Seminars in Cancer Biology 86 (2022) 633–642

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

The oral microbiota and its role in carcinogenesis

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ARTICLE INFO

Keywords:
Oral microbiota
Oral cancer
Carcinogenic mechanisms
Oncogenic bacteria
Oncogenic viruses

ABSTRACT

Despite decades of research, cancer continues to be a major global health concern. In recent years, the role played by microorganisms in the development and progression of cancer has come under increased scrutiny. The aim of the present review is to highlight the main associations between members of the human oral microbiota and various cancers. The PubMed database was searched for available literature to outline the current state of understanding regarding the role of the oral microbiota and a variety of human cancers. Oral squamous cell carcinoma (OSCC) is associated with carriage of a number of oral bacteria (*e.g.*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Streptococcus* sp.), certain viruses (*e.g.*, human papilloma virus, human herpes virus 8, herpes simplex virus 1 and Epstein-Barr virus) and yeast (*Candida albicans*). Moreover, members of the oral microbiota are associated with cancers of the esophagus, stomach, pancreas, colon/rectum and lung. Furthermore, the present review outlines a number of the carcinogenic mechanisms underlying the presented microbial associations with cancer. Such information may one day help clinicians to diagnose neoplastic diseases at earlier stages and prescribe treatments that take into account the possible microbial nature of carcinogenesis.

1. Introduction

Cancer remains a major global health concern, despite recent advances in prevention, detection and treatment, it remains in the top 5 leading causes of death in 135 countries as of 2019 [1]. Many incidents of cancer can be attributed to random mutations in highly dividing stem cell populations [2]. However, the etiology is complicated by the fact that a high proportion (estimated to be around 1/3) of cancers are attributable to environmental and heritable risk factors [2]. Among others, the classic cancer-associated environmental risk factors are tobacco smoking, alcohol consumption, a high body-mass index (BMI), and exposure to ultraviolet radiation [3,4]. Additionally, infectious agents are known to contribute to the development of cancer, with upwards of 15 % of cases being associated with a specific pathogenic microorganism [5]. Among viruses, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, human T-cell leukemia virus-1, Kaposi sarcoma associated herpesvirus, Merkel Cell polyoma virus and Simian 40 virus are known to be directly implicated in the development of neoplasia [6]. Among bacteria, *Helicobacter pylori* is well known for its association with various gastrointestinal cancers [7]. This suggests that prokaryotic microorganisms play a role in the development and progression of cancer.

The microbiota is a collection of microbial taxa associated with humans [8]. It includes trillions of microorganisms including bacteria, fungi, archaea and viruses inhabiting a particular host. These microorganisms may have beneficial or deleterious effects on their host [6]. The study of the human microbiota has been made possible by the development and refinement of 16S rRNA sequencing techniques, with studies such as the Human Microbiome Project (HMP), providing insight into the makeup of a typical healthy microbiome [9]. The HMP likewise highlighted the fact there is high interpersonal variability with regards to the composition of the microbiome. Moreover, the makeup of the microbiota differs greatly by anatomical location with certain taxa predominating at specific sites [9]. Despite the unique makeup of each individual microbiome, there are changes in its composition which are broadly associated with disease states and which can predispose individuals to certain diseases [10].

The oral microbiome exhibits the second highest level of alpha diversity (*i.e.* diversity within individuals) following that of the gut [11]. It includes over 700 species of bacteria, over 100 species of fungi, and protozoa including *Entamoeba gingivalis* and *Trichomonas tenax* [12]. The oral cavity may be divided into 'microhabitats', each with a different microbiota composition [11]. Despite the high intrapersonal diversity,

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https://doi.org/10.1016/j.semcancer.2021.11.002
Received 25 August 2021; Received in revised form 29 October 2021; Accepted 1 November 2021
Available online 4 November 2021

the oral cavity exhibits very low levels of beta diversity when samples are taken from individuals living in the same areas [11]. An imbalance in the makeup of the oral microbiota (*i.e.* dysbiosis) is often associated with exposure to certain environmental factors, such as tobacco smoking, high-sucrose intake, and antimicrobial use [13]. Dysbiosis of the oral microbiota is associated with a number of intraoral and systemic diseases [14]. The link between microorganisms and intraoral diseases such as dental caries, gingivitis, periodontitis and oral candidiasis is well established [13,15]. The number of microorganisms ingested daily has been estimated to be between 10^{11} and 10^{12} [16,17]. This indicates that microorganisms within the oral cavity have fairly unrestricted access to the gastrointestinal tract, and thus a number of organ systems. As such, it comes as no surprise that dysbiosis of the oral microbiota has been associated with systemic diseases such as colorectal cancer, pancreatic cancer, Alzheimer's disease and cardiovascular disease [14,18,19]. Additionally, oral pathogens such as *Capnocytophaga* and *Veillonella* have been found to coinfect the lungs, with the most notable recent example being a coinfection with SARS-CoV-2 [20].

Information regarding the composition of the oral microbiome and its effects on intraoral and systemic health are being updated very rapidly. Given this, the present review aims to present the current state knowledge as it pertains to the oral microbiota and its relationship with cancer, placing an emphasis upon the associations between specific species and certain cancers, as well as the mechanisms underlying these associations. The PubMed database was searched for articles relevant to the subject matter of this review, with more recently published literature being favoured. Specifically, key words such as: *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Tannerella forsythia*, *Streptococcus anginosus*, oral microbiota, inflammation, human papilloma virus (HPV), herpes simplex virus (HSV), human herpes virus 8 (HHV-8), Epstein-Barr virus (EBV), oral cancer, esophageal cancer, gastric cancer, colorectal cancer, orodigestive cancer, lung cancer and cancer were used to generate search results. Additionally, a manual review of references from the materials found in PubMed was performed.

2. Oral microbiota and cancer

For the last two decades, the scientific community has broadly recognized that there are certain hallmarks of cancer. In their seminal paper, Hanahan & Weinberg outline that the six basic hallmarks are: sustaining proliferative signaling, the ability to evade growth suppressors, resisting cell death, limitless replicative potential, the ability to induce angiogenesis and the activation of invasion and metastasis [21]. A decade later, the authors amended the hallmarks to include an additional two; the reprogramming of energy metabolism and the ability to evade immune destruction [22]. Oral microbiota-mediated carcinogenesis has been found to satisfy or induce a majority of the hallmarks [23]. In fact, several periodontal disease-associated species, namely *Porphyromonas gingivalis*, *Tannerella forsythia* and *Prevotella intermedia* were found to be associated with an increased risk of developing GI cancer [24]. Interestingly, these cancers are not limited to the oral cavity, with oral microbiota-associated primary tumors being observed in the esophagus, stomach, pancreas and colon/rectum [25]. Below, the associations between specific microbial members of the oral microbiota and certain cancers are outlined; the associations are likewise presented in Fig. 1. Where possible, the mechanisms underlying these associations are likewise included in Section 3.

2.1. Oral Squamous Cell Carcinoma (OSCC)

2.1.1. Porphyromonas gingivalis

OSCC is the most common cancer of the head/neck, accounting for approximately 2% of all cancers globally [1]. Although, classically associated with tobacco use and alcohol consumption, recent evidence

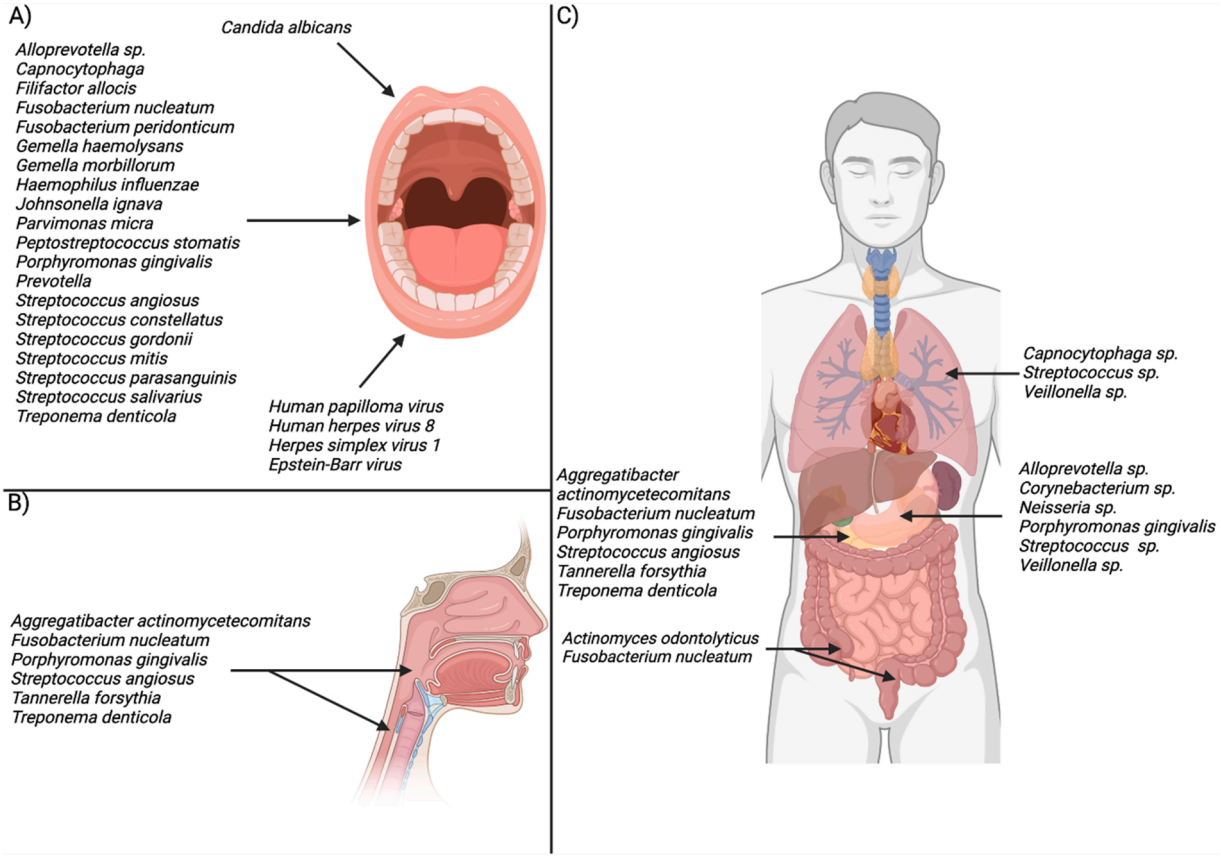

Fig. 1. Oral microbiota associations with A) oral cancer; B) esophageal cancer; C) lung, gastric, pancreatic and colorectal cancer.

suggests that individual members of the oral microbiome are likewise associated with the development of OSCC. In particular, *P. gingivalis* is well known to be associated with the development and progression of cancer within the oral cavity [26]. In fact, the relationship between oral carcinomas and *Porphyromonas* has been known about for decades [27]. In a study examining the microbiota composition of OSCC and opposite healthy tissue from 50 patients with OSCC, Zhang et al., found that OSCC samples were among others, enriched for *Porphyromonas* [28]. This is in line with the work of Katz et al., who found that levels of *P. gingivalis* were elevated in gingival samples from patients with OSCC when compared to healthy controls [29]. These two studies highlight the fact that even within the same oral cavity, the microbiota composition differs between healthy and diseased tissue. Specifically, tumor sites exhibit higher levels of pathogenic organisms. Sayehmiri et al., performed a systematic review and meta-analysis examining the relationship between *P. gingivalis* and oral cancer [30]. The authors found that carriage of this bacteria increases the risk of cancer development by as much as 1.36 (95 % CI = 0.47–3.97), with most of the resultant cancers being gingival. In fact, through their murine model, Wen et al., demonstrated that *P. gingivalis* increased tumor multiplicity and size, as well as contributed to tumor progression [31]. In addition to *P. gingivalis*, a recent study by Rai et al., revealed that *Porphyromonas endodontalis* is likewise elevated in the saliva of patients with OSCC [32].

2.1.2. *Fusobacterium nucleatum*

Fusobacterium nucleatum is also known to be associated with the development and progression of oral cancer [26]. Similarly to *Porphyromonas*, the relationship between oral carcinomas and fusobacteria has been known to researchers for years [27]. However, as with all microbiome related research, the advent of NGS has greatly increased the volume of data available about this relationship. Using such techniques, Zhao et al., demonstrated that *Fusobacterium* is enriched in OSCC samples compared to normal tissue samples from the same patients [33]. Al-hebshi et al., likewise found that *F. nucleatum* was found at a higher relative abundance in OSCC biopsies compared to non-cancerous swabs obtained from the same patients [34]. In their study of 50 patients with OSCC, Zhang et al., also found that cancer tissues are enriched for *Fusobacterium* [28]. The 2018 study by Perera et al., who found that *Fusobacterium* is enriched in OSCC samples, further corroborates the above mentioned relationship [35]. Harrandah et al., used an *in vitro* model to demonstrate that fusobacteria may enhance the invasiveness, survival and epithelial-mesenchymal transfer (EMT) of cancer in the oral tumor microenvironment [36]. Yang et al., note that *Fusobacterium periodonticum* is likewise associated with OSCC, with its abundance increasing from stage 1 to stage 4 of cancer progression [37]. This study is interesting because it showcases that fusobacteria other than *F. nucleatum* are associated with OSCC development and progression.

2.1.3. *Alloprevotella sp.*

Recently, carriage of *Alloprevotella* has been found to increase the risk of oral cancer. In a study examining the salivary microbiota in Japanese patients with oral cancer and healthy controls, Takahashi et al., observed that *Alloprevotella* was more abundant in patients with oral cancer [38]. Zhang et al., who noted the increased relative abundance of *P. gingivalis* and *F. nucleatum* in OSCC tumor samples observed the same for *Alloprevotella* [28]. Ganly et al., observed that *Alloprevotella* was enriched in patients with oral cancer, independent of the classically recognized risk factors (smoking, alcohol, HPV) [39]. This suggests that these bacteria may in fact present a risk for the development and progression of oral cancer in and of itself.

2.1.4. *Prevotella sp.*

For some time, it has been known that *Prevotella* is associated with oral cancer. In fact, the association between this bacterium and keratinizing squamous cell carcinomas of the oral cavity has been recognized for over 20 years. In 2005, Mager et al., reported that *P. melaninogenica* is increased in the saliva of patients with the disease [40]. More recently, Zhang et al., noted that OSCC tumor biopsies are found to be enriched for *P. intermedia* [28]. Torralba et al., likewise noted that there is an increase in the levels of *Prevotella* in some patients with OSCC [41]. Similarly to *Alloprevotella*, *Prevotella* was also found by Ganly et al., to be elevated in non-smoking, HPV-negative OSCC patients [39].

2.1.5. *Capnocytophaga sp.*

In a study involving 25 patients with OSCC and 27 fibroepithelial polyp controls, Perera et al., found that *Capnocytophaga* were over-represented in OSCC [35]. Takahashi et al., reported similar findings in their examination of the oral microbiota of 60 patients with oral cancer and 80 controls [38]. Specifically, the authors found that the saliva of cancer patients contained a higher relative abundance of *Capnocytophaga*. Zhang et al., as well as Mager et al., likewise report that *Capnocytophaga* is enriched in patients with OSCC, with the latter group reporting that the species *Capnocytophaga gingivalis* is specifically implicated [28,40].

2.1.6. *Streptococcus sp.*

As early as 2000, the connection between certain streptococci and carcinogenesis in the oral cavity has been known [42]. That year, Tateda et al., reported that *Streptococcus anginosus* could be detected in cancer samples obtained from the oral and pharyngeal cavities of patients. Five years later, Sasaki et al., noted that *S. anginosus* is indeed elevated in patients with oral cancer, but not in patients with other cancers (namely, lymphoma, rhabdomyosarcoma and precancerous leukoplakia) [43]. Interestingly, the authors found that *S. anginosus* was solely detected in dental plaque and not in the saliva of patients who were found to carry these bacteria. A recent study by Rai et al., who found that *S. anginosus* is elevated in patients with OSCC, highlights the continued relevance of this bacteria in the carcinogenesis of oral cancer [32]. In 2020, a number of the same co-authors proposed that *S. anginosus* may serve as a non-invasive biomarker of oropharyngeal cancer [44]. In 2005, Mager et al., noted that another species of streptococci, *Streptococcus mitis*, was likewise elevated in patients with OSCC [40]. In contrast to this, during a study involving 197 OSCC patients in Taiwan, Yang et al., found that the relative abundance of *Streptococcus* decreased with cancer progression, with *S. mitis* levels being inversely related to OSCC progression [37]. Perera et al., likewise report that *S. mitis* was found to be more abundant in the fibroepithelial polyp samples used as non-cancer controls in their study [35]. Furthermore, evidence exists of an association between the following streptococci and oral cancer: *Streptococcus constellatus*, *Streptococcus salivarius*, *Streptococcus gordonii* and *Streptococcus parasanguinis* [37,45].

2.1.7. *Human papilloma virus (HPV)*

HPV has for many years been recognized as an etiological agent of anogenital cancers. Increasingly, it is being credited with playing a role in the development and progression of oral cancer, and as a possible reason for the increased incidence of the disease [46]. Martín-Hernán et al., report that patients with HPV-associated cancers of the head and neck are typically younger and present with a reduced tobacco use and/or alcohol intake [47]. In 2019, Robayo et al., found that 84 % and 61.5 % of patients with OSCC were positive for HPV and HPV-16, respectively [48]. Among non-cancer patients, 34.6 % were positive for HPV and 30.7 % were positive for HPV-16. In a meta-review encompassing 1497 cases of OSCC, Chaitanya et al., found that 588 patients (39.27 %) were positive for HPV DNA [49]. According to their calculations, HPV-positivity increased the risk of OSCC by 2.82 when compared to controls.

2.1.8. *Human herpes virus 8 (HHV-8)*

Also known as Kaposi's sarcoma-associated herpesvirus, HHV-8 has been implicated in HIV-associated carcinogenesis in the oral cavity, especially with regards to oral Kaposi sarcoma (KS) [50]. A high

proportion of KS lesions in patients with AIDS were found to contain HHV-8 DNA by Flaitz et al., [51]. Furthermore, recent research by Gruffaz et al., seems to indicate that HIV/HHV-8 coinfection and the oral microbiota may interact to influence the development and progression of KS [52]. Despite its close association with HIV, HHV-8 may cause KS in isolation as well; one such case was reported by Lombardi et al., in 2020 [53].

2.1.9. Herpes simplex virus 1 (HSV-1)

The relationship between HSV-1 and oral cancer has been known for decades, with Shillitoe et al., finding that anti-HSV-1 titres increased with the progression of cancer [54]. In 2016, Jain reported that patients with OSCC lesions or precancerous lesions exhibited higher levels of antibodies against HSV-1 than their healthy counterparts [55]. This is in line with the work of Yang et al., who in 2004 showed that HSV-1, but not HSV-2, is associated with OSCC [56]. Jalouli et al., likewise found that HSV was associated with oral cancer, with 29 % of toombak users having detectable levels of HSV DNA found in brush samples [57]. Unfortunately, research into the relationship between HSV and OSCC seems not to have gained the same attention as that of other microorganisms since the advent of NGS.

2.1.10. Epstein-Barr Virus (EBV)

The association of EBV with cancer is well established; however, its role in the carcinogenic process is still being investigated. In infected individuals, EBV if often detected in oral and pharyngeal lymphoid tissues, with B lymphocytes constituting the primary reservoir for the virus [58]. It is therefore not surprising, that in addition to OSCC, EBV is known to be associated with oral diffuse large B-cell non-Hodgkin's lymphoma, oral Burkitt's lymphoma and salivary gland epithelioma [58,59]. With respect to OSCC, Kis et al., found that 73.8 % of OSCC patient samples were positive for latent membrane protein-1 (LMP-1), a marker of most EBV-related malignancies, compared to 19.1 % in controls [60]. Additionally, in a meta-analysis published in 2019, de Lima et al., reported that EBV-infected individuals have a 2.5 higher risk for developing OSCC (95 % CI = 1.23–5.36) [61].

2.1.11. Candida albicans

It has been known for many years that candidiasis is a common infection in patients undergoing chemotherapy. However, recent years have seen an increase in research linking these fungi to oral carcinogenesis as well [62,63]. A recent review by Di Cosola et al., highlights that oral cancer is often preceded by precancerous lesions such as leukoplakia and oral lichen planus [64]. There are numerous studies which have attributed oral leukoplakia and oral lichen planus to *Candida* spp., thus suggesting that this fungal genus is at least partially responsible for these precancerous lesions [65,66]. However, Artico et al., highlight that the ability of *Candida* strains to induce such precancerous changes is dependent upon the production of carcinogenic enzymes [67]. One such carcinogenic mechanism is outlined by Alnuaimi et al., who found a positive association between the ability of oral *Candida* to metabolize alcohol to acetaldehyde and promote cancer development [68]. In 2017 Chung et al., reported that individuals with a *Candida* infection had an overall higher risk for developing cancer (OR = 1.19, 95 % CI = 1.09–1.30) [69]. This is in line with findings obtained by Nørgaard et al., who in 2013 reported that the risk for developing mouth and throat cancer remained more than 3-fold increased in *Candida*-infected patients for several years [70].

2.1.12. Remaining microbial associations with OSCC

In addition to the members of the oral microbiota singled out above, Listyarifah et al., report that *Treponema denticola* chymotrypsin-like proteinase (Td-CLP) was found in 95 % of mobile tongue squamous cell tumor samples they tested, suggesting the presence of *T. denticola* [71]. Additionally Yang et al., found that *Fusobacterium periodonticum*, *Parvimonas micra*, *Haemophilus influenzae* and *Filifactor alocis* were associated with OSCC [37]. Interestingly, the authors also revealed that the abundance of these five species progressively increased in abundance from stage 1 to stage 4 of OSCC. Furthermore, *Peptostreptococcus stomatis*, *Gemella haemolysans*, *Gemella morbillorum* and *Johnsonella ignava* have been found to be highly associated with tumor sites [45].

2.2. Esophageal & oropharyngeal cancer

Contents from the oral cavity are constantly entering the esophagus, it is therefore unsurprising that many of the same oral bacteria are implicated in both oral and esophageal cancer. The members of the oral microbiota with the most evidence supporting their association with esophageal cancer are outlined below.

An early study by Morita et al., found that *S. anginosus* is not only detected more frequently in samples of esophageal cancer than oral cancer, but that the relative abundance is higher as well [72]. In 2004, Narikiyo et al., reported that esophageal cancer patients presented with the preferential and frequent infection of *S. anginosus* and *S. mitis* [73]. This relationship is likewise highlighted in a recent study conducted by Kawasaki et al., who calculated that carriage of *S. anginosus* was associated with a high risk of esophageal cancer [74]. In 2016, Gao et al., reported that *P. gingivalis* could be detected in 61 % of cancerous esophageal tissue, 12 % of adjacent tissues and not at all in healthy esophageal mucosa in their study involving 100 patients with esophageal squamous cell carcinoma (ESCC) [75]. Very similar results were obtained by Chen et al., who in 2021 reported that 57 % of patients enrolled in their study were infected with *P. gingivalis* [76]. Moreover, the authors highlighted that presence of *P. gingivalis* was associated with advanced clinical stages of ESCC and poor prognosis. Although Kong et al., found that only between 42–46 % of patients with esophageal cancer were infected with *P. gingivalis*, they confirm that detectable levels of this bacteria were associated with poor prognosis [77]. With regards to the type of esophageal cancer, Peters et al., report that *P. gingivalis* is associated with the development development of ESCC, while other bacteria such as *T. forsythia* are associated more greatly with esophageal adenocarcinoma (EAC) [78]. The aforementioned study by Kawasaki et al., likewise found an association between *T. forsythia* and esophageal cancer [74].

In addition to the three bacteria highlighted above, an association exists between esophageal cancer and *T. denticola* [73], *A. actinomycetecomitans* [74,79], *Atopobium* and *F. nucleatum* [80]. Interestingly, Agalliu et al., report that oral HPVs may not contribute to the risk of esophageal cancer, this despite their strong association with oral cancers [81].

2.3. Pancreatic cancer (PC)

Carriage of certain oral pathogens is associated with an increased risk of developing pancreatic cancer. There are a number studies reporting associations with *P. gingivalis* and PC [82–85]. *F. nucleatum* is likewise known to be found within pancreatic tumors [86,87]. In fact, Mitsuhashi et al., note that the presence of *F. nucleatum* within pancreatic tumors is associated with a worse prognosis [88]. In addition to *P. gingivalis* and *F. nucleatum*, Fan et al., have shown that *A. actinomycetemcomitans* and *Alloprevotella* are also associated with an increased risk of developing PC [82]. Furthermore, Wei et al., noted that both *Leptotrichia* and *Streptococcus* were associated with a higher risk of developing PC [89]. In an early study examining the relationship between the oral microbiota and PC, Farrell et al., found that *Granulicatella adiacens* was increased in PC [90]. Moreover, the authors reported that *Neisseria elongata* and *S. mitis* are present at different levels between patients with PC and healthy controls. With its low early detection rates, PC is characterized by high-mortality rates, prompting a number of research groups to examine the feasibility of using specific members of the oral microbiota as biomarkers [83,91].

2.4. Colorectal cancer

Through the examination of human colonic adenomas, Kostic et al., found that *Fusobacterium* spp. are enriched in tumors relative to healthy surrounding tissue [92]. This work is in line with several other studies such as that by Casterllarin et al. [93], Li et al. [94], and McCoy et al. [95], all of which show that the relative abundance of *F. nucleatum* is higher in cancer tissue obtained from CRC patients than healthy tissue. Kagemaya et al., note that *Actinomyces odontolyticus* is observed to be present in greater abundance in patients with CRC [96].

2.5. Gastric cancer (GC)

Hu et al., measured the thickness of the tongue coat microbiota by means of a tongue manifestation acquisition instrument [97]. They found that gastric cancer patients had significantly thicker tongue coats. During examinations of composition tongue coat microbiota, Wu et al., found that *Streptococcus* was associated with an increased risk of GC [98]. The authors also note that *Alloprevotella* and *Veillonella* trended with the higher risk of cancer in the cardia of the stomach. In a study involving 293 patients, Huang et al., found that patients with GC had a higher relative abundance of the pro-inflammatory taxa *Corynebacterium* and *Streptococcus* in their salivary microbiota than patients with atrophic and superficial gastritis [99]. *Neisseria* and *P. gingivalis* were found to be higher in GC patients by Kageyama et al., [96]. In a recent review, Bakhti & Latifi-Navid attempt to outline the possible interplay between members of the oral microbiota and *H. pylori* [100]. However, the authors note that studies aimed at examining the interactions between oral microbial populations and *H. pylori* are sorely lacking, thus leaving potentially critical pathomechanisms as yet undiscovered. Further strengthening the case for the desperate need for research in this area is the study by Wu et al., who suggest that the ectopic colonization of oral microorganisms in the gastric mucosa may be necessary for the gastric dysbiosis induced by *H. pylori* [101].

2.6. Lung cancer

A recent study involving 114 individuals who developed lung cancer and matched healthy controls, found that a low alpha diversity in oral microbiota was associated with an increased risk for developing lung cancer [102]. This is in line with work done by Yang et al., which revealed lower oral microbial diversity in non-smoking female lung cancer patients [103]. With regards to specific members of the oral microbiota, Yan et al., observed that significantly higher levels of *Capnocytophaga* and *Veillonella*, were observed in patients with squamous cell carcinoma (SCC) of the lung [104]. In fact, the authors suggest that these two bacteria may be used as an oral biomarker for lung cancer. *Veillonella* and *Streptococcus* were found to be increased in the salivary microbiota samples of non-small cell lung carcinoma (NSCLC) patients by Zhang et al. [105]. Moreover, Liu et al., found that *P. gingivalis* may be involved in the promotion of malignant lung cancer progression [106].

3. Carcinogenic mechanisms

Many of the oral microorganisms associated with cancer are primarily associated with halitosis. However, it is important to note that the same mechanisms often underlie both phenomena, particularly with regards to the production of malodorous/carcinogenic substances such as aldehyde [107]. Despite the similarities in the pathomechanisms leading to cancer and other diseases, this section aims specifically to highlight the carcinogenic mechanisms employed by select members of the oral microbiota. An important caveat as outlined by Koliarakis et al., is that several of the microorganisms highlighted below have been implicated in the induction of dysbiosis in the gut, with the subsequent perturbations of gut microbiota contributing mechanistically to carcinogenesis [108]. Although this aspect of their carcinogenic potential is critically important, it is beyond the scope of this review. Fig. 2 outlines the carcinogenic mechanisms employed by select members of the oral microbiota.

3.1. Porphyromonas gingivalis

Gram-negative organisms such as *P. gingivalis* contain LPS, a component of the bacterial outer membrane. LPS is recognized by TLR4 which stimulates MyD88-dependent and independent pathways, ultimately liberating NF-κB, resulting in the production of proinflammatory cytokines [26]. The increased expression of pro-inflammatory cytokines creates an inflammatory environment conducive to the development and progression of cancer [109]. Inflammation associated DNA damage in stem cell populations and reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been linked to the development of cancer [110]. Furthermore, epithelial-mesenchyme transition (EMT) is enhanced by *P. gingivalis* through the increase in expression of Snail, Slug and β-catenin, with the latter transcription factor promoting epithelial proliferation and migration [111]. In addition to inflammatory-related mechanisms, much of the pathogenic potential of *Porphyromonas* has been attributed to its immunosuppressive capabilities [112]. Olsen & Yilmaz noted that *P. gingivalis* is able to promote survival and proliferation in epithelial cells through the increased expression of PI3K/Akt signaling [111]. The authors likewise highlight that the pro-survival and proliferative phenotype of cancer is promoted by *P. gingivalis*-mediated suppressing of p53 function. *P. gingivalis* gingipains (cysteine proteases) are also able to mediate T cell anergy through the upregulation of B7-H1 receptor in oral squamous carcinoma cells [113]. Through their *in vitro* and mouse models Liu et al., were able to demonstrate that *P. gingivalis* prevents phagocytosis of Cal-27 cells (an OSCC cell line) and drives the polarization of macrophages to the pro-tumor, M2 tumor-associated macrophage (TAM) phenotype [114]. Moreover, Carvalho-Filho et al., found that upon exposure to the *P. gingivalis* protein HmuY, PBMCs from patients with periodontitis more greatly downregulated genes associated with apoptosis than PBMCs from healthy controls [115]. Lee et al., likewise demonstrated that *P. gingivalis* subverts host cell apoptosis by means of phosphorylating heat shock protein 27 (HSP27) [116]. Work by Saito et al., demonstrates that the pathogenic potential of *P. gingivalis* is increased synergistically by coinfection with *F.* nucleatum [117].

3.2. Fusobacterium nucleatum

F. nucleatum is the most common oral bacteria observed in extra-oral infections [118]. A major facet of the pathogenic potential of *F. nucleatum* is the ability to invade host epithelial tissues, allowing for colonization, dissemination and evasion of host defenses [119]. *Fusobacterium* adhesion A (FadA) enables the bacteria to bind host cells through interactions with cadherins [120]. Specifically, FadA binds vascular-endothelial (VE) cadherin, allowing for subsequent internalization into the intracellular compartment [121]. Additionally, the expression levels and cellular distribution of tight junction proteins zonula occludens-1 and occludin are altered by *F. nucleatum*, thus changing the integrity of epithelial barriers, for example, in the intestine [122]. Similarly to *P. gingivalis*, *F. nucleatum* induces an inflammatory response *via* NF-κB mediated cytokine production [123]. More specifically, Liu et al., found that *F. nucleatum* promotes the secretion of TNF-alpha, IFN-gamma, IL-1beta, IL-6, and IL-17 [122]. By means of a murine model, Kostic et al., observed that fusobacteria increase tumor multiplicity and selectively recruit tumor-infiltrating myeloid cells, which are known to promote tumor progression [92]. Further exacerbating aberrant immune responses, the virulence factor familial adenomatous polyposis 2 (Fap2) acts to suppress the cytotoxic function of NK cells and lymphocytes through interactions with the receptor T cell immunoreceptor with Ig and ITIM domains (TIGIT) [124]. Chen et al., report that *F. nucleatum* upregulated long non-coding RNA Keratin7-antisense (*KRT7-AS*), in an *in vitro* and *in vivo* murine model of

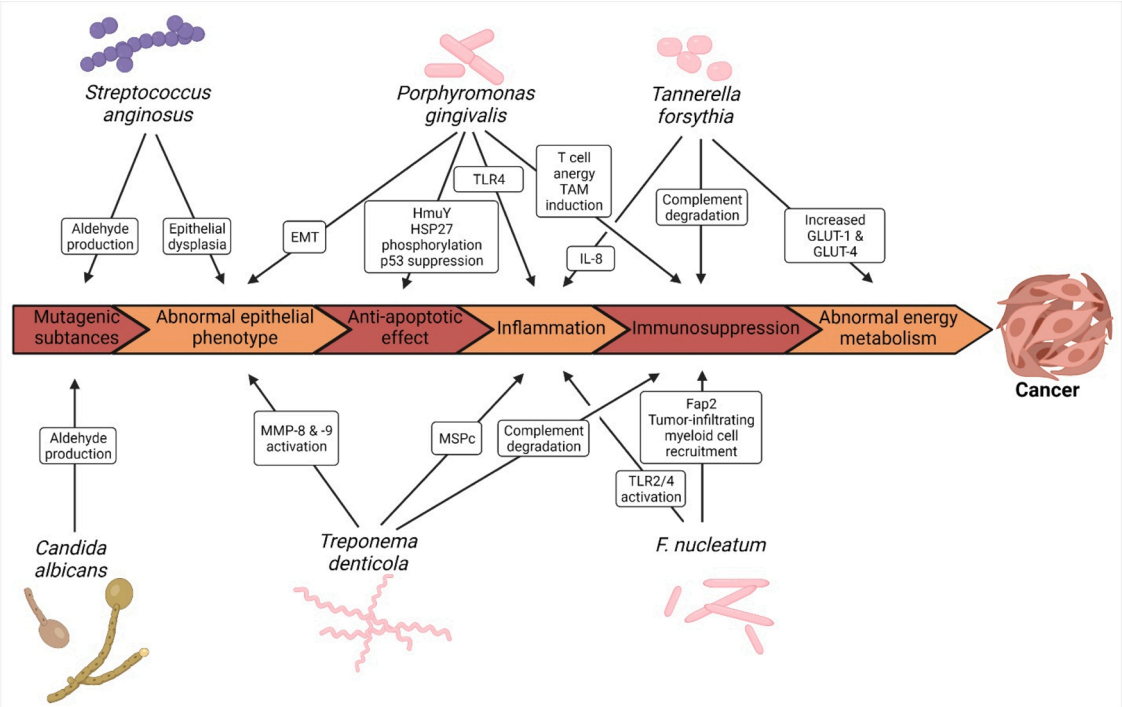

Fig. 2. Carcinogenic mechanisms employed by select members of the oral microbiota.

CRC [125]. The authors report that such long non-coding RNAs are essential in metastatic processes.

3.3. *Streptococcus anginosus*

Narikiyo et al., suggest that *S. anginosus* stimulates the recruitment of neutrophils and monocytes, which may lead to epithelial dysplasia and subsequent neoplasia [73]. Additionally, evidence for the conversion of ethanol to acetaldehyde by *S. anginosus* exists [126,127]. Acetaldehyde is known to contribute to carcinogenesis, through DNA damage and the point-mutations that result from its repair [128,129]. *S. anginosus* presents an interesting case, because this particular member of the oral microbiota, is associated with a number of anti-tumor processes. Wang et al., highlight that *Streptococcus* reactive- CD8 + T cells exhibited lower levels of PD-1 and TIM-3 than non-*Streptococcus* reactive CD8 + T cells [130]. PD-1 is implicated in attenuating T cell responses in tumors, thus promoting an immunosuppressive environment conducive to tumor progression [131].

3.4. *Tannerella forsythia*

T. forsythia employs the protease mirolysin to evade host immune defenses through the degradation of complement pathway components and antimicrobial peptides [132]. *T. forsythia* is known to induce the increased expression of glucose transporters GLUT-1 and GLUT-4 in cancer cells, thus allowing for increased nutrient supply and subsequent proliferation [133]. Additionally, *T. forsythia* detaching factor (FDF), has been shown to induce the production of the pro-inflammatory cytokine, IL-8 [134].

3.5. *Treponema denticola*

The pathogenesis of orodigestive cancers as they relate to *T. denticola* is attributed in large part to the chronic inflammation and immunomodulation mediated by this species [128]. *T. denticola* chymotrypsin-like protease (Td-CLP) has been implicated in the conversion of MMP-8 and MMP-9 into their active forms [135]. It is well known that MMPs are instrumental in the processes of tumor invasiveness and metastasis [136]. Nieminen et al., further report that Td-CLP is capable of fragmenting complement C1q; thus suppressing complement-mediated immune functions [135]. Gaibani et al., report that major surface protein complex of *T. denticol*a increases the expression of proinflammatory cytokines, namely TNF-alpha, IL-1beta, IL-6, as well as MMP-9 in human peripheral monocytes [137].

4. Clinical implications

Members of the host microbiota are known to be associated with both pro-inflammatory and immune dampening responses, both of which contribute to the development and progression of cancer. A number of such mechanisms have been outlined above; however, the microbiota is likewise associated with drug metabolism and as such affects the efficacy and toxicity of chemotherapeutic agents [138].

Yu et al., found that *F. nucleatum* reduces chemotherapeutic induced apoptosis by means of an *in vitro* study utilizing Oxaliplatin and 5-fluorouracil (5-FU) [139]. However, the authors observed no protective effect when the cells were treated with Doxorubicin. Mechanistically, *F. nucleatum* mediates this chemoresistance by targeting TLR4 and MyD88 immune pathways and through MiR-18a* and MiR-4802 to activate autophagy pathways and modify the response to chemotherapeutics. In contrast, Cremonesi et al., note that patients treated with adoptive cell therapy exhibited increased survival when their tumors contained *F. nucleatum* [140]. The authors believe this to be the result of an increase in chemokine production and thus T cell infiltration. Interestingly, as noted in Section 3.2, *F. nucleatum* is also known to inhibit T cell function.

Although more limited in its volume, there is some evidence suggesting that *P. gingivalis* likewise affects the effectiveness of chemotherapy. In 2017, Woo et al., reported that tumor xenografts composed of *P. gingivalis*-infected OSCC cells exhibited a higher resistance to Taxol through Notch1 activation [141]. Two years later, a number of the authors from the first study revealed that oral administration of *P. gingivalis* to mice with OSCC xenografts increased resistance to Paclitaxel [142].

5. Conclusions

Several members of the oral microbiota are associated with the development and progression of cancer, both within the oral cavity and in distant anatomical locations. In particular, carriage of *F. nucleatum* and *P. gingivalis* is associated with the development of cancer. The mechanisms of bacterial-mediated carcinogenesis include the generation of pro-inflammatory conditions, immune suppression and the suppression of apoptosis. In this manner, oral bacteria are capable of inducing several of the hallmarks of cancer. In addition to driving the development and progression of cancer, the microbiota has been implicated in mediating resistance to anti-cancer therapies [26]. However, the role of the oral microbiota as it relates to the outcome of chemotherapeutic treatment is only beginning to come to light, as research in this field is still in its infancy. As more information regarding the relationships between the oral microbiota and various cancers becomes available, it may become possible to use its members as biomarkers for disease. Additionally, the presence or absence of certain bacteria may inform clinical decisions with respect to treatment.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

The authors did not receive any external funding.

Authors' contributions

Conceptualization, M.S. and T.M.K.; data analysis, M.S.; writing - original draft preparation, M.S. and T.M.K.; visualization, M.S.; supervision, T.M.K. Both authors approved the final manuscript.

Availability of data and material

Not applicable.

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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