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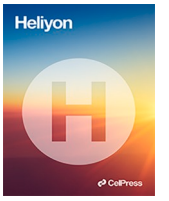

Review article

Dysbiosis linking periodontal disease and oral squamous cell carcinoma-A brief narrative review

Swetha Acharya [a,1], Usha Hegde [a,*], Anirudh B. Acharya [b,1], Priyanka Nitin [a]

[a] Department of Oral Pathology, JSS Dental College and Hospital, JSS Academy of Higher Education and Research (JSSAHER), Mysuru, 570004, Karnataka, India
[b] Department of Preventive and Restorative Dentistry, College of Dental Medicine, University of Sharjah, Sharjah, United Arab Emirates

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ABSTRACT

An association between periodontal disease and oral squamous cell carcinoma (OSCC) has been recognized. However, there is no causal relationship between the two. The polymicrobial etiology of periodontal disease is confirmed, and so are the proven etiological factors for OSCC. Inflammation lies at the core of periodontal pathogenesis induced by the putative microbes. OSCC has inflammatory overtures in its pathobiology. Bacterial species involved in periodontal disease have been extensively documented and validated. The microbial profile in OSCC has been explored with no specific conclusions. The scientific reasoning to link a common microbial signature that connects periodontal disease to OSCC has led to many studies but has not provided conclusive evidence. Therefore, it would be beneficial to know the status of any plausible microbiota having a similarity in periodontal disease and OSCC. This brief review attempted to clarify the existence of a dysbiotic "fingerprint" that may link these two diseases. The review examined the literature with a focused objective of identifying periodontal microbial profiles in OSCC that could provide insights into pathogen commonality. The review concluded that there is great diversity in microbial association, but important bacterial species that correlate with periodontal disease and OSCC are forthcoming.

1. Introduction and background

Periodontitis is recognized as a multifactorial inflammatory disease primarily initiated by a polymicrobial etiology, associated with dysbiosis, and characterized by progressive destruction of the periodontal tissues [1]. Eleven percent of the worldwide population is affected by severe periodontitis [2,3]. Oral squamous cell carcinoma (OSCC) is the most common oral cancer (90 %), and the 8th most common of all malignancies [4–6]. It has tobacco and alcohol consumption, areca nut, and betel quid chewing as major risk factors [7]. Other than these risk factors, host genetics and microbial infections are potential risk factors [8,9]. Microbial dysbiosis is associated with tumorigenesis across various cancers [10]. The oral microbiome seems to be associated with OSCC pointing to a noteworthy and consistent shift in the microbial signatures. It is posited that the microbiota promotes oncogenesis by inducing inflammation, producing carcinogenic substances, and inhibiting apoptosis [11]. A connection between periodontitis and OSCC was explored, and a positive association has been indicated [12–15].

* Corresponding author.
E-mail addresses: publicationusha@gmail.com, dr.ushahegde@jssuni.edu.in (U. Hegde).
[1] These authors contributed equally to this work.

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The microbial pathogenic mechanism of periodontitis can be viewed as three phases that are, disease initiation, exacerbation, and resolution. The periodontal microbiome and its relationship to periodontitis is intricate. The concept of the "Inflammation-Mediated Polymicrobial-Emergence and Dysbiotic-Exacerbation" or the IMPEDE model has been proposed by Van Dyke et al. [15] in 2020. Such a dysbiotic infection promotes persistent low-grade inflammation that in turn, can be linked to cancer. Subgingival biofilms in periodontitis become reservoirs of anaerobic, Gram-negative bacteria. Periodontal pathogens such as *Porphyromonas gingivalis (P.g)* and *Aggregatibacter actinomycetemcomitans (A.a)* produce enzymes that digest extracellular matrix components like collagen to release substrates to support their nourishment and to invade tissue. Such enzymes and toxic metabolic by-products, endotoxins, result in DNA damage to the host epithelial cells. Also, in sites of infection and inflammatory microenvironment, proto-oncogenes and tumor suppressor gene mutations occur, and cell proliferation and survival are affected [16–19]. Variations exist in the composition of the bacterial communities of oral cancer tissue when compared with non-cancerous tissue, and this shift in bacterial colonization may relate to a higher risk of OSCC. The oral microflora, for instance, may encourage oral carcinogenesis by stimulating toll-like receptors (TLRs) which have been associated with inflammatory responses, epithelial and tumor cells [20,21]. A wealth of data about the characterization and understanding of the oral microbiome has been possible because of studies like the Human Microbiome Project [22], Metagenomics of the Human Intestinal Tract [23], and a massive improvement in metatranscriptomics, as well as in Next Generation Sequencing (NGS) technologies for 16S rRNA examination, and the development of the Human Oral Microbiome Database [24].

In such a background, this narrative review will consider dysbiosis as the central theme interlinking a conceivable relationship between the dysbiotic microbial signatures in periodontal disease and OSCC. The focus will be on bacteria as these microbes are the most important from a periodontal point of view, to establish a possible link with OSCC.

2. Discussion

2.1. Dysbiosis

Humans and their resident microbiota have co-evolved for more than a billion years, so much so, that humans have become the "holobiont" or a "superorganism", owing to the combination of commensal, symbiotic and pathogenic aspects of the microbial communities residing on or in the human body. The contributions of the endogenous microbiome to human biological function include the generation of energy, nutrition, and digestion of food, regulation of metabolism, immune regulation, detoxification, maintenance of the mucosa, and resistance to pathogenic microbial infection [25–27]. Discomposure of the endogenous microbiome due to any reason can be unfavorable to human health, i.e., a dynamic equilibrium of the resident microflora (symbiosis) maintains health, whereas a disruption of this equilibrium (dysbiosis) leads to disease wherein a dysbiotic microbiome is established. Dysbiosis is a "condition in which the normal microbiome population structure is disturbed, often through external burdens such as disease states or medications" [28]. Oral dysbiosis is caused due to age, hormonal changes(puberty/pregnancy) [29], salivary gland dysfunction,

Table 1
Bacterial species in health, gingivitis, and periodontitis [40,41,80].

Health	Gingivitis	Periodontitis
Streptococcus mitis	*Streptococcus mitis*	*Porphyromonas gingivalis*
Streptococcus sanguinis	*Streptococcus sanguinis*	*Fusobacterium nucleatum sub spp. vincenti*
Saccharibacteria	*Streptococcus oralis*	*Fusobacterium nucleatum sub spp. animalis*
Rothia aeria	*Streptococcus cristatus*	*Fusobacterium nucleatum sub spp. polymorphum*
Corynebacterium matruchotii	*Streptococcus gordonii*	*Fusobacterium nucleatum sub spp. nucleatum*
Corynebacterium durum	*Leptotrichia buccalis*	*Veillonella parvula*
Lautropia mirabilis	*Leptotrichia hongkongenesis*	*Filifactor alocis*
Actinomyces spp.	*Leptotrichia wadei*	*Prevotella intermedia*
Neisseria flava	*Leptotrichia hofstadii*	*Prevotella nigrescens*
Neisseria elongata	*Actinomyces* spp.	*Neisseria flavescens*
Veillonella parvula	*Actinomyces naeslundii*	*Tannerella forsythia*
Rothia dentocariosa	*Veillonella parvula*	*Lachnospiraceae bacterium*
Capnocytophaga granulosa	*Abiotrophia defectiva*	*Treponema* spp.
Capnocytophaga leadbetteri	*Neisseria flavescens*	*Treponema denticola*
Capnocytophaga sputigena	*Neisseria macacae*	*Fretibacterium* spp.
Haemophilus parainfluenzae	*Neisseria sicca*	*Aggregatibacter actinomycetemcomitans*
Fusobacterium nucleatum sub spp. vincenti	*Granulicatella adiacens*	*Parvimonas micra*
Aggregatibacter	*Rothia aeria*	*Acinetobacter johnsonii*
	Haemophilus parainfluenzae	*Alloprevotella tannerae*
	Prevotella melaninogenica	*Streptococcus mitis*
	Capnocytophaga granulosa	
	Capnocytophaga leadbetteri	
	Fusobacterium periodonticum	
	Fusobacterium nucleatum sub spp. polymorphum	
	Porphyromonas pasteri	

Note: Some species/genus appear in more than one category due to detection, isolation and an integrated overview based on the comparative enrichment of bacteria and the significant differences in their relative abundances.

lifestyle habits (smoking/diet), oral hygiene status, antibiotics/antimicrobials, host genetics, immune factors, systemic diseases, and also because of major ecological pressure (variations in temperature, pH, gingival crevicular fluid {GCF}flow, and inflammation) that alter bacterial competitiveness [30–33]. Bacteria associated with diseases are found to be higher (relative abundance) in oral dysbiosis as compared with health [34]. The tooth structure(non-shedding) and the periodontal soft tissue interface provide a unique site for the oral plaque biofilm to accumulate, and if not removed by oral hygiene measures will drive dysbiosis.

2.2. Dysbiosis in periodontal disease

The bacterial species majorly associated with periodontal health are *Capnocytophaga Actinomyces*, *Streptococcus*, *Bergeyella* spp, *Lautropia mirabilis*, *Rothia* spp, *Neisseria Flava, Corynebacterium* spp, *Gemella* and *Kingella oralis.* [35,36] In the early stages of oral plaque biofilm development, it is largely composed of commensals that initiate gingivitis, the putative periodontopathogens or "pathobionts" implicated in the progression to periodontitis are in minor proportions [37]. Gram-negative bacteria, many being obligate anaerobes such, as *Porphyromonas*, *Leptotrichia*, Selenomonas, *Fusobacterium*, *Campylobacter*, *Tannerella,* and *Lautropia* were found to be positively correlated with bleeding on probing in gingivitis cases [38]. Only about 20 % of bacterial taxa associated with gingivitis are also associated with periodontitis [39]. *Fusobacterium, Corynebacterium*, *Campylobacter*, *Tannerella*, *Prevotella*, *Leptotrichia*, and *Saccharibacteria* are cluster A bacteria associated with mild to moderate forms of periodontitis, whereas the "red complex", i.e., *P.g.*, *Treponema denticola (T.d.), Tannerella forsythia (T.f.)* including *Fretibacterium* spp, and *Filifactor alocis* are considered cluster B bacteria that are associated with widespread and/severe periodontitis [40,41]. A detailed list is provided in Table 1. As per the polymicrobial synergy and dysbiosis (PSD) model [42], the essential factors for the development of a periodontitis-associated microbial community are for the bacteria to express, for example, adhesins, and having physiologic compatibility and being non-antagonistic, resisting host immune responses and contributing to destructive inflammatory mechanisms. Because of the microbiological diversity in periodontitis lesions, potential periodontopathic bacteria are found frequently to contribute to the periodontitis pathology. This requires the role of keystone pathogens. Keystone pathogens are those species that influence the entire microbial community that is much larger than their own biomass [43]. But, for this, the keystone periodontal pathogens (such as *P.g.*) need to be active, wherein they will engage with other pathogens having an accessory role to upset the host immune reactions and enhance the pathogenic potential of the entire biofilm microbial community, with the dysbiotic behavior restricted to few species. The existence of such keystone pathogens to initiate periodontal destruction is dependent on the presence of other species [41]. Hence, periodontal dysbiosis is characterized by inter-bacterial synergy and environmental disturbances caused by inflammation/immune dysregulation [44,45].

2.3. Dysbiosis in OSCC

Helicobacter pylori (*H. pylori*) was established as a cause of inflammatory gastric disease [46]. This was the foundation associating it with cancer of the stomach, which led to the World Health Organization recognizing *H. pylori* as a bacterial etiology of cancer for the

Table 2
Oral bacterial species associated with cancers [9,10,48,68,101].

Oral cancer	Esophageal cancer	Gut cancer	Lung cancer
Fusobacterium nucleatum	*Aggregatibacter actinomycetemcomitans*	*Aggregatibacter actinomycetemcomitans*	*Capnocytophaga* spp.
Fusobacterium periodonticum	*Porphyromonas gingivalis*	*Porphyromonas gingivalis*	*Streptococcus* spp
Capnocytophaga spp.	*Streptococcus angiosus*	*Streptococcus angiosus*	*Veillonella* spp.
Haemophilus influenzae	*Tannerella forsythia*	*Tannerella forsythia*	
Alloprevotella spp.	*Treponema denticola*	*Treponema denticola*	
Filifactor alocis	*Fusobacterium nucleatum*	*Fusobacterium nucleatum*	
Gemella haemolysans		*Actinomyces odontolyticus*	
Gemella morbillorum		*Streptococcus* spp.	
Parvimonas micra		*Alloprevotella* spp.	
Prevotella spp.		*Corynebacterium* spp.	
Porphyromonas gingivalis		*Neisseria* spp.	
Streptococcus mitis		*Veillonella* spp.	
Streptococcus parasanguinis			
Streptococcus constellatus			
Streptococcus angiosus			
Streptococcus gordonii			
Streptococcus salivarius			
Treponema denticola			
Johnsonella ignava			
Peptostreptococcus stomatitis			
Enterococcus spp.			
Slackia spp.			
Prevotella melaninogenica			
Enterobacteriaceae			

Note: Some species/genus appear in more than one category due to detection, isolation and an integrated overview based on the comparative enrichment of bacteria and the significant differences in their relative abundances.

first time. This paved the way for great interest in the bacterial association with cancer [47]. Periodontopathogens like *P.g.*, *T.f.*, *Fusobacterium nucleatum* (*F.n.*), *T.d.,* and *Prevotella intermedia* (*P.i.*) have been associated with cancers [48], and a list is in Table 2.

Three mechanisms have been proposed regarding the association of oral/periodontal bacteria in the pathogenesis of carcinomas [49]. They include the initiation of inflammation, anti-apoptotic influence, and production of carcinogenic substances by the bacteria. First, among the oral microbiota, periodontopathogens bring about inflammatory reactions by stimulating the production of pro-inflammatory mediators that have a destructive effect on the periodontal cellular and extracellular components. They also increase the concentrations of various pro-inflammatory cytokines including TNF-α, several interleukins, and matrix metalloproteinases (MMPs). These play a role in tumor development and progression. Second, the anti-apoptotic mechanism can affect the development of oncogenic phenotypes [50]. Third, the production by the oral bacteria, of carcinogenic substances such as organic acids, volatile sulfur compounds, reactive nitrogen species, and reactive oxygen species, are triggered by pro-inflammatory mediators of the host [51,52]. In other words, breaching the epithelial barrier, invasion by bacteria, the resultant host inflammatory response, and genetic and epigenetic modulation are mechanisms by which oral microbial dysbiosis can be associated with carcinogenesis [53].

Hence, it is imperative to exemplify the functional pathogenic role of some of the most important periodontal bacteria.

2.4. *P.g., F.n. and T.d. in dysbiosis*

It is worthwhile to have an overview of the extensively studied *P.g., F.n.,* and *T.d* (as outlined in sections 2.2 and 2.3). for a perspective on dysbiosis. *P.g.* is crucial in the progression of periodontitis because of its virulence factors such as lipopolysaccharides, fimbriae, and extracellular proteases (gingipains), which destroy periodontal tissue [54,55]. *P.g.* facilitates the development of oral biofilm by encouraging coaggregation of *P.g.* with other bacterial species, and further growth of the bacterial community. These interactions assist the adhesion of *P.g.* in the oral tissue/structures and strengthen the pathogenicity of *P.g* [56]. Some bacterial species (such as *F.n.*) aid the attachment of *P.g.* to human cells. Invasion of tissues by *P.g.* is dependent on its growth phase (the lag phase shows lower invasion), higher invasion at low multiplicity, and maximum at higher multiplicity [57]. Gingipains (arginine-specific gingipains [Rgp, including RgpA and RgpB] and lysine-specific gingipain [Kgp], trypsin-like cysteine proteinases that help in peptides hydrolysis, fimbrial maturation, increased vascular permeability/activation of blood coagulation cascade) contribute to the pathogenic behavior of *P.g.* by enhancing inflammation and tissue destructive processes [58]. *P.g.* fimbriae are involved in the adhesion and invasion of epithelial cells of the gingiva [59]. Apoptosis inhibition by *P.g.* in gingival epithelial cells (inhibiting caspase 3, a pro-apoptotic enzyme, not dependent on fimbriae) is a key adaptation for *P.g.'s* survival. This mechanism ensures the survival of *P.g* [60]. *P.g.* grows inside the gingival epithelial cells, maintaining its viability. *P.g.* activates PI3K/Akt, inhibits mitochondrial transmembrane depolarization, and blocks the cytochrome C release, thereby increasing the survival of the cell [61]. The host-bacteria interactions are facilitated by gingipains [62]. TNF-α amplifies the capability of *P.g.* invasion in epithelial cells of the gingiva by increasing the levels of Intercellular Adhesion Molecule-1 and triggering Rab5 [63]. It has been suggested that *P.g.* infection of immortalized human oral epithelial cells resulted in higher cell proliferation, promotion of cell migration, invasion, and anomalous morphological changes, that may lead to the development of oral cancer [64]. In the context of cancer metastasis, *P.g.* exhibits a notable capability to influence and regulate the epithelial-mesenchymal transition pathways and encourage at best a restricted shift toward the mesenchymal state and may elevate the production of some MMPs-1, 2, 7, 9, and 10, from primary/transformed oral epithelial cells [65–67]. Also, in OSCC, *P.g.* gingipains stimulate proteinase-activated receptors −2 and −4, which increases signaling through extracellular signal-regulated kinase 1/2-Ets1, p38/Heat Shock Protein 27, and nuclear factor kappa B pathways, consequently elevating MMP-9 proenzyme expression [68,69].

Another important player related to dysbiosis is *F.n.* [70–73] It is one of the most frequent and abundant Gram-negative oral anaerobes that outgrow in dysbiosis before periodontal disease and aids *P.g.* in initiating periodontitis [74–76]. It colonizes the dorsal surface of the tongue and the gingival margin as part of the biofilm contributing to the development of subgingival oral biofilm, where it is hypothesized to play an important role in the development of the subgingival dental plaque biofilm [77,78]. *F.n.* binds several bacterial species because of its mechanism of adhesion (coaggregation). *F.n.* coaggregates with *Streptococcus* species (by the adhesin RadD) that are early colonizers able to attach to various surfaces in the oral cavity [79], and with the secondary anaerobic periodontopathic colonizers like *P.g.*, *T.d.,* and *A.a.*, thus bridging them. The strong adhesion mechanisms render *F.n.* the property to resist washing away by oral fluids. Bridging also enables multi-species interactions for co-existence. Apart from binding, *F.n.* can invade different cell types such as epithelial cells of the oral tissues, placenta, and colon, macrophages, keratinocytes, and T-cells, via adhesins Fap2 and FadA [80–82]. These adhesins are implicated in carcinogenesis [83]. *F.n.* is associated with colorectal cancer, and cancer of the pancreas, breast, esophagus, and stomach [84–88]. This has fueled the exploration of the association of *F.n.* in OSCC. A murine OSCC study model provided evidence that *F.n.* (along with *P.g.*) has a role in carcinogenesis [89]. As per this evidence *F.n.* can stimulate carcinogenesis by directly interacting with the oral epithelial cells via TLRs and signaling mechanisms through the interleukin-6/STAT3 axis. Also, *F.n.* induces cyclin D1 and MMP-9, which are involved in tumorigenesis and invasiveness/cancer metastasis [90]. The proposed mechanistic role of *F.n.* in OSCC is (i)the production of cytokines and reactive oxygen species; (ii) the hypermethylation of CpG of tumor suppressor genes LXN and SMARCA2 leading to their inactivation; downregulation of p27, Ku70, and p53 tumor suppressor genes that causes increased cell proliferation; (iii) lipopolysaccharides/TLR4 signaling and nuclear factor kappa B activation that promotes pro-tumor inflammation; the activation of STAT3 that results in cell proliferation and invasion/metastasis; upregulation of microRNA-21 that promotes cancer cells proliferation; (iv) FadA secreted by *F.n.* that binds to E-cadherin which decreases phosphorylation of β-catenin translocating it to the nucleus thereby bringing about cell proliferation along with higher expression of oncogenic genes [91].

T.d. is a Gram-negative spirochete that is pathogenic in periodontal disease. It has several virulence factors such as dentilisin for

adherence, immunomodulation and cytotoxicity [92–94], tissue penetration by flagella and chemotaxis [95,96], and hemin binding protein [97]. Some of these virulence mechanisms bring about the expression/degradation of cytokines which are similar to other pathogenic periodontal bacteria. *T.d.* can inhibit migration of neutrophils and fibroblasts which is a unique characteristic in the pathogenesis of periodontitis [98]. *T.d.* drives cancer aggressiveness through TLR- 2 and, -4/myeloid differentiation primary response 88 protein and integrin/focal adhesion kinase crosstalk [99].

2.5. Dysbiotic signatures connecting periodontal disease and OSCC

Inflammation is one of the drivers of OSCC and periodontal disease can induce a pro-inflammatory milieu that connects it to tumorigenesis. Periodontal disease has been designated as an "enabling characteristic" of carcinogenesis and may increase oral cancer risk by almost double [100–102]. The inflammatory process in periodontal disease, has a unique immunological setting that is initiated by putative pathogens that could facilitate tumor progression. *P.g., F.n.,* and *T.d.* boost cell migration, invasiveness, stemness, and oral tumorigenesis of OSCC [103].

Table 3
Selected reports of putative periodontal bacteria associated with OSCC.

Author (Year)	Bacterial species demonstrated	Source	Method	Conclusion
Nagy et al. (1998) [106]	*Veillonella, Fusobacterium, Prevotella, Porphyromonas, Actinomyces, Streptococcus*	Tumor scraping	Culture	Positive correlation between bacteria and OSCC
Mager et al. (2005) [107]	*Capnocytophaga gingivalis, Prevotella melaninogenica, Streptococcus mitis*	Saliva	Checkerboard DNA-DNA hybridization	Increased presence in saliva of patients with OSCC
Hooper et al. (2006) [108]	*Streptococcus anginosus, Prevotella, Veillonella, Fusobacterium*	Direct culture	Sanger sequencing	Positively associated with OSCC
Pushalkar et al. (2012) [20]	*Peptostreptococcus stomatis, Streptococcus salivarius, Streptococcus gordonii, Gemella haemolysans, Gemella morbillorum, Johnsonella ignava* and *Streptococcus parasanguinis*	Homogenized tumor	Sanger sequencing	Increased abundance in patients with OSCC
Schmidt et al. (2014) [109]	*F. nucleatum, Streptococci*	Oral swab	454 Pyrosequencing	Positive correlation with *F. nucleatum*, negative correlation with *Streptococci*
Sztukowska et al. (2016) [65]	*P. gingivalis*	Biopsy	Immunohistochemistry	Increased presence of *P. gingivalis* in OSCC biopsies
Mukherjee et al. (2017) [110]	*Streptococcus*	Homogenized tumor	Ion Torrent Personal Genome Machine	Increased abundance in patients with OSCC
Zhao et al. (2017) [111]	*Fusobacteria, Peptostreptococcus, Filifactor*	Lesion surface scraping	Illumina MiSeq sequencing	Increased colonization in patients with OSCC
Shin et al. (2017) [112]	*Fusobacteria, Firmicutes, Actinobacteria, Streptococcus and Proteobacteria*	Biopsy	Ion Torrent Personal Genome Machine	Relative abundance of *Fusobacterium* increased but *Streptococcus* decreased in both primary and metastatic samples.
Listyarifah et al. (2018) [113]	*T.denticola*	Oral swab	Immunohistochemistry	Positive association of *T. denticola* surface protease dentilisin with OSCC and stage
Yang et al. (2018) [114]	*Fusobacteria, Bacteroidetes, Filifactor, Streptococci*	Oral rinse	Illumina MiSeq sequencing	Increased colonization by *Fusobacteria, Bacteroidetes*, and *Filifactor* was positively associated with OSCC and stage, whereas *Streptococci* were negatively associated
Ganly et al. (2019) [115]	*Fusobacteria, Prevotella, Streptococcus*	Oral rinse	454 FLX platform sequencing	Positive association between *Fusobacteria* and *Prevotella* with OSCC and negative association with *Streptococcus.* This association was independent of HPV status
Chang et al. (2019) [116]	*P. gingivalis, F. nucleatum*	Subgingival plaque and homogenized tumor	Illumina MiSeq sequencing	Increased colonization of cancerous and paracancerous tissue vs. healthy sites
Sarkar et al. (2021) [117]	*Prevotella, Corynebacterium, Pseudomonas, Deinococcus, Noviherbaspirillum, Actinomyces, Sutterella, Stenotrophomonas, Anoxybacillus, and Serratia*	Biopsy	MiSeq platform sequencing	*Prevotella, Corynebacterium, Pseudomonas, Deinococcus and Noviherbaspirillum,*

The "passenger-turning-driver" (PSD) model [104], may provide insights into the role of periodontal bacteria in OSCC. As per this model, the microbiota (periodontal and/or others) does not initiate OSCC. The tumor is just a "passenger" because of the microbiota inside the tumor microenvironment. When this microbiota competitively matures, there is a higher expression of proinflammatory mediators and mechanisms that change to a dysbiotic microbiota, which becomes the "driver" that maintains a chronic state of inflammation, thereby enhancing tumorigenesis. The PSD model [42], described earlier, is similar to this mechanism and has been extrapolated to colorectal cancer [105]. The PSD model proposes that host cell mutations create a tumor microenvironment for variable microbiomes in different sites. When periodontal keystone pathogens such as *P.g.*, are relatively overabundant, the microbial community develops the potential for tumorigenesis. Inhibition of apoptosis, higher cell proliferation, and migration, along with sustained dysbiotic inflammation promote oncogenesis and enhance *P.g.* colonization favoring inflammation through a feed-forward mechanism. This can now be considered a "hitchhiker-turned-car-jacker" model [47]. OSCC harbors diverse microbes like periodontal disease; the microbes develop into communities that bring about codependence amongst the individual species in the community resulting in a collective but singular pathogenic unit. This community pathogenicity known as nososymbiocity, is a driver of periodontal disease and the same may be applied to the tumor microenvironment in OSCC.

Reports have demonstrated the association of putative periodontal pathogens in OSCC showing a wide variety of species (selected studies in Table 3) [20,65,106–117]. This makes it challenging to identify a constant microbial signature. To illustrate this further, Radaic et al. [118], have concluded that *P.g., F.n.,* and *T.d.* enrich genetic processes related to cancer progression, while *S. sanguinis* enrich processes related to RNA processing and adhesion. Also, a review by Pignatelli et al. [119], points to species of *Streptococcus*, *Prevotella, Fusobacterium*, and *Capnocytophaga* to have significantly increased in salivary samples of OSCC patients. A systematic review indicates *Fusobacterium, Peptostreptococcus, Alloprevotella, Capnocytophaga, Catonella,* and *Prevotella* species to be associated with head and neck squamous cell carcinomas [120]. Yet, it is observable that *P.g.* and *F.n.* seem to have the hallmarks of synergistic capabilities in periodontal disease and the tumor microenvironment in OSCC. It is interesting to know that apart from the bacterial interaction with the tumor cells, they also have an impact on other elements in and around the tumor. *P.g.* may be able to affect epithelial-mesenchymal transition (by upregulating the transcription factor Zinc Finger E-Box Binding Homeobox-1) and by disrupting cell-to-cell interaction, migration, and degradation of the extracellular matrix [65,67]. *P.g.* can increase the collagen degrading ability of gingival fibroblasts, by increasing activation of MMPs and by influencing the mRNA expression of MMPs [121],avoiding immune destruction by bringing about T-cell and B-cell apoptosis and inhibiting tumor phagocytosis by macrophages [122–124]. These mechanisms are intricately connected to *P.g.* affecting sustained proliferative signaling (by activating P13K/AKT), evading apoptosis of tumor cells (by activating JAK/STAT, P13K/AKT), evading growth suppression(by inactivating PTEN and P53), and sustaining angiogenesis (by inducing vascular endothelial growth factor) [125].

For an added perspective, it is of interest to know about the translocation of these pathobionts that link periodontal disease and OSCC. Based on the location of the tumor, periodontal bacteria may infiltrate the OSCC lesion through the periodontal tissue. OSCC sites may be more permeable and at higher risk of being exposed to the inflammatory influence of these periodontal bacteria [126]. Katz et al. [127], have demonstrated the presence of *P.g.* in gingival squamous cell carcinoma. Other than the periodontal sites *per se*, periodontal bacteria can play a part in carcinogenesis in the lateral border of the tongue because of its proximity to the lingual aspects of the molars which harbor oral biofilm with periodontal inflammation, thereby exposing it to periodontal pathogens. *P.g.* and *T.f.* were higher in the tongue of periodontitis patients [128].

Undoubtedly, diverse genera and species have been identified in periodontal disease and OSCC. However, based on the current literature, it is not feasible to unequivocally ascribe a microbial "fingerprint" linking periodontal disease and OSCC, causal or correlative. Thus far, this narrative opines that *P.g.* and *F.n.* seem to have a more pathogenic involvement in both periodontal disease and OSCC. This is based on the abundant evidence that these two "alpha bugs" are explicitly pathogenic in periodontal disease and have been frequently associated with OSCC. It is recommended that future investigations use *P.g.* and *F.n.* as the primary "inflammophilic" microbes, with more attention to their specific interactions with other species that would promote a pro-inflammatory tumor microenvironment. This would be of immense importance *vis-à-vis* identification or association studies and stimulating the discovery of such pathobionts as possible contributing factors in OSCC. It is to be noted that many methods have been used for isolation, identification, and characterization of the bacteria such as DNA hybridization methods, polymerase chain reaction methods, and the invaluable NGS methods. Although NGS techniques offer the advantage of being a "gold standard", the limitations of NGS techniques generally may include cloning bias, relatively short read lengths, high error rates, relatively low throughput, etc. [129], that needs to be considered in additional research investigating the microbial "fingerprint" of periodontal disease and OSCC.

The clinical therapeutic implications of treating dysbiosis are to be contemplated based on pharmacobiomics (the use of antibiotics, probiotics, and prebiotics) influencing both gut and oral dysbiosis in OSCC. This may affect other therapeutic interventions(surgical, radiation, or chemotherapy) for OSCC before, during, or after treatment [11]. Considerations include antibiotic resistance [130], stabilization of the microbiome during radiation therapy [131], and their role in immunotherapy of OSCC [132,133].

3. Conclusion

This review attempted to find the dysbiotic microbial profile linking periodontal disease and OSCC. We conclude that based on inflammation as a common platform for periodontal disease and OSCC, the putative periodontal bacteria *P.g.* and *F.n.* are seemingly the candidates of the highest importance in the microbial connection between periodontal disease and OSCC. It is recommended that systematic reviews with a focus on specific bacteria may be of great value for further investigations in this intriguing field.

Ethics statement

Not applicable.

Data availability statement

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Swetha Acharya: Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. **Usha Hegde:** Writing – review & editing, Writing – original draft, Validation, Formal analysis. **Anirudh B. Acharya:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. **Priyanka Nitin:** Writing – review & editing, Writing – original draft, Validation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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