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Oral Microbiota and Cancer Development

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Abstract
Oral microbiota are among the most diverse in the human body. More than 700 species have been identified in the mouth, and new sequencing methods are allowing us to discover even more species. The anatomy of the oral cavity is different from that of other body sites. The oral cavity has mucosal surfaces (the tongue, the buccal mucosa, the gingiva, and the palate), hard tissues (the teeth), and exocrine gland tissue (major and minor salivary glands), all of which present unique features for microbiota composition. The connection between oral microbiota and diseases of the human body has been under intensive research in the past years. Furthermore, oral microbiota have been associated with cancer development. Patients suffering from periodontitis, a common advanced gingival disease caused by bacterial dysbiosis, have a 2–5 times higher risk of acquiring any cancer compared to healthy individuals. Some oral taxa, especially *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have been shown to have carcinogenic potential by several different mechanisms. They can inhibit apoptosis, activate cell proliferation, promote cellular invasion, induce chronic inflammation, and directly produce carcinogens. These microbiota changes can already be seen with potentially malignant lesions of the oral cavity. The causal relationship between microbiota and cancer is complex. It is difficult to accurately study the impact of specific bacteria on carcinoma development in humans. This review focuses on the elucidating the interactions between oral cavity bacterial microbiota and cancer. We gather literature on the current knowledge of the bacterial contribution to cancer development and the mechanisms behind it.

Introduction

Healthy bacterial microbiota and homeostasis between the human host and microbiota is important for normal human body function [1]. The microbiota interacts with several human body functions. It can, e.g., modulate immune responses, modify the food intake, affect appetite, take part in vitamin biosynthesis, protect humans from exogenous pathogens, and produce some an-

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timicrobial substances [2]. These effects are considered beneficial, and life without bacteria would not be the same – and maybe not even possible [1]. If microbiota homeostasis is distorted and some pathogenic bacteria becomes more prevalent, disease may occur.

When abnormalities occur in an otherwise balanced system, the term dysbiosis is used. However, the microbiota are continually changing as a result of internal and external stimuli. Therefore, it is difficult to investigate and understand the complex nature of microbiota-host interactions and the triggers of disease onset in the human body. Despite this fact, several different diseases have been connected to alterations in microbiota composition. It has been suggested that alterations in the bacterial microbiota composition might affect at least the onset of inflammatory bowel disease, type 1 and type 2 diabetes, obesity, allergies, asthma, autism, and Alzheimer disease [2–11].

The interaction between an individual's microbiota and the environment is dynamic. Individually there are usually no major fluctuations in the microbiota composition over time [12]. Between individuals the microbiota composition varies according to age, sex, and diet in health and disease, in addition to geographical variations [13, 14]. The human microbiota starts to develop gradually before and after the delivery [15–17]. Most of these initial changes in the bacterial microbiota composition start to settle after some months of life, also in the oral cavity [18–28].

Bacterial dysbiosis in the adult oral cavity can cause, e.g., gingivitis, periodontitis, dental caries (tooth decay), and endodontic abscesses. Nevertheless, due to the continuous interplay between microbiota and the human host's immune response, acute infections in the oral cavity are rather rare taking into consideration the dense microbial colonization [29–32]. Besides this, oral bacteria have been implicated in numerous systemic diseases as well. Oral cavity-linked bacterial species have been found in bacterial endocarditis, aspiration pneumonia, osteomyelitis, rheumatoid arthritis, and cardiovascular disease [33–36]. Furthermore, poor oral hygiene and periodontitis have been associated with an increased risk of oral squamous cell carcinoma (OSCC) [37].

The prevalence of OSCC is increasing, but it has been detected to be highly variable according to gender, behavior (etiological factors), and geography [38]. While the treatment has improved in recent years, an early diagnosis remains very important for a better prognosis [39]. Unfortunately, patients treated with the first primary OSCC have a high risk of developing recurrent or secondary primary OSCC [40]. This has been explained by field cancerization, which is caused by long-term use of tobacco products and/or heavy alcohol use [41]. Another explanation might be the oral cavity bacterial microbiota composition that could have contributed to a malignant transformation in the first place.

OSCC does not often present any major symptoms, but it is easily detectable via direct examination. Therefore, it is vitally important for the oral cavity mucosa to be screened regularly by an experienced (dental) professional, especially for patients with risky behavior [42, 43]. OSCC is a relatively rapidly progressing carcinoma and it metastasizes early to local neck lymph nodes [44–46]. The most often seen clinical lesion are symptomless nonhealing ulcers [43]. Pain is a late symptom [42, 43]. Tobacco and alcohol consumption are known risk factors for OSCC, accounting for a population-attributable risk of 74% [37]. It has been estimated that some 15% of OSCC are of unknown origin, e.g., from bacterial microbiota contribution [47].

This review focuses on oral cavity bacterial microbiota and the known interactions between oral cavity microbiota and OSCC. We have excluded oropharynx-related diseases and other cancer entities such as salivary gland tumors, cancers of the lymphatic tissues, and metastatic manifestations. In addition, the oral cavity anatomy and healthy oral bacterial microbiota are presented. We also describe some significant oral diseases and conditions that may precede OSCC progression.

The Anatomy of the Oral Cavity

The oral cavity begins from the mucosa of the lips. On the palate, the hard palate belongs to the oral cavity and the soft palate belongs to the pharynx. Similarly, the mobile (oral) tongue is part of the oral cavity and the base of the tongue behind the vallate and the foliate papillae is the pharynx.

The anatomy of the oral cavity is exceptional compared to that of other human body sites. A unique feature is hard tissue, i.e., teeth that protrude through the mucosa covering a major part of the oral cavity. Teeth provide nonshedding surfaces for distinct bacterial biofilm formation, whereas mucosal surfaces are continuously renewing and older epithelial layers are shedding from the surface, presenting challenges to permanent bacterial colonization.

The oral mucosal surfaces differ according to anatomical location; roughly it can be divided to masticatory and

nonmasticatory mucosa. Masticatory mucosa, also known as keratinized stratified squamous epithelium, is found from the attached gingiva around the teeth, the hard palate, and the tongue's upper surface. The tongue's upper surface is, in addition, embedded with lingual papillae with taste buds. Everywhere else, the mucosa in the oral cavity is called nonmasticatory mucosa or stratified squamous nonkeratinized epithelium at buccal and labial sites as well as at the floor of the mouth. In cases of continuous trauma, the nonkeratinized epithelium can transform into keratinized epithelium by nonneoplastic hyperkeratinization [48–50].

Teeth are hard calcified structures that are in close contact with mucosa in the oral cavity. This unique structure cannot be found anywhere else in the human body. Babies are born without teeth, and the first primary (deciduous) teeth erupt usually around the age of 6 months. The transition to permanent teeth starts at around 7 years of age and continues until the early 20s (wisdom teeth). Between the teeth and the mucosal gingiva is the gingival sulcus, which is an important anatomical site for bacterial biofilm formation, i.e., plaque [51, 52].

One important aspect of oral cavity health is saliva production. Saliva is produced from the major and minor salivary glands. The major salivary gland openings are located on the floor of the mouth (i.e. sublingual caruncles) and in the buccal mucosa, known as the Stensen duct. Around 1–2 L of saliva are produced and swallowed daily [52]. Saliva is mainly composed of water, electrolytes, mucus, antibacterial compounds (such as IgA), and enzymes that help to digest food and kill bacteria [53, 54]. Saliva function is critically important to maintain oral health. Without saliva, the prevalence of oral bacterium-related diseases (such as dental caries, gingivitis, and periodontitis) increases significantly [53, 54].

The Healthy Oral Microbiota

The Human Oral Microbiome Database (HOMD) lists the most prevalent phyla in the adult human oral cavity as being composed of Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria [30, 55, 56]. This has also been corroborated in other studies [35, 57]. In March 2020 the HOMD listed 784 different bacterial taxa and 1,567 genomes detected in the human oral microbiome taxonomic hierarchy (HOMD, www.homd.org). The majority of these belong to the Firmicutes phylum (266 taxa and 588 genomes) and furthermore to the Streptococcaceae family (38 taxa and 200 genomes).

The total volume of oral bacteria is around 10^{11} bacteria/mL [30–32]. The main genus in the oral cavity is *Streptococcus,* in addition to *Haemophilus, Leptotrichia, Porphyromonas, Prevotella, Propionibacterium, Staphylococcus, Veillonella,* and *Treponema* [30, 35, 56, 57]. Nonetheless, some bacterial species are more site specific while others can flourish in multiple locations simultaneously [35, 55]. Oral microbiota present the lowest β diversity but the highest α diversity compared to other body sites, and there are only few alterations in oral cavity microbiota composition between different individuals [51, 55]. Since the oral cavity is under constant exposure to exogenous microorganisms while eating, drinking, and breathing, it is not always easy to determine which specific species are indigenous and which are only transient [30]. In addition, oral microbiota vary according to age, gender, and even level of education [58]. Nevertheless, once established, oral microbiota remain relatively stable [59].

The HOMD also provides information about the oral anatomical site-specific bacterial composition (Fig. 1) [30, 35]. Nonetheless, oral bacteria can somewhat freely translocate from subgingival sites and other niches with saliva [60].

As mentioned earlier, this review focuses on bacterial microbiota and the known interactions between bacteria and cancer development. Furthermore, microbes other than bacteria can contribute to cancer development. For example, in the oral cavity, persistent oral fungi infections (mainly with *Candida* spp.), persistent high-risk human papillomavirus (HPV) infection, and Epstein-Barr virus (EBV) infection can be involved in oncogenic mutation formation, leading to OSCC development [61–63]. High-risk HPV DNA has been detected already in newborns [64], but it is not known how this early HPV oral positivity can affect health later in life. These different microbes may interact. We have shown differences in bacterial microbiota composition in the oral cavity in oral-HPV-positive women and neonates compared to HPV-negative individuals [64].

Periodontal Disease

Periodontitis is classified as an advanced inflammatory gingival disease caused by bacterial dysbiosis and eventually it can lead to tooth loss [67, 68]. It starts as gingival bleeding in response to inflammation to bacterial biofilm accumulation (plaque) around the tooth marginal gingival surfaces [69]. Periodontitis develops over years

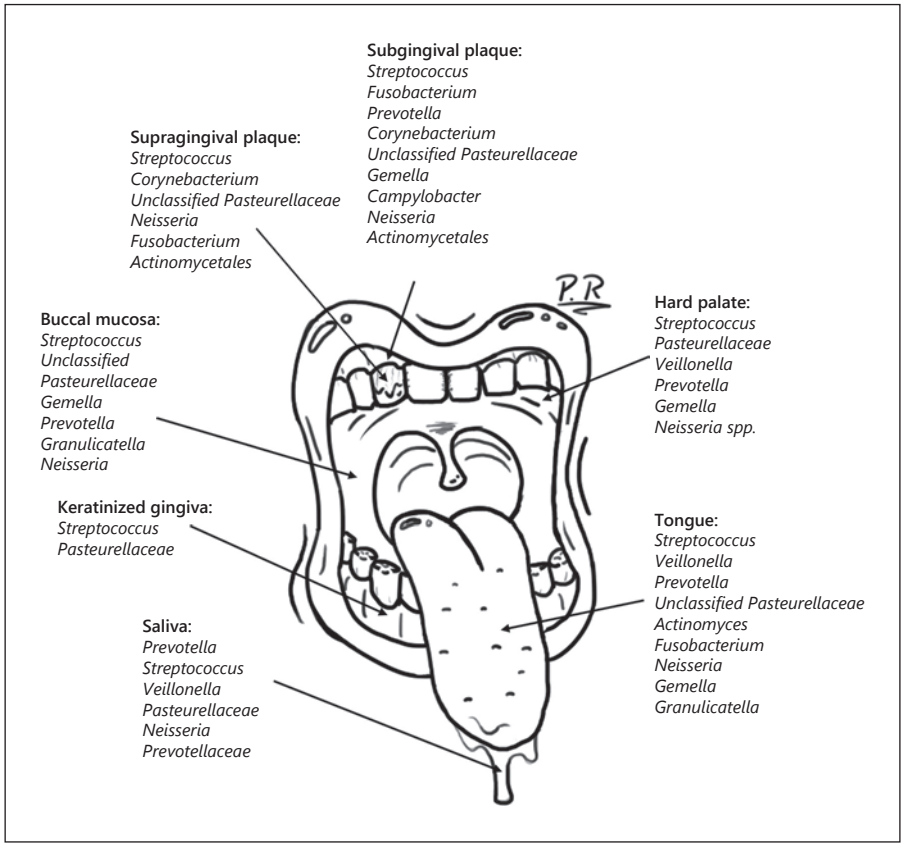

Fig. 1. Most abundant bacterial species in oral cavity according to different anatomical areas [35, 55, 65, 66].

when dental plaque continues to accumulate, leading to the formation of periodontal pockets and tissue destruction, and it is therefore classified as a chronic infection [69]. If this chronic disease is left untreated, it maintains low-level inflammation and increases blood CRP levels [70, 71]. Periodontitis is a relatively common oral disease; it is estimated that the majority of adults (50–70%) present some clinical symptoms of periodontal disease [72].

Known periodontal pathogens, such as *Tannerella forsythia, P. gingivalis,* and *Treponema denticola*, are not usually detected in oral cavities of healthy humans [35]. The literature in fact presents a unique set of so-called periodontal pathogens. This unit consists of *Aggregatibacter actinomycetemcomitans, P. gingivalis, T. forsythia, T. denticola, Prevotella intermedia, P. nigrescens, Parvimonas micra, Campylobacter rectus,* and *Fusobacterium nucleatum* [56, 73, 74]. But, as these species sometimes can be detected in healthy individuals it has become obvious that the dysbiosis and the relative abundance of pathological species is the main trigger of disease onset [75–77]. Furthermore, multiple bacteria, rather than a single bacterium, work synergistically.

Patients suffering from periodontitis have a 2–5 times higher risk of acquiring any cancer compared to healthy controls, even among patients who have never smoked [68, 78–81]. The correlation to OSCC in particular seems to be consistent [57, 69, 81–84]. Thus, an increased number of missing teeth, as a sign of periodontitis, has been linked to a higher OSCC prevalence [69, 84–86].

The elevated cancer risk of periodontitis patients is thought to be associated with differences in the oral bacterial microbiota composition. These periodontopathogenic bacteria (especially *P. gingivalis*, *P. intermedia,* and *F. nucleatum*) enable and maintain constant chronic infection and the systemic inflammation response [57, 69, 82–84, 87–90]. The bacterial impacts are mainly indirect changes observed based on increased levels of leukocytes and cytokines after the initial inflammatory response [89, 91]. Some periodontal pathogens can also directly affect specific intracellular pathways, promote cell survival, activate oncogenic pathways, reduce proapoptotic protein expression, and increase cell migration and invasion, in addition to enhancing metastasis [89]. *P. gingivalis* and *F. nucleatum* can additionally activate cell transformation

[82, 89, 92–95]. Other periodontal pathogens, i.e., *A. actinomycetemcomitans, T. forsythia,* and *T. denticola*, can produce virulence factors that induce the release of proinflammatory cytokines [57].

All of these changes in chronic periodontal disease maintain the chronic inflammation process and destruction of periodontal tissue. These alterations at the cellular level can furthermore induce permanent genetic alterations in epithelial cells [57]. After several years this continuous exposure to cell metabolites can trigger abnormal cell divisions and eventually even carcinoma development [68].

Oral Potentially Malignant (Precursor) Mucosal Lesions

The World Health Organization has classified a number of oral lesions as potentially malignant (precursor) lesions for OSCC [96]. Lichen planus, leukoplakia, and erythroplakia are the most often encountered clinical manifestations in the human oral cavity, and these patients that are known to have a somewhat higher risk of malignant transformation compared to their healthy counterparts [57].

Oral Lichen Planus

Oral lichen planus (OLP) is a chronic inflammatory mucosal disease of unknown origin [97]. Some 0.1–4.0% of the population is estimated to have OLP lesions (females more than males), and most of the lesions are asymptomatic [98, 99]. OLP is known to be potentially malignant, and around 1.0–3.0% of the lesions progress to OSCC [99–101]. It is important to regularly check OLP patients in order to detect suspicious changes early. Some OLP patients do not require any treatment, while others benefit from local corticosteroid treatment. Occasionally, some patients experience symptom relief and diminished clinical lesions with chlorhexidine mouthwash alone, which suggests a bacterial contribution to the disease [102].

As a matter of fact, oral bacterial dysbiosis has been detected in OLP patients [73, 103]. Higher levels of *Porphyromonas* and *Solobacterium* and *P. melaninogenica* have been observed in OLP patients, with a significantly lower abundance of *Haemophilus, Corynebacterium, Cellulosimicrobium,* and *Campylobacter* compared to the healthy control group [73]. Furthermore, another study detected more abundant *Fusobacterium, Leptotrichia,* and *Lautotropia* in OLP lesions, while *Streptococcus* was detected more in healthy patients [103]. *Porphyromonas* has been correlated with the severity of OLP [73]. Nevertheless, the possible causative role of bacteria in OLP and/or malignant transformation has not yet been elucidated [104].

Leukoplakia and Erythroplakia

Leukoplakia is defined as a whitish lesion on the oral mucosa that is not related to any other specific disease and is mainly being asymptomatic [99, 105]. Erythroplakia, on the other hand, is a similar red lesion of the oral mucosa [99]. Both leukoplakia and erythroplakia are clinical terms and the diagnosis must be confirmed by biopsy and histopathological analysis. The prevalence of leukoplakia is around 1.0–20.0% and that of erythroplakia is 0.01–0.2% [99, 106, 107]. OSCC development is observed in 15.6–39.2% of cases with leukoplakias, while the rate is 51.0% in erythroplakias [99].

Leukoplakia has been detected to harbor more *Haemophilus, Leptotrichia, Campylobacter, Rothia mucilaginosa,* and *Fusobacteria*, with lower levels of Firmicutes [108, 109]. No literature is currently available describing the potential bacterial microbiota changes observed in erythroplakia patients; this is probably due to the low prevalence of the condition.

Tobacco and Ethanol

Cigarette smoke contains hundreds of toxic chemicals. Regular smoking is known to increase individuals' risk of OSCC and other cancers, as well as chronic obstructive pulmonary disease, cardiovascular disease, and periodontitis [110, 111]. In addition, smoking directly affects oral mucosal sites and therefore also the oral bacterial composition. Smoking has been detected to reduce bacterial diversity (α diversity), especially in buccal mucosa and by changing the bacterial composition favoring *R. mucilaginosa, Streptococcus salivarius,* and *S. mitis* [111, 112]. Furthermore, higher levels of *Prevotella*, *Veillonella,* and *Leptotrichia* have been observed in current smokers [113]. On the other hand, lower levels of *F. nucleatum* and *Leptotrichia* have been detected in patients who smoke and have OLP [108]. Nonetheless, the levels of *S. mutans* and *Lactobacillus* have been observed to be unchanged even with regular smoking [114]. Elevated levels of *R. mucilaginosa, Veillonella, Streptococcus,* and *Leptotrichia* have been connected to OSCC independently, without the presence of smoking [47, 108, 113, 115–118].

Ethanol is not carcinogenic on its own, but its metabolites acetaldehyde, hydroxyl ethyl radicals, and hydroxyl radicals are [119]. Acetaldehyde has the potential to cause chromatic changes and point mutations to DNA and hyperproliferation of the epithelium [106, 120]. Some known oral pathogens, such as *R. mucilaginosa, Neisseria* spp., and *S. mitis,* have been detected to be able to transform ethanol to acetaldehyde [121]. Also the endogenous production of acetaldehyde by oral bacteria is higher with poor oral hygiene [122].

Oral Microbiota and OSCC

The decrease in Firmicutes and increased levels of Fusobacteria have been linked to OSCC [116, 118]. Significantly higher levels of *Peptostreptococcus, Fusobacterium*, *Prevotella* (especially *P. melaninogenica*), *Porphyromonas, Veillonella* (mainly *Veillonella parvula*), *Haemophilus, Rothia,* and *Streptococcus* have been detected in OSCC samples [47, 113, 115–117]. OSCC can be divided into different disease stages by the TNM (tumor, node, metastasis) classification [123]. These TNM stages of OSCC have been observed in significantly different oral bacterial microbiota compositions. Yang et al. [118] detected that levels of *Streptococcus, Haemophilus, Porphyromonas*, and *Actinomyces* decreased in carcinoma progression while *F. periodonticum, P. micra, S. constellatus, Haemophilus influenza,* and *Filifactor alocis* were associated with OSCC and their levels increased along with disease severity with the TNM classification. Furthermore, the most severe OSCC at stage 4 represented significantly more complex microbiota than those at lower stages. Differences have also been detected between precursor lesions and OSCC [113, 118]. Severe dysplasia, before the onset of OSCC, has been associated with elevated levels of *Leptotrichia* spp. and *C. concisus* [108]. Zhang et al. [124] suggested 3 possible mechanisms behind these changes. Bacteria might influence tumorigenesis by: (1) stimulating chronic inflammation, (2) acting as an antiapoptotic agent, or (3) producing carcinogenic substances [124].

Strong evidence of two potentially carcinogenic oral bacteria has accumulated in recent years with in vitro and in animal models. *P. gingivalis* and *F. nucleatum* have both been shown to be able to induce the production of inflammatory cytokines, as well as cell proliferation and cellular invasion, in OSCC with various different mechanisms [8, 57, 125, 126]. *P. gingivalis* was responsible for induction of the production of interleukins, tumor necrosis factor (TNF)-α, and matrix metalloproteinases (MMP) and for inhibition of apoptosis [125]. It also prevented the activity of the p53 tumor suppressor gene [57, 125]. Continued exposure to *P. gingivalis* has also been demonstrated to increase the invasiveness of OSCC [125].

F. nucleatum, on the other hand, was responsible for the promotion of cell proliferation and for the increase in the production of interleukins and other MMP that drive tumor invasion and metastasis [57, 125]. All of these changes resulted in an elevated transcriptional activity of oncogenes and proinflammatory cytokines [125]. Both of these bacteria, i.e., *P. gingivalis* and *F. nucleatum*, were able to release endotoxins, such as lipopolysaccharides, which in turn can activate inflammation-associated cytokine production. Inflammation-associated cytokine production is the major factor in bacteria-induced inflammation and a contributor to carcinogenesis [57, 127, 128].

The previous studies are observational studies or in vitro findings. However, there is also evidence of a bacterial contribution to tumorigenesis with an animal model. Stashenko et al. [129] colonized germ-free mice with different oral microbiomes and exposed them to a 4-NQO carcinogenic agent. Mice with oral microbiome and 4-NQO had more and larger OSCC compared to controls with only 4-NQO treatment.

Oral Microbiota and Cancers of Other Body Sites

Several specific oral pathogenic bacteria have been linked to cancers of other body sites, in addition to OSCC development. Since the oral cavity is the starting point of the digestive system, pathogenic bacteria may, e.g., disseminate via saliva from the oral cavity and have an impact on distant organs. It has been estimated that, on a daily basis, 10^{11} oral bacteria make their way through the digestive system [130]. Oral dysbiosis have been connected mainly to patients with tumors of the gastrointestinal tract and esophageal, gastric, pancreatic, and colorectal cancers [51, 131–134].

As previously discussed, bacteria, such as the periodontal pathogens *P. gingivalis* and *F. nucleatum*, have several different mechanisms via which they can interfere with cell signaling and cause tumorigenesis [126, 135]. These specific bacteria, in addition to *Rothia, T. denticola,* and *P. intermedia*, have been detected in colorectal cancer specimens where they are thought to cause disruption in the intestinal microbiota, ultimately causing dysbiosis [51, 131, 136, 137]. Colorectal cancer has also been connected to *Streptococcus* and *Prevotella,* both oral bacterial species [131].

In addition, a higher prevalence of the periodontopathogens *P. gingivalis, Porphyromonas, S. mitis,* and *A. actinomycetemcomitans* in the oral cavity has been found to increase the risk of pancreatic cancer [132]. Periodontal disease itself, in general, elevates the risk of acquiring pancreatic cancer [69, 134, 138, 139]. On the other hand, *Fusobacteria* showed protective association [132]. Inconsistent results have been detected with *Leptotrichia* according to different studies in pancreatic cancer patients' oral cavity [132, 140]. Furthermore, higher levels of circulating *P. gingivalis* antibodies have been linked to a higher risk of pancreatic cancer [133, 140–142].

Peters et al. [143] found the oral periodontal pathogens *T. forsythia* and *P. gingivalis* to be more abundant in esophageal cancer. In addition, levels of *T. denticola, S. mitis,* and *S. anginosus* have also been detected to be increased in esophageal cancer patients [144].

Discussion

Accumulating evidence suggests a link between oral cavity bacterial microbiota and cancer. This is most widely shown with OSCC. However, OSCC is caused by multiple simultaneous factors [106] and the contribution of bacteria is difficult to separate from them [145]. As we have presented, there seem to be significant changes in the bacterial microbiota composition in the oral cavity either preceding or with OSCC. This can be seen already with potentially malignant precursor lesions, such as leukoplakia and OLP [99, 101, 105, 107–109, 146]. In addition, infection is a major cause of chronic inflammation which, on its own, facilitates increased cell proliferation, mutagenesis, and oncogene activation preceding OSCC development [147].

Periodontal disease and periodontopathogens have a known pathological impact not only on the teeth supporting connective and bone tissues but also on the human immune defence. It has a direct disturbing effect on cell-signaling pathways. These changes are known to predispose to cancer development [57, 68, 69, 82–84, 87–93, 95]. Nevertheless, since the causal relationship is complex, it is extremely difficult to accurately study the impact of specific bacteria on carcinoma development in humans.

Chronic inflammation, triggered by pathogenic bacteria infections, has a significant effect on carcinogenesis in several different stages, i.e., induction, progression, invasion, and metastasis [148]. It has been suggested that precisely chronic inflammation would be the missing link between bacteria and oral carcinogenesis [125]. This is demonstrated most clearly by the previously discussed periodontal pathogens *P. gingivalis* and *F. nucleatum*.

Many of the bacteria have been shown to be linked to potentially harmful mechanisms at the cellular level. However, it is not yet confirmed that these bacteria actually influence OSCC development in humans. [57, 68, 69, 82–84, 87–93, 95]. Alterations of oral cavity bacterial microbiota communities could as a diagnostic tool to screen patients in the future and possibly even predict OSCC development. Especially the presence of *P. gingivalis* and *F. nucleatum* could predispose individuals to carcinogenesis, and these bacteria have been reported to be present at significantly higher levels in OSCC surfaces [117, 126]. *P. gingivalis* has also been detected with immunohistochemistry from gingival OSCC, and orodigestive cancer mortality is related to high *P. gingivalis* antibody levels [141, 149]. Nonetheless, there is a need for studies showing causal evidence and population-based epidemiological evidence of the association of these bacteria with OSCC. Bacteria can also be detected as part of a secondary colonization to the tumor site because of a lowered immune defence due to the carcinoma itself [150]. Well-designed follow-up studies are still lacking.

Alterations in oral cavity bacterial microbiota to more pathogenic microbes in addition to known etiological factors, smoking, and alcohol consumption contribute to oral carcinogenesis [151]. Thanks to the achievements of future research, there might be possibilities to manage known possibly carcinogenic bacteria with personalized medicine, such as phage therapy [152, 153]. In the meantime, mechanical biofilm disruption and good oral hygiene are essential in preventing harmful bacteria from colonizing the oral cavity. Furthermore, avoiding alcohol and tobacco products decreases the exposure to acetaldehyde production directly or indirectly by oral cavity bacteria.

Conclusions

It is evident that oral bacteria can have profound effects on human health inside and outside the oral cavity. Oral pathogenic bacteria can have indirect or direct effects on the human immune response and affect to normal cell signalling pathways preceding carcinoma development. Since the onset of carcinoma development is a complex and time-consuming procedure, it is difficult to determine the causal relationship between oral cavity bacteria and carcinoma development. However, it is known that certain oral pathogens, such as *P. gingivalis* and *F. nucleatum,* can promote pathways that might trig-

ger carcinoma development. Nonetheless, it is important to understand that in the human body the microbiota works synergistically and one bacterium cannot determinate the entity. We need more research to truly understand the complex mechanisms behind the impact of bacterial microbiota on cancer development.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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