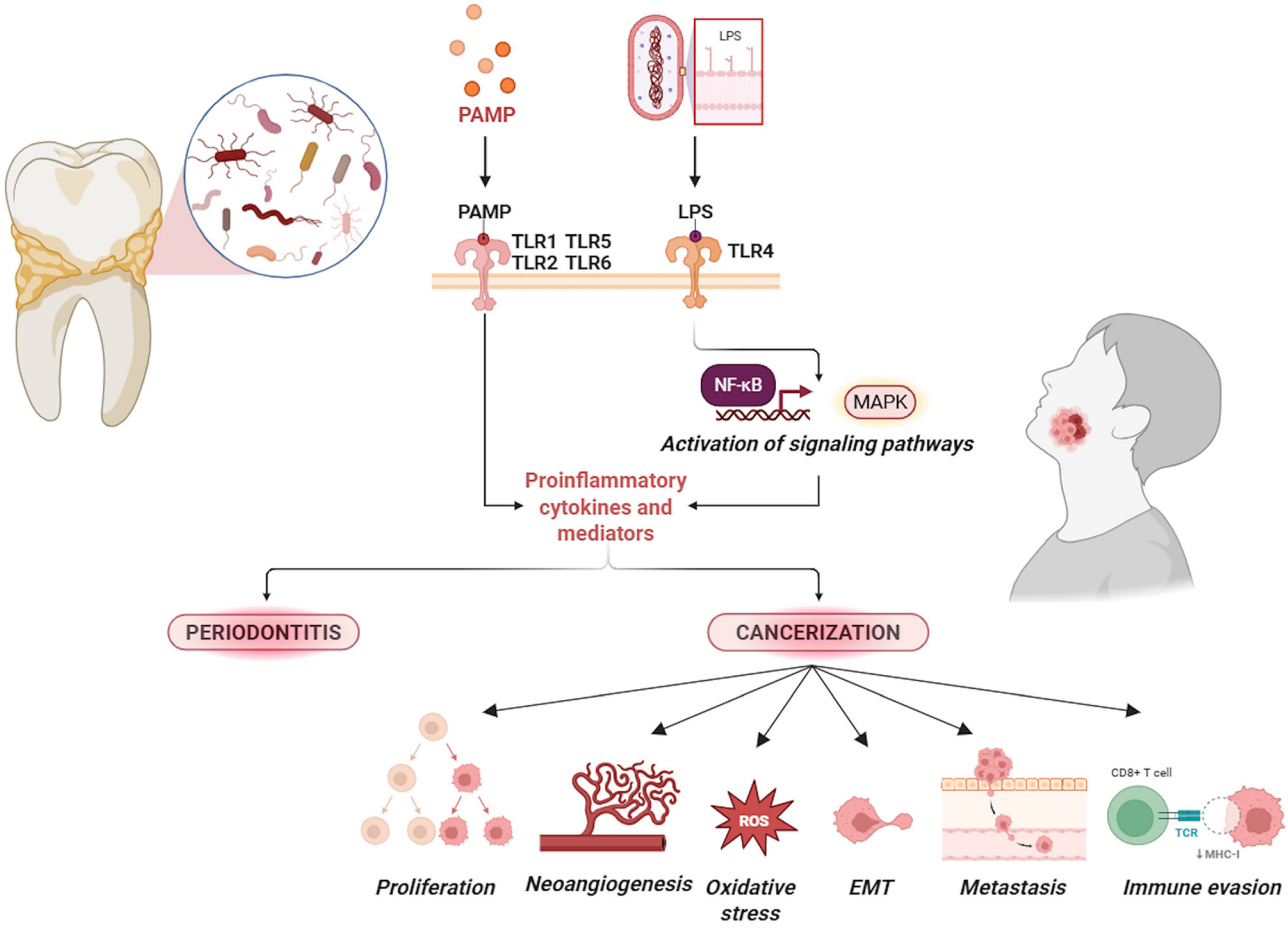

Figure 1: Bacterial virulence factors and their role in periodontitis and carcinogenesis. Bacterial products, including bacterial products (PAMPs) and lipopolysaccharide (LPS) within the cell membrane, are recognized by Toll-like receptors (TLRs) on the surface of immune cells. This recognition activates intracellular signaling pathways that lead to increased production of pro-inflammatory cytokines and mediators involved in both the pathogenesis of periodontitis and carcinogenesis and tumor progression. Carcinogenesis entails multiple mechanisms, including cancer cell proliferation, neoangiogenesis, oxidative stress, epithelial–mesenchymal transition (EMT), metastasis, and immune evasion. Created in https://BioRender.com, accessed on 18 April 2025.

TLR4, triggering signaling pathways that result in the secretion of IL-1α, IL-1β, IL-6, IL-8, and matrix metalloproteinases (MMPs) and the nuclear translocation of the transcription factor NF-κB [4, 9]. (Figure 1). The activation of these signaling pathways contributes to the host's immune and inflammatory response, thereby promoting the formation of a pro-tumoral environment [42]. The MMPs produced following *F. nucleatum* infection – particularly MMP-9 and MMP-13 – lead to the degradation of the basement membrane, promoting the dissemination of tumor cells [4].

Aggregatibacter actinomycetemcomitans

Aggregatibacter actinomycetemcomitans is an intracellular pathogen generally associated with aggressive or advanced forms of periodontitis [37]. Evidence presents conflicting data regarding the levels of *Aggregatibacter* in patients with OSCC. For instance, a study by Unlu et al. reports a 1.3-fold reduction in *Aggregatibacter* levels compared to controls, whereas research by Isono et al. indicates a higher concentration relative to healthy subjects [42, 44]. 16S ribosomal RNA sequencing of salivary samples in the study by Deo et al. revealed a significant increase in the concentration of *A. actinomycetemcomitans* in individuals with OSCC, while a smaller increase was observed in patients with OL and OSF [48]. This Gram-negative bacillus is capable of expressing various virulence factors, including LPS, leukotoxin (LtxA), cell surface components, and enzymes [43]. The recognition of LPS induces the production of inflammatory mediators such as IL-1β, IL-6, IL-8, and TNF-α; moreover, it is implicated in the production of reactive nitrogen species, ROS, acetaldehyde, nitrosamine, sulfides, thereby contributing to oxidative stress, tissue and DNA damage through mutations, impaired repair, and DNA alkylation [43, 45]. It is involved in the regulation of the immune system and in modulating the phagocytic and autophagic activities of macrophages [52]. Moreover, it promotes immune evasion and tumor progression through the production of IL-10 and other cytokines with immunosuppressive activity [45]. LtxA is a crucial factor for the pathogenicity of *A. actinomycetemcomitans*; the leukotoxin primarily targets immune cells (monocytes and macrophages), inducing apoptosis [37].

Tannerella forsythia and *T. denticola*

Tannerella forsythia and *T. denticola* are recognized as periodontopathogen bacteria that have been associated with OSCC. Their role is linked to the stimulation of pro-inflammatory cytokines and metalloproteinases, as well as the expression of various virulence factors, including proteases, sialidases, and surface proteins [4].

Tannerella forsythia, a red-complex periodontopathogenic bacterium belonging to the phylum *Bacteroidota*, has shown potential involvement in the onset of epithelial dysplasia and OSCC. Comparative studies have reported a high abundance of *T. forsythia* in healthy subjects, with a progressive reduction in its presence among individuals with leukoplakia and OSF [48]. Moreover, the study by Radaic et al. highlighted that the abundance of *Bacteroidia* is greater in cases of low-grade dysplasia and tends to decrease in patients with OSCC [32]. *T. forsythia* interacts with the host via multiple virulence factors, including LPS, sialidase, proteases, outer membrane vesicles (OMVs), and the cell surface antigen BspA. The BspA protein mediates adhesion and epithelial cell invasion and stimulates the production of key factors such as interleukin-1 receptor antagonist (IL-1Rα), IL-8, and vascular endothelial growth factor (VEGF), all of which are involved in neoangiogenesis, tumor growth, invasion, and metastasis [53, 54]. Evidence has also shown that *T. forsythia* can invade OSCC cells via its sialidase and may alter host immune responses by impairing polymorphonuclear leukocyte (PMN) function and modulating the immune response to other pathogens, such as *F. nucleatum* [54]. Nevertheless, bibliometric analyses and reviews focusing on the relationship between oral bacteria and cancer tend to highlight the limited evidence supporting a significant correlation between *T. forsythia* and OSCC [47].

Treponema denticola has been associated with esophageal, intestinal, and OSCC through various mechanisms mediated by virulence factors such as LPS, FadA adhesin, dentilisin, flagella, and hemin-binding proteins. Several of these virulence mechanisms, similar to those of other pathogenic periodontal bacteria, contribute to carcinogenic processes including: (i) tissue damage via cytokine modulation and the production of reactive oxygen species (ROS); (ii) cellular proliferation through molecular and epigenetic pathways that inactivate tumor suppressor genes and activate oncogenes; (iii) neoangiogenesis; and (iv) immune modulation through the inhibition of leukocyte migration. *T. denticola* is capable of independently inducing the proliferation of OSCC cells in animal models through the activation of TGF-β [43, 55]. Additionally, *T. denticola* has been associated with the onset of epithelial dysplasia, keratinization, and the progression and invasiveness of oral cancer via TLR-2 and TLR-4 [32, 56, 57].

The role of microbiota throughout the entire carcinogenic process

Our study highlights the mechanisms through which various periodontal bacteria promote carcinogenesis, but changes in the oral microbiome affect not only the early stages of oral cancer development but also its progression [33]. Other studies shed light on the changes induced by periodontal bacteria in later stages, such as cancer progression and metastasis. *P. gingivalis*, *F. nucleatum*, *Porphyromonas intermedia*, and *A. actinomycetemcomitans* can cause genomic instability, thereby enhancing carcinogenesis by producing toxic substances such as volatile sulfur compounds, hydrogen sulfide, and methyl mercaptan [58]. Furthermore, the results demonstrate an increase in *Fusobacterium* abundance during tumor progression, whereas in patients with regional metastases, a decrease in *Fusobacterium* along with *Tannerella* is observed. Conversely, *Haemophilus*, *Porphyromonas*, and *Actinomyces* decrease during tumor progression, while *Prevotella* increases in cases of metastasis [33].

Histological features and inflammation in periodontitis and OPMDs

Given that OPMDs' malignant transformation is closely linked with their tissue microenvironment, which comprises epithelial cells, underlying connective tissue, and inflammatory immune cells, through histopathological analysis, it is possible to diagnose and classify OPMDs [23].

OPMDs are epithelial precursor lesions, ranked by WHO, as oral epithelial hyperplasia (OEH), Oral epithelial dysplasia (OED), and lastly carcinoma *in situ* (CIS) [23]. In dysplasia, cells are characterized by hyperchromasia; enlargement of nuclei, decreased nuclear-cytoplasmic ratio; mitoses in suprabasal layers; loss of differentiation of keratinocytes towards the surface, and keratinization/cornification [32]. OED is divided in turn in mild, moderate, and severe dysplasia, according to extension of cytological and architectural alterations involving the oral epithelium; in fact, the alterations can affect the lower third of the epithelium, the middle third, and full thickness with intact basement membrane. Additionally, the WHO, with the Binary system, further categorized OPMDs as low-risk and high-risk OPMDs [23]. Using the WHO classification is possible to analyze the prevalence of each type of lesion [23].

Paying attention to the effect of periodontal inflammation on the histopathological features of OPMDs, some studies demonstrate that periodontal bacteria play a crucial role in the transition from healthy mucosa to dysplasia and to OPMDs in OSCC. In fact, there is a different microbiome between healthy tissue, dysplasia, and OSCC [32]. In conditions of dysplasia has been identified an increase of *F. nucleatum*, *P. gingivalis*, and *T. denticola* which promote cancer progression through positive regulation of cell migration and cell motility, angiogenesis, regulation of vasculature development, regulation of leukocyte migration, and cytokine activity processes [32]. Additionally, these three pathogens are particularly involved in the upregulation of gene expression for epidermal and keratinocyte differentiation and cornification/keratinization processes, especially in non-keratinized mucosa. This finding is noteworthy because dysplastic lesions of the upper aerodigestive tract have this characteristic, while a lot of oral cavity mucosa is non-keratinized [32].

The molecular mechanisms underlying epithelial dysplasia are driven by bacterial virulence factors and involve the induction of chronic inflammation, promotion of cellular proliferation and survival, as well as the emergence of DNA damage and genomic instability. For example, LPS produced by periodontal pathogens activates TLR2 and TLR4, leading to the activation of NF-κB, which in turn induces the production of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-α) and antimicrobial peptides (Table 2). This signaling pathway contributes to the establishment of a chronic inflammatory state that predisposes tissues to dysplastic transformation [10, 47]. The secretion of IL-8, a cytokine with both pro-inflammatory and chemotactic functions, can be further enhanced by OMV from *F. nucleatum*, *P. gingivalis*, and *T. forsythia* [54] (Table 2). Overexpression of IL-8 has been associated with the progression, invasion, and metastasis of OSCC [53]. Gingipains from *P. gingivalis* and the BspA protein from *T. forsythia* contribute to the activation of the PI3K/Akt pathway through interactions with TLRs and protease-activated receptors (PARs) [47, 54] (Table 2). *P. gingivalis* and *F. nucleatum* also interact with host receptors to activate the MAPK/ERK pathway. Furthermore, *F. nucleatum* can stimulate IL-6 production via TLR engagement, thereby activating the JAK/STAT3 pathway and inhibiting apoptotic mechanisms [46, 50, 59] (Table 2).

New studies show that periodontal bacteria play a role in carcinogenesis, as well as EMT. In particular, *P. gingivalis* invades epithelial cells and induces EMT with the help of cell surface fimbriae (FimA) [10]. Normally, epithelial cells are characterized by cobblestone appearance and adherent junctions (AJs), but during EMT, they acquire the typical

Table 2: The role of periodontal bacteria on the molecular pathways driving epithelial dysplasia.

Periodontal bacteria	Activity changes in dysplasia [references]
Periodontal bacteria LPS	Increase in IL-1β, IL-6, IL-8, TNF-α production [10, 47]
Porphyromonas gingivalis/*Treponema denticola*/*Fusobacterium nucleatum*	Increase in IL-8 production [54]
P. gingivalis/*Tannerella forsythia*	Activation of PI3K/Akt pathway [47, 54]
P. gingivalis/*F. nucleatum*	Activation of MAPK/ERK pathway [46, 50, 59]
F. nucleatum	Activation of the JAK/STAT3 pathway [46, 50, 59]

spindle-shaped mesenchymal morphology, losing epithelial markers, such as epithelial cadherin (E-cadherin), occludin, and cytokeratins, which leads to the loss of cell–cell adhesion and apical-basal polarity. After EMT, cells become more aggressive, gaining the ability to invade and migrate [10]. The process of mesenchymal transition is characterized by the upregulation of mesenchymal markers such as N-cadherin and vimentin, along with the downregulation of epithelial markers [45]. Evidence suggests that gingipains – particularly Rgp and Kgp – are responsible for this shift, as they reduce the expression of epithelial markers like E-cadherin [45]. Gingipains also stimulate PAR-2 and PAR-4, increasing downstream signaling via the ERK1/2–Ets1, p38/HSP27, and NF-κB pathways. This signaling cascade leads to the overexpression and activation of pro-MMP-9, enhancing OSCC invasiveness [57]. Moreover, *P. gingivalis* has been shown to modulate the transcriptional activity of key EMT-related factors, such as ZEB1 (Zinc Finger E-Box Binding Homeobox-1) [57, 60]. Its proteases have also been implicated in extracellular matrix (ECM) degradation, further facilitating EMT and tumor progression [43].

As we know, periodontitis is characterized by the chronic inflammation of the gingiva and subsequent tissue destruction, in which neutrophils play a key role [41]. In healthy conditions, there is an equilibrium between the oral microbiota and the immune system, and this condition is maintained by neutrophils present in the gingival sulcus. Here, these immune cells interact with the oral biofilm, regulating it and ensuring periodontal health [41].

Neutrophils represent the first line of defense. In fact, they eliminate pathogens through phagocytosis or with neutrophil degranulation, a process characterized by the release of different enzymes such as myeloperoxidase (MPO), elastase, cathepsin G contained in specialized granules in the extracellular space [41] (Figure 2).

In periodontitis, neutrophils are not able to eliminate or control microbial pathogens, therefore, there is the accumulation of neutrophils in periodontal tissue, with tissue damage and potential bone loss [41]. The destruction of periodontal tissues is due to the release by neutrophils of ROS, matrix metalloproteinases (MMPs), elastase, and cathepsins that degrade extracellular matrix components [41]. In addition, periodontal bacteria such as *P. gingivalis*, *A. actinomycetemcomitans*, and their LPS contribute to the enhanced recruitment and activation of neutrophils in the periodontium, indeed, patients with periodontitis show increased neutrophil counts [41]. On the other hand, *P. gingivalis* can also limit neutrophil phagocytosis, leading to prolonged inflammation [41]. Neutrophils can eliminate microorganisms, also generating neutrophil extracellular traps (NETs), but periodontal bacteria like *P. gingivalis*, *T. forsythia*, *F. nucleatum*, *P. intermedia*, evade NETs with the production of DNases to degrade the DNA backbone of NETs, facilitating bacterial infiltration of periodontal tissues, with an increased inflammatory response and tissue destruction [41] (Figure 2). Moreover, neutrophils can release proinflammatory cytokines, including TNF-α and IL-1β, promoting local inflammation and recruiting other immune cells to the site of infection [41].

Neutrophils have a key role in both chronic inflammation and tumors [41]. For this reason is used neutrophil-to-lymphocyte ratio (NLR) is used as a biomarker for oral cancer [61]. NLR is employed because both neutrophils and lymphocytes T help develop tumors with different mechanisms; in fact, neutrophils secrete various molecules, including vascular endothelial growth factor (VEGF), chemokines, and proteases, which facilitate angiogenesis, promoting the development and progression of tumors. Moreover, they can suppress T-cell proliferation through the involvement of integrin Mac-1 and hydrogen peroxide [61]. On the other hand, T lymphocytes primarily inhibit the proliferation and metastasis of tumor cells through cytotoxic cell death and cytokine production [61]. Consequently, a high NLR is a negative predictor of OSCC [61]. Some studies calculated NLR in the blood samples of patients, recognizing systemic inflammation, while other studies used salivary samples, which reflect localized inflammation within the oral cavity. Focusing on the salivary sample, there is a high chance of malignant transformation in patients with OPMDs with salivary NLR values≥4. Such individuals should be subjected to a strict follow-up, particularly if they have oral erythroplastic lesions affecting the floor of the mouth, and they are exposed to other risk factors like alcohol or tobacco use [61].

Also, NETs have been associated with the promotion of cancer, too; in fact, they create a proinflammatory environment and promote angiogenesis and metastasis [41].

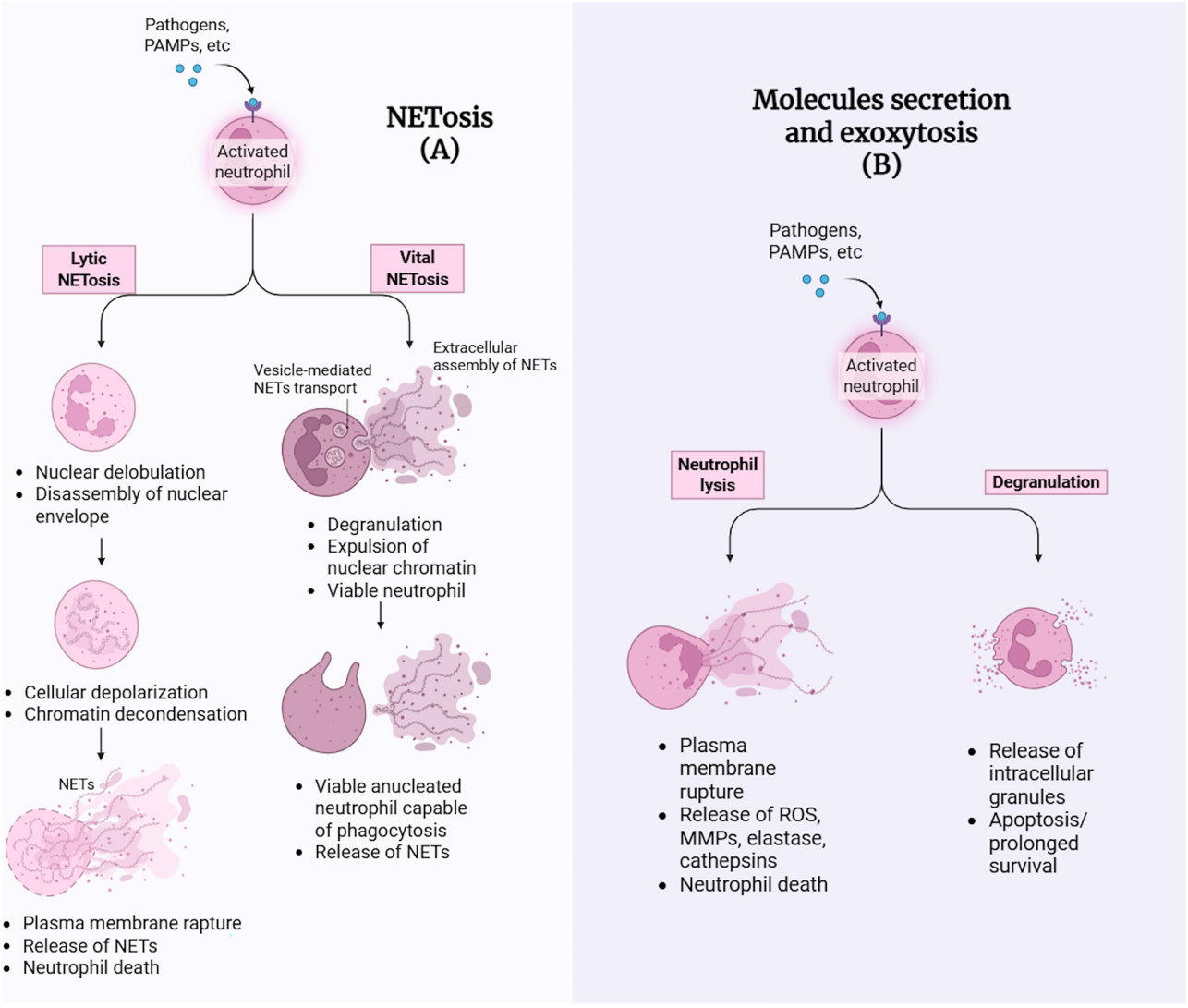

Figure 2: Mechanisms of NETosis and mediator release by neutrophils. (A) Upon activation through TLR-mediated pathogen recognition, neutrophils can release NETs via two pathways: Lytic NETosis and vital NETosis. In lytic NETosis, plasma membrane rupture leads to neutrophil death, whereas in vital NETosis, the neutrophil expels its nuclear contents as NETs while remaining viable and retaining phagocytic function. By contrast, (B) exocytosis and secretion of other mediators may occur either through cell lysis and death or via the regulated release of granule contents (degranulation). In the latter scenario, the neutrophil may survive or subsequently undergo apoptosis. Created in https://BioRender.com, accessed on 18 April 2025.

Current limitations

Although the aim of our review is to examine recent evidence on the role of periodontitis as a risk factor in the onset and progression of OSCC, some studies highlight that this epidemiologic correlation may be influenced by confounding factors, including alcohol consumption and tobacco smoking which constitute consolidated risk factors for different type of cancers [8], Evidence indicates that various lifestyle factors increase the probability of developing both periodontitis and oral cancer [62]. However, considering the reduction in tobacco exposure alongside the concomitant increase in the incidence of oral cavity cancer, recent studies have focused on an emerging population of patients with OSCC who are non-smokers, non-drinkers, and HPV-negative, to identify other possible etiological factors [63]. Among the potential causes, the role of microbiome has been investigated, and results have shown a loss of commensal bacteria in OSCC patients, regardless of alcohol consumption. In HPV-negative and non-smoking individuals, an increase in virulence factors associated with *Fusobacterium* was observed, along with enhanced biosynthesis, chemotaxis, iron transport, and greater activity at the tumor site. Furthermore, in a study by Ganly et al. analyzing 16S rRNA, individuals with these same characteristics

exhibited an increased presence of periodontal pathogens such as *Fusobacterium* and *Prevotella*. [63]. These results corroborate the association between periodontal bacteria-mediated inflammation and OSCC in patients without confounding risk factors [64].

Future directions

The relationship between cancer and periodontitis has been extensively debated, and the inconsistent findings across studies highlight the need for further investigation. Current literature emphasizes that elucidating the mechanisms through which periodontitis may contribute to carcinogenesis would benefit from the application of several epidemiological methodologies, in order to strengthen the evidence supporting a causal relationship between these two conditions [19]. Although traditional randomized controlled clinical trials (RCTs) represent the gold standard for demonstrating causality between an exposure and an outcome, they have limitations, including the study population [19], the presence of confounding factors, and reverse causality, which can lead to erroneous conclusions [65]. Another epidemiological approach capable of uncovering potential causal relationships is Mendelian randomization analysis. This method uses genetic variants as instrumental variables associated with the exposure and is less prone to bias compared to observational studies, thereby proving to be more effective [65].

Future research should focus on innovative approaches to cancer treatment; immunotherapy, which aims to activate the host immune system, represents one of this [66]. Recent studies have thus explored the role of the microbiome in cancer treatment response, proposing that periodontitis may affect both the efficacy and tolerability of immunotherapy. Specifically, the results of the study by Pai et al. showed that *P. gingivalis*, through the production of gingipains, alters the complement pathway by proactively generating C5a. Since dysregulation of C3 or C5 can negatively affect the efficacy of immune checkpoint blockade (ICB) therapy, untreated periodontitis may impede the response to immunotherapy [67]. It is important to highlight that the study in question refers to various types of cancer, without specifically addressing oral cancer. Further research on the role of periodontal bacteria in the response to immunotherapy will help develop new strategies for the treatment of OSCC.

The investigation into the mechanisms by which *P. gingivalis* contributes to cancer progression has identified novel therapeutic targets aimed at improving the efficacy of immunotherapy in patients with OSCC. Recent studies have demonstrated that *P. gingivalis* induces PD-L1 overexpression in gingival keratinocytes, altering the host's immune response against cancer, in fact, individuals with chronic periodontitis showed an increase in PD-L1 expression on peripheral blood leukocytes [34]. Programmed death-ligand 1 (PD-L1) is an immunomodulatory molecule expressed on various immune cells, epithelial cells, and tumor cells. The binding of PD-L1 to its receptor, programmed death-1 (PD-1), on activated T cells, induces T cell apoptosis or anergy. In several types of cancer, including OSCC, PD-L1 overexpression facilitates tumor immune evasion and is associated with poor prognosis. Therefore, PD-L1 may represent a promising therapeutic target in the treatment of OSCC [34].

Considering the role of periodontal inflammation in tumorigenesis, periodontal therapy should be integrated into the management of patients at risk. Periodontal therapy, in fact, exerts a significant impact both locally and systemically, while the oral cavity also benefits in terms of microbial composition. The control of supra- and subgingival plaque contributes to the control of dysbiosis and may therefore reduce the risk of onset and progression of cancer in general, and potentially of oral cancer. Indeed, the study by have shown a reduced overall cancer risk in patients with periodontitis who received treatment, as compared to those who did not (aHR=0.41; 95 % CI=0.38–0.44) [17]. Furthermore, the risk is further reduced by increasing the frequency of treatment. With regard to OSCC, scaling has been shown to significantly reduce local inflammation and to exert a significant impact on the onset of oral cancer. Oral hygiene measures and maintenance visits may represent an innovative strategy for the prevention and management of patients with dysplasia and OSCC [68].

Conclusions

In conclusion, our study points out is evidencing the role of periodontal inflammation in oral carcinogenesis.

The mechanisms by which periodontal bacteria such as *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans*, *T. forsythia*, and *T. denticola* promote the development and progression of oral cancer have been described in detail. From the results, we can say periodontitis predisposes individuals to tumorigenesis through chronic inflammation, oxidative stress, microbiome alterations, and immune system disruption. Furthermore, our study reinforces the significance of oral dysbiosis and the role of periodontal pathogens such as *P. gingivalis* and *F. nucleatum* in promoting chronic inflammation and potentially contributing to epithelial dysplasia and the progression of OPMDs toward OSCC.

The limitations encountered in establishing a definitive correlation between oral cancer and periodontitis, due to various confounding factors, are critically examined. Given the relevance of this topic, the application of novel epidemiological approaches is proposed to further clarify their association. Finally, recognizing the epidemiological significance and clinical impact of OSCC in the population, the study suggests new treatment strategies targeting the pathogenic mechanisms employed by periodontal bacteria in the development of this malignancy.

Considering the effects of periodontal inflammation, its reduction contributes to improving patients' health. Indeed, periodontal therapy results in a significant reduction of both local and systemic inflammation. Therapeutic approaches, including mechanical instrumentation and plaque removal, lead to a decrease in inflammation, while the oral microbiome benefits from a reduction in periodontal pathogens. These findings highlight the need for an integrated approach that addresses both periodontal health and the associated cancer risk.

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