

Review

Mechanisms and Potential Clinical Implications of Oral Microbiome in Oral Squamous Cell Carcinoma

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Abstract: Microorganisms in the oral cavity are abundant in the human body. At present, more than 700 species of oral microorganisms have been identified. Recently, a lot of literature has indicated that the oral microbiota plays an important role in the occurrence, development, and prognosis of oral squamous cell carcinoma (OSCC) through various mechanisms. And researchers are now trying to utilize oral microbiota in cancer diagnosis and treatment. However, few articles systematically summarize the effects of oral microbes in the diagnosis, treatment, and disease outcomes of oral cancer. Herein, we made a summary of the microbial changes at cancerous sites and placed more emphasis on the mechanisms by which the oral microbiome promotes cancerization. Moreover, we aimed to find out the clinical value of the oral microbiome in OSCC.

Keywords: oral squamous cell carcinoma; oral potentially malignant disorders; oral microbiome; inflammation; immunity

1. Introduction

More than 90% of oral cancers, which rank 16th among all the common malignant tumors, are oral squamous cell carcinomas (OSCCs) originating from the squamous tissues [1]. Advances in medical imaging and therapy have improved the 5-year overall survival from 59% during 1990–2000 to 70% during 2001–2010 [2]; however, there were 377,713 cases of oral and lip cancer and 177,757 deaths in 2020 [3]. The etiology of OSCC is attributed to genetics; microbes; and unhealthy habits, including alcoholism [4], smoking [5], and chewing betel [6]. Periodontal diseases and tooth loss are also risk factors for OSCC [7,8], indicating that several oral bacteria (*Streptococcus*, *Peptostreptococcus*, and *Prevotella*) may be related to the development of OSCC [9]. Microorganisms that colonize the human body were found to be associated with 20% of cancers and are known to modulate tumor occurrence and development since *Helicobacter pylori* (*H. Pylori*) was found to contribute to gastric cancer in the 1990s [10]. The number of bacteria is almost equal to that of human cells in the body, and these microorganisms have at least 100 times more metagenomes than humans, which can be utilized to modulate the biological behavior of cancer cells [11] by promoting cell proliferation, resisting cell death, inducing angiogenesis, reprogramming energy metabolism, and evading immune destruction [12]. Increasing evidence suggests that microorganisms play a significant role in oral cancer development. Therefore, the mechanisms of microbial carcinogenesis should be explored, and a cure must be developed for oral cancer. In this review, we summarized the current knowledge of oral microbiota and its relationship with OSCC, placed an emphasis on the mechanisms by which oral microbiota promote oral cancer, and aimed to determine the potential clinical role of oral microbiota in OSCC.



Citation: Wang, J.; Gao, B. Mechanisms and Potential Clinical Implications of Oral Microbiome in Oral Squamous Cell Carcinoma. *Curr. Oncol.* **2024**, *31*, 168–182. <https://doi.org/10.3390/curroncol31010011>

Received: 21 November 2023

Revised: 14 December 2023

Accepted: 18 December 2023

Published: 28 December 2023



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2. Oral Microbiota Participating in the Occurrence, Development, and Prognosis of OSCC

2.1. Oral Microbiota and Oral Potentially Malignant Disorders

Transformation of normal oral mucosa into OSCC involves multiple steps, of which oral potentially malignant disorders (OPMDs) have received increasing attention owing to the high risk of malignant transformation (the overall malignant conversion rate is 7.9% [13]). More than 80% of oral cancer cases develop from OPMDs [14]. Common OPMDs with a high risk of transformation include oral leukoplakia, proliferative verrucous leukoplakia, erythroplakia, oral lichen planus (OLP), and oral submucous fibrosis.

Although the microbiome community structure in oral cancer is different from that in normal samples, the community in OPMDs overlaps with both [15]. Specifically, according to the research of Amer et al., 35% of leukoplakia samples showed considerable *Candida* spp. colonization (>300 CFUs/mL) [16]. *Candida* spp. produce carcinogens and proteinases that degrade the basement membrane [17]. However, patients with leukoplakia have high levels of *Fusobacteria* and *Bacteroidetes* and low levels of *Firmicutes* [16,18]. Interestingly, *Firmicutes* were often identified in the cancer group. Additionally, many periodontal pathogens (*F. nucleatum*, *P. intermedia*, and *P. gingivalis*) are found in patients with both oral leukoplakia (OLK) and oral cancer. Although similar bacteriomes were detected in the whole-mouth fluid of patients with oral leukoplakia and OSCC, there were slight differences in *Megasphaera*, unclassified *Enterobacteriaceae*, *Salmonella*, and *Prevotella*. For instance, *Rothia mucaliginosa* is abundant in OLK lesions, but less abundant in OSCC [19]. Thus, it can be inferred that some oral bacteria may be driving factors in the early stages of oral carcinogenesis. *C. albicans* was found to shield *P. gingivalis* by decreasing cytokine and chemokine production and reducing macrophage and fibroblast responses [20], indicating a protective effect among oral microbes. So far, viruses in OPMDs have rarely been reported. A meta-analysis found that HPV 16/18 was strongly associated with OLP and OLK [21]. In general, continuous microbial changes are observed throughout the development of OSCC [22]. However, further research is required to elucidate the relationship between microbes and the risk of malignant transformation [23].

2.2. Oral Microbiota and OSCC

Yang et al. identified *Fusobacterium periodonticum*, *Parvimonas micra*, *Streptococcus constellatus*, *Haemophilus influenza*, and *Filifactor alocis* as the five most representative microorganisms in patients with OSCC [24]. Periodontitis-related bacteria (including *Prevotella tannerae*, *F. nucleatum*, and *P. intermedia*) associated with dentition loss and poor oral condition were considered risk factors for OSCC [7,8,25,26]. However, Hayes et al. argued the opposite [27]. The HPV and Epstein–Barr virus (EBV) are two popular viruses associated with OSCC [28]. The number of patients with HPV-positive HNSCC has been increasing, especially those with pharyngeal cancer [29], and these patients present with a significantly better prognosis than patients with HPV-negative HNSCC under similar treatments. Therefore, HNSCC is further divided into HPV-positive and HPV-negative types, which is conducive to exploring different causes and treatment options. The EBV is related to OSCC as well, as 55% of 155 OSCC samples from eight different countries and ethnicities were EBV-positive [30,31]. As to yeasts, *Candida albicans* is more prevalent in patients with oral cancer than in healthy people [32].

The mechanisms of oral microbial carcinogenesis have been extensively studied and can be roughly summarized as follows (Figure 1): (I) production of carcinogenic substances, (II) regulation of inflammatory and immune responses, (III) promotion of cell proliferation and anti-apoptotic activity, and (IV) contribution to cellular invasiveness (discussed in Section 2.3).

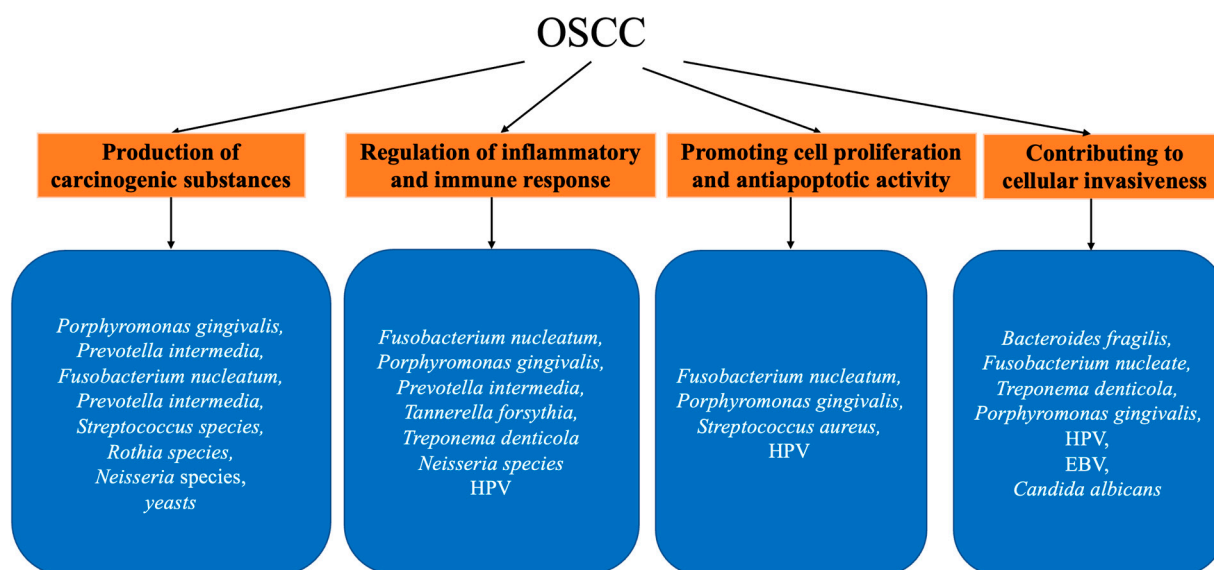


Figure 1. Summary of mentioned oral microbiota and their association with OSCC.

2.2.1. Production of Carcinogenic Substances

Microorganisms produce metabolites, such as nitrosamines, sulfides, oxides, and acetaldehyde, which induce tumorigenesis. In advanced precancerous lesions, *Candida albicans* strains with high nitrosation potential can be isolated [33], whereas nitrosamines can interfere with DNA replication by binding to chemical bonds in the DNA, which contributes to carcinogenesis. Volatile sulfur compounds produced by *P. gingivalis*, *P. intermedia*, and *F. nucleatum* modulate cellular behavior [34]. Yaegaki et al. found that after incubation with hydrogen sulfide (H₂S) for 72 h, histone-complexed DNA fragmentation in human gingival fibroblasts increased, resulting in apoptosis [35,36]. Moreover, reactive oxygen species (ROS) and reactive nitrogen species secreted by microbiota-induced inflammatory cells contribute to tumor invasion, angiogenesis, and metastasis. Another possible hypothesis is that bacteria contribute to the development of oral cancer by activating procarcinogens. *Streptococcus*, *Rothia*, *P. gingivalis*, *Neisseria*, yeasts, and fungi possess alcohol dehydrogenase (ADH), which is an enzyme that can metabolize ethanol to acetaldehyde (ACH) [37,38]. As shown by Alnuaimi et al., highly ethanol-derived ACH-producing *Candida* could be isolated from patients with oral cancer [39]. Although pure ethanol is not carcinogenic, ACH leads to the formation of DNA protein adducts, causing point mutations and chromosomal aberrations by intervening in normal DNA replication. Smedra proposed a different point of view that ACH can originate from oral autobrewery syndrome owing to microbial dysbiosis in the oral cavity, aside from the breakdown of ingested alcohol by oral mucosal ADH, the oral microbiome, and alcoholic beverage itself [40].

2.2.2. Regulating Inflammatory and Immune Suppression

The link between cancer and inflammation has been recognized and confirmed by epidemiological investigations and experimental studies [41,42]. Toll-like receptors (TLRs) are host pattern recognition receptor molecules that recognize lipopolysaccharide (LPS), which is a component of the Gram-negative bacterial cell wall, bacterial flagellin, and bacterial nucleic acids. In response to LPS activation, inflammatory cells (such as monocytes/macrophages, neutrophils, fibroblasts, and mast cells) secrete IL-1 β , which are in charge of the release of phospholipase A2, prostaglandins, acute phase proteins, proinflammatory cytokine IL-6, and TNF. On the one hand, IL-1 β promotes angiogenesis and tumor progression by activating endothelial cells, which produce vascular endothelial growth factor and other proangiogenic factors (e.g., TNF). On the other hand, IL-1 β enhances tumor invasiveness and aggression by decreasing E-cadherin expression and inducing MMP-9. IL-6 induces oxidative stress and causes mitochondrial damage. Moreover, TNF- α

can produce ROS to induce DNA damage and contribute to tumor progression through angiogenesis. Through the TLR/MyD88 pathway, the transcription factor nuclear factor of kappa beta (NF- κ B) is activated, contributing to inflammation and cell proliferation. Periodontitis-related bacteria also initiate the overexpression of NLRP3 and activate the upstream signaling molecules of ATR-CHK1 [43]. Chymotrypsin-like proteinase (CTLP), which is a major virulence factor of *T. denticola*, is critical for regulating inflammation by degrading complement C1q [44].

Microbiome-related immunosuppression plays a significant role in the development of oral cancer by modulating immune cell activity. *P. gingivalis* suppresses CD8+ T-cell cytotoxicity by upregulating PD-L1 expression in dendritic cells through Akt-STAT3 signaling [45]. By increasing the FOXP3 + Treg response, *P. gingivalis* induces monocytes to become myeloid-derived dendritic suppressor cells, resulting in immune tolerance [46]. Upregulation of the immune checkpoint molecule B7-H4 and lysine demethylation of 5 B induced by *P. gingivalis* also promotes evasion and inhibition of the host immune response [47]. Gingipain K produced by *P. gingivalis* degrades immunoglobulins and the complement system (C3 and C5 components) and affects the host immune system [48]. Gur et al. found that the Fap2 protein of *F. nucleatum* interacts with TIGIT, which is an inhibitory receptor on all human NK cells and various T cells and assists tumor cells in escaping immune cell attack [49]. In addition to promoting the M2 polarization of macrophages through the TLR4-associated pathway [50], *F. nucleatum* induces cancer cells to produce more lactate via the GalNAc–Autophagy–TBC1D5–GLUT1 signaling axis, subsequently promoting M2-like tumor-associated macrophage formation and contributing to immune evasion [51]. In addition to bacteria, viruses, such as HPV, can promote cancer development through sophisticated immunity escape techniques. HPV E7 oncogene has been reported to inhibit the activation of NF- κ B family members, leading to viral immunosuppression [52].

2.2.3. Promoting Cell Proliferation and Antiapoptotic Activity

Oral microbes facilitate cancer development by promoting cell proliferation and anti-apoptotic activities. Cell cycle dysregulation is one of the most common features of human cancers. *P. gingivalis* contributes to OSCC proliferation by accelerating the G1 phase of the cell cycle through the upregulation of cyclin D1 expression via the miR-21/PDCD4/AP-1 signaling pathway [53]. The intact fimA fimbrial structure and gingipain proteases of *P. gingivalis* also assist in cancer cell apoptosis and proliferation [54,55]. In the presence of *F. nucleatum*, p27, which is associated with abnormal cell proliferation, is downregulated, causing cell cycle arrest in the S phase and strengthening cell proliferation [56]. Meanwhile, the DNA repair proteins Ku70 and p53 are downregulated, weakening their cell repair ability [56]. p53, along with pRb, is the target substrate of HPV E6/E7 oncogenes, leading to continual cell proliferation. *F. nucleatum* is also associated with high levels of putrescine, which induces the malignant proliferation of cancer cells [57]. *Staphylococcus aureus* can facilitate human oral keratinocyte proliferation by activating the COX-2/PGE2 pathway [58].

The body clears necrotic cells through apoptosis or programmed death, which may interfere with pathological conditions and lead to tumor formation. Apart from reducing IL-1 β production and inhibiting ATP-dependent apoptosis, nucleoside-diphosphate-kinase secreted by *P. gingivalis* also abrogates epithelial cell death by phosphorylating heat-shock-protein-27 [59]. Through the JAK1/AKT/STAT3 pathway, *P. gingivalis* phosphorylates the pro-apoptotic protein Bad and inhibits the release of cytochrome c, reducing the intrinsic mitochondrial apoptotic activity [60,61]. Similarly, in a study of infection with *F. nucleatum*, the expression of MYC, JAK1, and STAT3 was significantly stimulated [62]. *T. denticola* can invade CAL-27 cells and directly promote cell proliferation, regulate the cell cycle, and inhibit cell apoptosis [63]. Recently, HPV E7 was found to inhibit pyroptosis by recruiting TRIM21 for ubiquitination and degradation of the IFI16 inflammasome [64].

2.3. Microbiome and Oral Cancer Prognosis

The oral microbiome also promotes cancer development by increasing cellular migration and invasiveness, leading to the aggressiveness and metastasis of OSCC, which is associated with a poor prognosis.

The epithelial–mesenchymal transition (EMT) is a cell-reprogramming process by which cancer cells complete differentiation and become aggressive [65]. Upon infection by *P. gingivalis*, both the JAK1/STAT3 and EMT phenotypes are activated, and tumor-associated neutrophils are recruited to promote OSCC progression via the CXCL2/CXCR2 axis [66]. Tumor growth and lung metastasis are remarkably enhanced by activating TGF β signaling. The *Bacteroides fragilis* toxin cleaves E-cadherin, resulting in a decrease in cell–cell attachment. *Fusobacterium* adhesin A (FadA) also dissociates adherence junctions by disconnecting the E-cadherin– β -catenin complex [67]. β -catenin then transits to the nucleus and induces the Wnt pathway. Wnt target genes, including ZEB1, SNAI1, MT1-MMP-9, and LAMC2, are also associated with invasiveness. Although some studies declared that *Fusobacterium* is related to a reduced recurrence rate and a low rate of lymph node metastasis [68,69], others found that *Fusobacteria* can enhance cancer cell invasiveness, survival, and EMT via the JAK/STAT3 pathway [62] and lncRNA MIR4435-2HG/miR-296-5p/Akt2/SNAI1 signaling pathway [70]. Matrix metalloproteinases (MMPs) degrade extracellular matrix components, enabling tumor cells to spread [71]. *P. gingivalis* increases signaling through extracellular signal-regulated kinase 1/2-Ets1, p38/HSP 27, and NF- κ B pathways, consequently elevating MMP-9 and downregulating E-cadherin [72]. MMPs can also be activated by methyl mercaptan by increasing the production of IL-1 and prostaglandin E2, thereby facilitating the degradation of collagen, especially type 4 collagen, and reducing its synthesis, which results in the inhibition of basement membrane synthesis [35]. EBV inhibits P53 via the CTAR family of proteins/programmed cell death protein 1 ligands to enhance the migration of epithelial cells and the production of MMPs [73]. In addition, Vadovics et al. demonstrated that *C. albicans* infection, instead of zymosan treatment, significantly increases the total MMP activity by means of *C. albicans* hypha generation [20], which can be further explained by Ho's study, which showed that the hypha-specific toxin candidalysin induces MMP activation and expression via a calcium influx [74]. Similarly, CTLP was found to increase cellular migration and tumor invasion by upregulating MMP-2 via TLR-7 and TLR-9 [75], as well as TLR/MyD88 and integrin/FAK crosstalk signaling [76]. Cytoskeleton remodeling is attributed to the EMT, which enhances cell mobility. Cytoskeleton assembly is realized by HPV16 E6 by downregulating NHERF1 to promote cell invasiveness [77].

3. Clinical Application of Oral Microbes in OSCC

3.1. Diagnosis and Grading

Several advanced approaches can detect oral cancer, such as lab-on-chip, microfluidics, nanodiagnosics, liquid biopsy, omics technology, and synthetic biology [78]. To date, numerous studies have applied different methods to describe the differences in oral microbiota between normal tissue and OSCC sites [28,79–81], including the surface of the tumor tissue, within the tumor, and saliva. Allan Radaic etc. made an exhaustive summary of potential oral microbiome-based biomarkers for OSCC [82]. It is possible to distinguish cancerous lesions from normal tissues and perform tumor staging by noninvasively detecting microbes [83].

Intratumoral bacteria potentially originate from normal adjacent tissues [84] and play the role of immunomodulation in the tumor microenvironment [85]. Hooper et al. were the first to study microorganisms in OSCC and suggested that they are mainly aciduric and saccharolytic secondary colonizers, such as *Micrococcus luteus*, *Prevotella melaninogenica*, *Exiguobacterium oxidotolerans*, and *Staphylococcus aureus*, because of their acidic and hypoxic environments [86]. The abundances of the phylum *Fusobacteria*, genus *Fusobacterium*, and phylum *Bacteroidetes* were found to be elevated in the saliva of patients with OSCC and were believed to be diagnostically specific [15]. Aside from viruses and bacteria, a variety

of molecular and genetic markers can be detected for treatment and monitoring [87]. A recent study reported that oral-cancer-related microorganisms in the mucosa, other than in gingival plaque or saliva samples, have the most diverse species differences and functional changes and are the most suitable sites for observing microbial dysregulation [88]. Another study that investigated unstimulated salivary microbial profiles found significant differences in *Bacillus*, *Enterococcus*, *Parvimonas*, *Peptostreptococcus*, and *Slackia* between epithelial precursor lesions and cancer groups [89]. As early as 2005, Madhura et al. found that with *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *Streptococcus mitis* as diagnostic markers, the sensitivity and specificity for the three species are 80% and 82%, respectively [90]. Zhou et al. adopted random forests and cross-validations to build a diagnostic model based on oral microbiota and found that Actinobacteria, Fusobacterium, Moraxella, Bacillus, and Veillonella species were strongly correlated with OSCC [91]. However, *Parvimonas micra* and *Streptococcus mitis* have been implicated in the reduced risk of OSCC development [27,92–94]. The presence of *Corynebacterium* and *Kingella* is also associated with a low incidence of head and neck squamous cell carcinoma, possibly because they are involved in the degradation of cancer-inducing metabolites [27,95]. Similarly, Shen et al. found that periodontitis-negative-associated bacteria (*Neisseria sicca* and *Corynebacterium matruchotii*) play an anti-cancer role in OSCC by upregulating DDR to repair DNA damage, inducing pyroptosis, and decreasing CD4+ T cells [96]. *P. gingivalis* IgG and IL-6 are also used as potential serum biomarkers for OSCC diagnosis [97]. As the expression patterns of CXCL10, DIAPH1, NCLN, and MMP9 genes are significantly correlated with interpain A, fadA, and bspA in OSCC cases, gene expression is an alternative target to detect OSCC [98].

With the progression of OSCC, the abundance of these bacteria increases, indicating that the microbiome can serve as a marker for staging and predicting prognosis. Yang et al. reported that *F. periodonticum*, *S. mitis*, and *P. pasteri* are bacterial marker panels that can be used to distinguish patients with stage 4 OSCC from healthy individuals [24]. Tumor MMP-9 expression is associated with poor outcomes in OPSCC, especially in HPV-negative disease, whereas Rgp immunoexpression in inflammatory cells is associated with better disease-specific survival, which can be utilized to predict prognosis [99].

In addition to diagnosing the disease, microorganisms can also be used to distinguish healthy from diseased mucosa. Su et al. demonstrated that *Fusobacterium* spp. is a successful marker species for identifying noncancerous tissues. However, compared with *Fusobacterium* spp., *Streptococcus* spp., especially *Streptococcus pneumoniae*, are more accurate when classifying lesion sites [80].

3.2. Oral Microbes and Cancer Treatment

Multidisciplinary therapeutic strategies are generally used for OPMDs to prevent OSCC progression and prolong survival. However, there is no consensus on the treatment of OPMDs owing to the variety and complex mechanisms of OPMDs. Tacrolimus, which is used as the first-line drug after transplantation, was found to be effective in treating OLP [100,101] by downregulating immunity [102] and downregulating cell-cycle-related proteins [103]. Tacrolimus treatment also significantly altered the proportion of *Allobaculum*, *Bacteroides*, and *Lactobacillus* in the colonic mucosa and the circulation [104], which indicated that it may improve microbial dysregulation of mucosal surfaces. Some studies reported that tacrolimus promotes tumorigenesis and leads to adverse events [105,106], while others have reached a different conclusion [107–109]. Topical tacrolimus can be an effective second-line therapy for patients who do not respond to corticosteroids. However, further studies on its adverse effects are required.

A combination of surgery, chemotherapy, and radiotherapy has been administered to patients with OSCC. Recently, more attention has been paid to the oral microbiome, as the structural, metabolic, and virulence characteristics of microbes are potential targets. The use of pre- or probiotics and salivary substitutes was also suggested based on differences in the salivary microbiota between patients with OSCC and healthy controls [110,111]. The concept of oncolytic bacterial immunotherapy has long been popular, as commonly used

radiotherapy and chemotherapy have side effects owing to damage to healthy tissues, while microorganism therapy shows the merits of accurate target specificity, tissue penetration, and less treatment expense. Many engineered bacterial strains were generated to overcome potential safety problems and improve tumor targeting [112]. *Salmonella typhimurium* [113], *Escherichia coli* [114], and *Bifidobacterium* [115] showed outstanding anti-cancer activities in both preclinical and clinical trials. *Bifidobacterium*, *Streptococcus*, *Caulobacter*, and *Clostridium* spp. are commonly found in the oral cavity and are promising candidates for OSCC tumor-targeting therapies [116]. Oncolytic or “cancer-killing” viruses have been highly used as immunotherapeutic drugs for the treatment of cancer as well [117] and are combined with radiotherapy, chemotherapy drugs, or other strategies. Nonetheless, concerns remain regarding the use of microorganisms in tumor therapies. Owing to the weakened immune system, bacteria-mediated tumor therapy is ineffective in patients who have undergone chemotherapy [118] and can cause serious infections. Moreover, bacterial monotherapy does not completely cure cancer, and bacterium-mediated synergistic cancer therapy was proposed to have promising potential [119,120]. Further studies are warranted to understand the interactions between oncolytic immunotherapies and other therapies.

3.3. Microbiota and Treatment Outcomes of OSCC

Increasing evidence indicates that the presence of a microbiome can affect treatment outcomes [121]. Recent research found an increase in *Lactobacillaceae* and *Bifidobacteriaceae* families and a decrease in *Porphyromonadaceae* and *Prevotellaceae* after OSCC treatment. Furthermore, they observed a change in DMBT1 expression accompanied by the microbiome change, suggesting DMBT1 to be a possible treatment indicator [122]. And a certain genus, namely, *Leptotrichia*, was shown to improve patient prognosis [123]. Another prediction model with five microbial signatures, namely, *Leptotrichia trevisanii*, *Capnocytophaga sputigena*, *Capnocytophaga*, *Cardiobacterium*, and *Olsenella*, displayed high accuracy [124]. Cancer-related intratumoral bacteria and gut microbiota influence the effectiveness of chemotherapy. Lehouritis et al. found that bacteria can both decrease or increase the effectiveness of chemotherapeutic drugs via enzymatic biotransformation and chemical modification [125]. In a mouse model of colon cancer, intratumor Gammaproteobacteria converted gemcitabine into its inactive form by expressing the bacterial enzyme cytidine deaminase [126]. Another study found that 5-FU is metabolized by *preTA*-encoding bacteria [127]. Microbes modulate drug toxicity and side effects. In mice raised in a germ-free environment and administered antibiotic prophylaxis, oxaliplatin-induced mechanical hyperalgesia was reduced, indicating that the gut microbiota enhanced chemotherapy-induced mechanical hyperalgesia [128]. Simultaneously, because microorganisms have a regulatory effect on immune-inflammatory responses, they also affect immunotherapy. *Fusobacteria* species are associated with the high expression of IL-12 and TGF- β , ultimately promoting the differentiation of T cells [129]. As for radiotherapy, antibiotic-mediated fungal reduction enhances the response to radiation, whereas antibiotic-mediated bacterial reduction presents the opposite results [130]. Significant microbiome changes can also affect radiation-induced osteoradionecrosis [131]. Current research on the microbial effects of cancer therapy mainly focuses on digestive tract cancers, requiring further exploration for oral cancer. Although the mechanism by which these microbes affect the efficacy of anti-cancer treatments remains unclear, a growing number of studies have shown that microbes are inextricably linked to anti-cancer treatments.

In addition to regulating cancer treatment, the microbiome can also be a target for regulating immune-related adverse events and even the prognosis of cancer treatment, as cancer treatments can lead to microflora dysregulation. Almost 75% of patients with head and neck cancer who undergo chemotherapy or radiotherapy treatment experience oral mucositis (OM) [132]. After receiving a 5-fluorouracil (5-FU) i.v. for 6 d, an increase in facultative and strictly anaerobic bacteria in the oral cavity and facultative anaerobes in the colon is observed [133]. Hong et al. also demonstrated that OM severity is associated with 5-FU [134]. Modification of oral microbiome is a promising preventive treatment for

OM [135,136]. Palifermin, which is the only pharmacological agent approved by the FDA to treat OM, is a recombinant human keratinocyte growth factor (KGF) that targets the KGF receptor to enhance the differentiation and maturation of epithelial cells [132,137]. A recent meta-analysis showed that palifermin reduces the incidence of severe mucositis by up to 30% in patients treated with chemotherapy and radiotherapy [138]. Therefore, palifermin can be used as a prophylactic to prevent severe OM in patients with oral cancer. Recent research found that palifermin affects the oral microbial community composition, though more studies are warranted to figure out the correlations between palifermin and community composition changes [139]. However, in the 2021 European clinical practice guidelines, palifermin is not recommended for pediatric patients receiving cancer treatment [140] because of its short-term adverse effects, potential long-term negative effects on cancer outcomes, high costs, and restricted availability. Palifermin can be used as a prophylactic to prevent severe OM in patients with oral cancer; more reliable evidence is needed on the safety and efficacy of palifermin. Interestingly, *Lactococcus* strains were shown to be effective in the control of 5-FU-dysbiosis [141], indicating that probiotic supplementation may be a prophylaxis to reduce the adverse effects of cancer therapies and improve the quality of patients' lives. Table 1 summarizes the promising clinical applications of oral microbes in OSCC.

Table 1. Summary of the role of microorganisms in the diagnosis, treatment, and prognosis of cancer.

Diagnosis and prognosis predicting markers	<i>Capnocytophaga gingivalis</i> , <i>Prevotella melaninogenica</i> , and <i>Streptococcus mitis</i> [90]
	<i>P. gingivalis</i> IgG and IL-6 [97]
	CXCL10, DIAPH1, NCLN, and MMP9 genes [98]
	<i>F. periodonticum</i> , <i>S. mitis</i> , and <i>P. pasteri</i> [24]
	<i>Fusobacterium periodonticum</i> , <i>Parvimonas micra</i> , <i>Streptococcus constellatus</i> , <i>Haemophilus influenza</i> , and <i>Filifactor alocis</i> [24]
	<i>Leptotrichia</i> [123,124]
	Tumoral MMP-9 [99]
Treatment targets	Tacrolimus [100,101]
	<i>Bifidobacterium</i> , <i>Streptococcus</i> , <i>Caulobacter</i> , and <i>Clostridium</i> spp. [116]
Affecting treatment outcome	Gammaproteobacteria convert gemcitabine into its inactive form by expressing the bacterial enzyme cytidine deaminase [126]
	<i>preTA</i> -encoding bacteria metabolizes 5-FU [127]
	Gut microbiota enhances chemotherapy-induced mechanical hyperalgesia [128]
	<i>Fusobacteria</i> species promote the differentiation of T cells [129]
	Antibiotic-mediated fungal reduction enhances the response to radiation and antibiotic-mediated bacteria reduction presents the opposite results [130]
	Palifermin [138]
	Lactococci strains relieve OM caused by 5-FU [141]

4. Conclusions

This review specifically introduces the mechanism of oral microbiota in OSCC. The oral microbiome can facilitate the occurrence and development of OSCC by producing carcinogens, promoting cell proliferation, suppressing cell death, and finally inducing angiogenesis. They can also impact the prognosis by enhancing invasiveness and metastasis. To sum up, strong evidence demonstrates that certain genera and species do play a specific role in the development of OSCC, while research has yet to clearly figure out the mechanisms by which oral microbiota lead to tumorigenesis. In addition, using oral microbes for treatment presented promising prospects given the fact that oral microbes have an impact on the therapeutic effect.

Although previous studies demonstrated changes in the oral microbiota during the development of OSCC and identified several typical pathogens, contradictory statements have been reported in the literature on some species, which were probably caused by different detection methodologies and different detection sites. 16S rRNA sequencing is the most popular technology for detecting the oral microbiome; however, it may be restricted by its small sample size [28]. Therefore, other molecular techniques for quantitative determination, such as LDA effect size analysis [68], fluorescent quantitative PCR, and flow cytometry [142], were introduced to obtain more accurate results. Additionally, many factors (habit, race, region, and economic background) can influence the composition of the oral microbiome, which should be excluded during sample collection.

Moreover, the progression of OSCC is complex. The inflammatory state caused by oral microbial dysregulation affects the systemic inflammatory state, which may be risky [143]. Simultaneously, the local inflammatory state caused by diseases changes the composition of the local microbiota [144], and the interaction between them affects the physiological state of the human body. Two theories were presented about “who comes first.” One states that microbes first change the microenvironment and accordingly lead to carcinogenesis, whereas the other states that changes in lesion sites attract bacteria. Therefore, long-term cohort studies are required to identify triggers and major factors. Perhaps the reality is a combination of both theories, as some bacteria, such as *F. nucleatum*, *P. gingivalis*, and *Streptococcus* species, show both tumor instigation and tumor tendency effects. Currently, microbiome descriptions mainly focus on bacteria, and further investigations on oral viruses are required. Beyond studying changes in microbial species and quantity, research should focus on the genomes and metabolites of microorganisms in the environment.

In addition to conventional surgery, chemotherapy, and radiotherapy, researchers are searching for other approaches to prevent OPMDs from progressing to OSCC and treat OSCC. Microbiota can be both a target for OSCC treatment and an adjunct to traditional therapies to enhance therapeutic effects or cut down on adverse effects.

Author Contributions: J.W.: conceptualization, investigation, writing—original draft, and writing—review and editing. B.G.: validation, writing—review and editing, and supervision. All authors read and agreed to the published version of the manuscript.

Funding: This work was supported by the Sichuan Science and Technology Program (2023NS-FSC0575) and Chengdu Key Application Projects of Science and Technology (2021-YF09-00078-SN).

Conflicts of Interest: The authors declare that they have no conflicts of interest.

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