Paradigm shift in the pathogenesis and treatment of oral cancer and other cancers focused on the oralome and antimicrobial-based therapeutics

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Funding information
Larry Berkelhammer funds to Yvonne L. Kapila

1 | INTRODUCTION

1.1 | Oral microbiome and its interactions with the host (oralome)

The oral cavity contains up to 1000 microbial species in total, comprised of bacteria, fungi, viral, archaea, and protozoan species that thrive in a very dynamic microenvironment.1-5 All of these microorganisms form a complex relationship among themselves, establishing a unique microbiome, known as the oral microbiome. Interestingly, the oral microbiome forms a close symbiotic relationship with human host cells in the oral cavity. Thus, the term oralome was coined to encompass not only the oral microbiome but also the host-microbial interactions that take place in the human oral cavity.5 In this sense, healthy symbiotic host-microbiome interactions between humans and these microorganisms are known as eubiosis.5-7

The microbial composition can be dramatically affected by interspecies and host-microbial interactions. These microbial changes can impact the health and disease status of the host, since eubiosis plays an essential role both in the development of natural oral physiology and host defense mechanisms.5,8,9 Although the oral microbiome can compensate for most overall perturbations,5,10 some changes can profoundly affect its composition, impacting the oral commensal populations and causing an unbalanced state known as dysbiosis.5,11

1.2 | Periodontitis and oral microbiome dysbiosis

Dysbiosis is an unbalanced microbiome state that is caused by internal and/or external microbial-ecologic changes to the oral microbiome.5 This specific state has been described as capable of promoting diseases in the host.12,13 Since periodontitis is considered an inflammatory disease that is initiated by pathogenic bacteria, the most accepted hypothesis for periodontitis initiation and progression is that there is a dysbiotic shift in the oral microbiome.5,14 This shift is driven by an enrichment of Prevotella intermedia, Fusobacterium nucleatum, Porphyromonas gingivalis, Tannarella forsythia, and Treponema denticola species in the microbiome.14-16 Specifically, a dysbiotic oral biofilm infiltrates the gingival pocket, which then triggers the host immune response. This reaction leads to gingival tissue inflammation (gingivitis) and, ultimately, tissue degradation and periodontitis.14

Oral dysbiosis has been associated with a variety of systemic diseases and conditions, including Alzheimer’s disease, diabetes, adverse pregnancy complications, and several types of cancer, including oral, gastrointestinal, lung, breast, prostate, and uterine cancer.5,17-20 Thus, the objective of this research is to (1) evaluate the epidemiologic evidence linking periodontitis to these types of cancer, (2) provide insights into the mechanisms by which oral microbial dysbiosis can cause these cancers, and (3) summarize the evolving evidence supporting the use of probiotics and related molecules.
2 | EVIDENCE LINKING PERIODONTITIS AND SEVERAL TYPES OF CANCER

Cancer, in a broad sense, refers to more than 277 different types of cancer diseases, each one caused by a series of genetic mutations that lead to abnormal cell proliferation and invasion. In the United States, cancer is the second leading cause of death. It is estimated that there will be 1.8 million new cases of cancer and more than 600,000 deaths in the United States in 2020.

Although genetic mutations are considered the main etiology agents of cancer overall, periodontitis has been recently associated with head and neck, gastrointestinal, lung, breast, prostate, and uterine cancers. In the following sections, we will further discuss the association between periodontitis and these cancers.

2.1 | Head and neck cancer

Head and neck cancer is a devastating disease, often disfiguring and debilitating affected patients. It is the sixth most common cancer worldwide, and it comprises cancers of the oral cavity, larynx, hypopharynx, and oropharynx. In 2018, head and neck cancer accounted for approximately 706,000 new cases and 358,000 deaths worldwide. In the United States, head and neck cancer accounts for 3% of all cancers and approximately 65,000 Americans are diagnosed with head and neck cancer annually. Table 1 shows the estimated US incidence and the estimated new cases and deaths in the United States (for 2020) and worldwide (for 2018) for each head and neck cancer subtype. In this chapter, we will focus on oral cancer in particular.

Oral cancers have a complex etiology that includes lifestyle factors such as alcohol and tobacco usage, which are strongly associated with most head and neck cancers progression and aggressiveness. It was recently demonstrated that alcohol consumption plus smoking have a synergistic effect in increasing head and neck cancer risk, particularly for oral and pharyngeal cancer. It has been demonstrated that alcohol and tobacco-induced head and neck cancer exhibit mutations in tumor suppressor protein p53 and inactivation of the tumor suppressor p16 gene via deletion of 9p21-22.

Besides tobacco and alcohol consumption, two recent cohort studies showed that poor oral hygiene decreased the survival rates of patients with oral cancers, whereas good oral health behaviors, such as daily tooth brushing and an annual dental visit, reduced the risk of head and neck cancer. These studies suggest that oral microbial dysbiosis may be an important contributor to oral cancer pathogenesis.

Recent studies have shed light on the possibility of periodontal disease–associated pathogenic bacteria having an important role in oral cancer tumorigenesis and aggressiveness. Anaerobic and facultative bacteria can colonize and grow in tumors. The possibility of pathogenic bacterial growth in tumors is currently attributed to unique pathophysiologic features known to many cancers that benefit the growth of these particular bacteria, such as impaired and abnormal vascular architecture, enhanced permeability and retenction effect, low oxygen pressure/hypoxia and extensive necrosis. Interestingly, the main periodontal disease pathogens (ie, P. denticola, P. gingivalis, F. nucleatum, and T. forsythia) are considered facultative anaerobes and oxygen-tolerant species.

Particularly for oral cancer, increased salivary bacterial counts of Lactobacillus spp, Capnocytophaga gingivalis, Prevotella melaninogenica, and Streptococcus mitis and loss of Haemophilus, Neisseria, Gemella, and Aggregatibacter genera have been reported in oral cancer patients compared with normal controls. Our group identified different bacterial species colonizing oral tumors compared with healthy sites and found a high fusobacterial and low streptococcal phenotype as part of the transition from primary to metastatic oral cancer. Interestingly, P. gingivalis and F. nucleatum (two periodontal pathogens) were detected up to 600 times more frequently in oral squamous cell carcinoma than in paracancerous and normal tissues. Mechanistically, F. nucleatum and P. gingivalis downregulate p53 pathway and promote increased cell proliferation of tongue and oral squamous cell carcinoma up to 125 times compared with control conditions.

Dysregulation of toll-like receptor expression may also influence the host response to periodontal pathogens, which then leads to an increase in inflammation and susceptibility to periodontitis. Periodontal pathogens predominately stimulate toll-like receptor 2 and 4. This receptor activation then leads to the production of proinflammatory cytokines via regulation by (bacteriocins) for prevention and treatment of cancer. For more details on oral host-microbial interactions and the role of oral dysbiosis on different systemic diseases, please refer to Radaic and Kapila.

| Head and neck cancer classification | Estimated annual incidence in United States (per 100,000) | Estimated new cases | Estimated deaths |
|------------------------------------|----------------------------------------------------------|---------------------|-----------------|
| Oral cavity                        | 11.7<sup>37</sup>                                        | 35,310              | 7110            |
| Larynx                             | 3.3<sup>37</sup>                                         | 12,370              | 3750            |
| Hypopharynx                        | <1.0<sup>38</sup>                                        | 17,950              | 3640            |
| Oropharynx                         | --                                                       | 92,887              | 51,005          |

TABLE 1  Head and neck cancer estimated incidence and estimated new cases and deaths in the United States and worldwide
transcription of nuclear factor kappa-light-chain-enhancer of activated B cells and subsequent alveolar bone resorption through the production of matrix metalloproteinases and osteoclastogenesis. Nuclear factor kappa-light-chain-enhancer of activated B cells has also been identified as an integral factor in regulating various processes associated with cancer progression, such as cell survival, proliferation, and resistance to both targeted therapy and chemotherapy. Recently, Kamarajan et al demonstrated that *T. denticola*, *P. gingivalis*, and *F. nucleatum* enhance oral squamous cell carcinoma migration, invasion, and tumor formation via integrin alpha V/focal adhesion kinase signaling; commensal bacteria were not able to trigger the same response. The authors also demonstrated that *T. denticola* triggers oral squamous cell carcinoma migration via crosstalk between toll-like receptor 2 and 4/myeloid differentiation primary response 88 protein and integrin alpha V/focal adhesion kinase signaling, thereby contributing to the aggressive nature of the pathogen-enhanced oral squamous cell carcinoma phenotype (Figure 1). These pathogen-mediated cancer properties were abrogated by treatment with an antimicrobial bacteriocin. Huang et al demonstrated that *Listeria monocytogenes* had a direct tumor-stimulating effect associated with its ability to activate toll-like receptor 2-dependent signaling pathways in ovary cancer cells. Moreover, the toll-like receptor 2-dependent activation of nuclear factor kappa-light-chain-enhancer of activated B cells caused by *L. monocytogenes* resulted in an enhanced resistance of tumor cells to chemotherapeutics. Additionally, metastasis and progression of oral tumors were essentially retarded in toll-like receptor 2 knockout mice, compared with wild-type mice. Thus, toll-like receptors have a tumor-stimulating effect on a variety of cancer cell types, and this mechanism may play a direct role in driving periodontal inflammation–induced carcinogenesis.

Among periodontal pathogens, *T. denticola* has also been implicated in oropharyngeal squamous cell carcinoma, since dentilisin, a major virulence factor of *T. denticola*, was found inside of the cellular cytoplasm of the majority (87%) of oropharyngeal squamous cell carcinoma tissues.

The focus has traditionally been on bacteria when discussing microbiological aspects of oral diseases. However, a causal link between various microbes in human immunodeficiency virus–infected individuals has been documented. Specifically, inflammation is known to stimulate human immunodeficiency virus type-1 gene expression and replication, and infection by bacterial pathogens usually involves production of proinflammatory cytokines that are associated with nuclear factor kappa-light-chain-enhancer of activated B cells activation. Additionally, human immunodeficiency virus–infected patients show a higher incidence of squamous cell carcinoma of the oral cavity and anus. As a means of establishing a link between the two diseases, Imai et al examined the effects of *P. gingivalis* on human immunodeficiency virus type-1 replication. The group readily demonstrated that butyric acid produced by *P. gingivalis* promoted increased expression of latent human immunodeficiency virus type-1–associated genes by inhibiting histone deacetylases and enriching for acetylation at histone 3, highlighting the role of bacteria as a risk factor for promoting acquired immune-deficiency syndrome progression. Similar findings in the intestine with other butyric acid–producing bacteria, such as *Clostridium*, *Fusobacterium*, and *Eubacterium*, suggest that these bacteria might also be involved in the accelerated replication of human immunodeficiency virus type-1. Latent human immunodeficiency virus type-1 proviruses also carry methylated histone H3, which has been either trimethylated on lysine 9 or lysine 27 or dimethylated on lysine 9. Each of these modified histones is considered to be a repressive mark for cellular genes. Immunohistochemical staining of diseased periodontal epithelium revealed an increased abundance of the histone lysine-specific demethylase 4B that correlates with inflammation in murine sections exposed to *Aggregatibacter actinomycetemcomitans* lipopolysaccharide. Taken together, these data suggest that bacteria-virus interactions play an integral role in promoting carcinogenesis in the oral cavity.

![FIGURE 1](treponema_denticola_drives_cancer_aggressiveness_through_toll-like_receptor_2_and_4/myeloid_differentiation_primary_response_88_protein_and_integrin/focal_adhesion_kinase_crosstalk.png)  
*Treponema denticola* drives cancer aggressiveness through toll-like receptor 2 and 4/myeloid differentiation primary response 88 protein and Integrin/focal adhesion kinase crosstalk. TLR2, toll-like receptor 2; MyD88, myeloid differentiation primary response 88 protein; FAK, focal adhesion kinase.
Alcohol and tobacco exposure influence the oral microbiome, increasing the prevalence of periodontal pathogens from *Fusobacterium, Cardiobacterium, Synergistes, Atopobium, Bifidobacterium, Lactobacillus*, and *Selenomonas* genera and decreasing the levels of *Capnocytophaga, Neisseria, Haemophilus*, and *Aggregatibacter* compared with nonsmokers. Among the enriched bacteria, *F. nucleatum* is also able to damage host cell deoxyribonucleic acid (DNA). Thus, it is possible that *F. nucleatum* may play a more prominent role in alcohol and tobacco-induced oral cancer, although these associations need further testing. On the other hand, a nested case-control study with 129 head and neck cancer patients demonstrated that *Corynebacterium* and *Kingella* species were associated with a strongly reduced risk of oral cancer in those with a history of tobacco use. Interestingly, these genera are functionally associated with xenobiotic biodegradative metabolic pathways, including the capacity to metabolize toxicants found in cigarette smoke. 

Despite numerous studies focusing on dysbiosis in oral cancer, most of these studies did not test for the human papillomavirus status of the samples. Among those that did, a distinct oral microbiome composition for human papillomavirus–positive oral cancer compared with human papillomavirus–negative oral cancer was revealed, namely an enrichment in *Lactobacillus, Gemella*, and *Leuconostoc* and *Weeksellaceae* genera in human papillomavirus–positive tumors compared with human papillomavirus–negative tumors. Interestingly, species from these four bacterial genera have been recently associated with the establishment and progression of oral cancer, implicating human papillomavirus as a driver of oropharyngeal and oral cancer tumorigenesis by influencing the composition of the oral microbiome.

### 2.1.1 | Mechanisms of oral microbiome dysbiosis–induced head and neck cancer

At least four main mechanisms have been proposed to explain how oral microbial dysbiosis can induce head and neck cancer carcinogenesis (Figure 2). All these mechanisms are not mutually exclusive, and they might even occur concurrently in mediating carcinogenesis.

**Epithelial barrier disruption**

To safeguard tissue homeostasis, the oral cavity relies on an anatomic separation between the host and the microbes, known as the oral and gingival epithelial barrier, comprised of a complex immunological network (eg, continuous neutrophil recruitment and extravasation into healthy sites) and antimicrobial peptides (eg, histatins and LL-37 produced by salivary glands). Maintaining the integrity of this barrier is key to promoting healthy host-microbial interactions.

![FIGURE 2](image-url)
Several studies have demonstrated that microbes can affect this epithelial barrier function. A proposed mechanism highlights that oral microbial dysbiosis induces epithelial barrier dysfunction, leading to head and neck cancer. A key example of this mechanism has been demonstrated with mucin-2 knockout mice, wherein gastrointestinal mucosa lacking mucin spontaneously develop colorectal cancer, but antibiotic treatment or a germ-free environment significantly reduced tumorigenesis. From a mechanistic standpoint, several oral microorganisms—such as *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, *Peptostreptococcus*, and *Streptococcus* spp—produce compounds, such as acids (eg, lactic, acetic, butyric, and isobutyric acids), that can alter the homeostasis of epithelial barriers, thereby disrupting the mucous barrier and leading to mucosal dysfunction. Although this mechanism has not yet been confirmed in the oral cavity, this seems relevant to head and neck cancer, since oral pathogens can degrade tight junction-associated proteins that regulate epithelial barrier function. For example, *P. gingivalis* can degrade gingival epithelial junctional adhesion molecule 1 in gingival cells, and *T. denticola* can degrade zonula occludens-1, Claudin-1, and occludin. The degradation of epithelial tight junctions enables increased permeability of the gingival epithelium, allowing bacterial virulence factors to penetrate further into the tissue and leading to bacterial invasion of the tissue, as *T. denticola*, *P. gingivalis*, and *F. nucleatum* are also able to intracellularly invade epithelial and gingival tissues.

### Chronic inflammation

A second main mechanism is chronic inflammation. Interestingly, periodontal disease is characterized by chronic inflammation of the supporting tissues of the teeth, which can lead to loss of periodontal ligament and alveolar bone. The disease is driven by a dysbiotic oral microbiome that interacts with the human host and leads to inflammation of the surrounding tissues. In this context, several pathogenic bacteria, such as *P. gingivalis* and *F. nucleatum*, are enriched. These pathogens are able to upregulate several cytokines and inflammatory mediators (eg, interleukins, matrix-metalloproteinases, and tumor necrosis factor alpha) in the surrounding tissues, but also facilitate invading, persisting, and spreading to adjacent cells, promoting chronic inflammation. This chronic inflammation can lead to alterations in cell metabolism, proliferation, and tumorigenesis.

### Genetic damage

A third main mechanism is genetic damage. Several lactobacilli (eg, *Lactobacillus acidophilus*, *Lactobacillus fermentum*, *Lactobacillus jensenii*, and *Lactobacillus reuteri*), and streptococci species (eg, *Streptococcus gordonii*, *S. mitis*, *Streptococcus oligofermentans*, and *Streptococcus oralis*) produce reactive oxygen species, nitrogen reactive species, sulfides, nitrosamines, and acetaldehyde that can lead to DNA damage in epithelial cells and, thus, promote tumorigenesis. For example, in alcohol-induced oral cancer, some oral microbial species, such as *S. gordonii*, *S. mitis*, *S. oralis*, *Streptococcus salivarius*, and *Candida albicans*, can metabolize ethanol to acetaldehyde. Acetaldehyde is an electrophilic molecule that reacts with nucleosides, forming DNA adducts. DNA adducts are sections of the DNA strand that are covalently bound to chemical compounds, which cause abnormalities during DNA replication that can lead to genetic mutations.

### Epigenetic modulation

Epigenetic modifications are defined as heritable alterations, not coincident with alterations in the underlying DNA sequence, that allow biologic systems to interfere with transcription in response to a variety of environmental stimuli. Altered expression of DNA methylation and histone modifications have been reported to play critical roles in the onset and progression of both chronic periodontitis and oral squamous cell carcinoma. Thus, a fourth mechanism is related to epigenetic modulation of the hosts’ gene expression.

Multiple studies have suggested that the hypomethylation status of the interleukin-6 and interleukin-8 gene promoters may be related to an overexpression of these cytokines in inflamed periodontal disease tissues compared with controls. It has been found that human gingival epithelial cells may be triggered by the release of these proinflammatory mediators, which may promote the recruitment and activation of inflammatory cells to facilitate oral malignant transformation, further supporting a link between periodontal infection and induction of cancer-related cellular processes. Although the carcinogenesis-associated epigenetic components governing interleukin-6 and interleukin-8 have yet to be fully determined, one might consider the connections between bacterial/microbial infection, cytokines, and cancer development as intriguing and intersecting points for systems biology that may reveal novel insights for the development of better diagnostics and gene and drug therapies.

DNA methylation and histone modifications are not separate events; they are linked and result in a unique tissue and cell-specific gene expression. A recent study showed that the activation of toll-like receptors by periodontal pathogens not only induced activation of nuclear factor kappa-light-chain-enhancer of activated B cells but also led to an enrichment in histone acetylation in oral epithelial cells. Histones are subjected to a myriad of post-translational modifications, which can open and closed regions of DNA that regulate the accessibility of transcription factors to bind to their targets. Interestingly, *P. gingivalis* and *F. nucleatum* can induce histone modifications, such as induction of histone acetylation, in oral epithelial cells. On the other hand, *T. denticola* seems to regulate cellular division/chromatid segregation (potentially inducing genetic instability) and histone methylation and acetylation, as aurora kinase, histone methyltransferase, and histone acetyltransferases inhibition seem to modulate matrix metalloproteinase-2 activation and expression in periodontal ligament cells in the context of *T. denticola* infection. Yet, few studies are available on histone modifications in periodontitis.

Although genetic and epigenetic similarities have been reported between chronic periodontitis and head and neck cancer,
knowledge in this domain lacks deeper mechanistic insight and is largely comprised of correlative findings.

2.2 | Gastrointestinal cancer

Gastrointestinal cancer, one of the most common causes of cancer worldwide, is often subdivided by anatomic location: the esophagus, stomach, liver, gallbladder, pancreas, colon, rectum, anus cancer. Combined, gastrointestinal cancers accounted for almost 5 million new cases and more than 3.5 million deaths worldwide in 2018. In the United States in 2020, more than 330,000 Americans are expected to be diagnosed with gastrointestinal cancer and more than 155,000 deaths from gastrointestinal cancer are expected. Table 2 shows the estimated new cases and deaths in the United States (for 2020) and worldwide (for 2018) for each gastrointestinal cancer subtype. In this particular section, we will focus on gastric, pancreatic, and colon cancers.

Recently, Zhang et al meta-analyzed 10 cohort studies and demonstrated a 23% increased risk for overall gastrointestinal cancer in periodontitis patients, compared with normal patients (hazard ratio, 1.23; 95% confidence interval, 1.10-1.37). Also, the authors found 59% increased mortality from gastrointestinal cancer in patients with periodontitis compared with healthy patients (hazard ratio, 1.59; 95% confidence interval, 1.16-2.16).

Regarding gastric cancer, in a meta-analysis, Zhang et al found a 12% increased risk of gastric cancer (hazard ratio, 1.12; 95% confidence interval, 0.88-1.42) and a 28% increased mortality rate for gastric cancer in patients with periodontitis compared with normal patients (hazard ratio, 1.28; 95% confidence interval, 0.71-3.37). Another meta-analysis showed that patients with lost teeth, a marker for severe periodontitis, have increased risk for gastric cancer. Unfortunately, lost teeth are not a unique marker for periodontitis; thus, these specific data must be taken carefully.

Interestingly, Salazar et al demonstrated that plaque colonization by periodontal pathogens (ie, P. gingivalis, T. forsythia, T. denticola, and A. actinomycetemcomitans) was associated with increased risk of precancerous lesions of gastric cancer, thereby suggesting that periodontal pathogens may have a role in gastric cancer. However, most patients included in this study were Hispanic (45.4%), female (63.0%), and had a mean age of 57 years, with high prevalence of smoking, and so the results may be more relevant to this demographic.

Regarding pancreatic cancer, a prospective study with more than 700 patients reported that the presence of P. gingivalis and A. actinomycetemcomitans in the oral cavity was associated with a 60% increased risk of pancreatic cancer (adjusted odds ratio, 1.60; 95% confidence interval, 1.15-2.22). The study reported that patients positive for the presence of P. gingivalis in the oral cavity have a 59% greater risk of developing pancreatic cancer than those who were negative for the pathogen. Even after excluding pancreatic cancer cases that occurred less than 2 years after oral samples were obtained, no significant changes were found in the risk factor, demonstrating that it is very unlikely that the oral dysbiosis occurred after or concurrently with pancreatic cancer. Similarly, a prospective cohort study found that patients with higher levels of P. gingivalis antibodies in the blood (>200 ng/mL) had a twofold greater risk of developing pancreatic cancer than those with lower levels of the same antibody. Zhang et al found a 25% increased risk on having pancreatic cancer (hazard ratio, 1.25; 95% confidence interval, 0.84-1.85) and a remarkable 120% increased mortality rate for pancreatic cancer in patients with periodontitis compared with those without periodontitis (hazard ratio, 2.20; 95% confidence interval, 1.44-3.37).

Regarding colon cancer, a prospective study with 17,904 women and 24,582 men found increased risks for colon precursor lesions—that is, serrated polyps and conventional adenomas, with hazard ratios of 1.17 (95% confidence interval, 1.06-1.29) and 1.11 (95% confidence interval, 1.02-1.19), respectively—in patients with chronic periodontitis compared with healthy patients. Losing teeth (four or more teeth) increased the risk for colon cancer by 20% for those with serrated polyps (odds ratio, 1.20; 95% confidence interval, 1.15-1.22) and 11% for those without serrated polyps (odds ratio, 1.11; 95% confidence interval, 1.06-1.16).

TABLE 2 Gastrointestinal cancer estimated new cases and deaths in the United States and worldwide

| Gastrointestinal cancer classification | Estimated new cases | Estimated deaths |
|---------------------------------------|---------------------|------------------|
|                                       | 2020 United States | 2018 worldwide  | 2020 United States | 2018 worldwide |
| Esophagus                             | 18 440              | 572 034          | 16 170             | 508 585        |
| Stomach                               | 27 600              | 1 033 701        | 11 010             | 782 685        |
| Colon                                 | 104 610             | 1 096 601        | 53 200             | 551 269        |
| Other intestines                      | 11 110              | —                | 1 700              | —              |
| Rectum                                | 43 340              | 704 376          | —                  | 310 394        |
| Anus                                  | 8 590               | 48 541           | 1 350              | 19 129         |
| Liver                                 | 42 810              | 841 080          | 30 160             | 781 631        |
| Gallbladder and other biliary ducts   | 11 980              | 219 420          | 4090               | 165 087        |
| Pancreas                              | 57 600              | 458 918          | 47 050             | 432 242        |
| Other organs                          | 7 600               | —                | 3 060              | —              |
interval, 1.03-1.39). In contrast, in a meta-analysis, Zhang et al. found no significant difference for risk of colon cancer but found a 66% increased mortality rate for colon cancer in patients with periodontitis compared with those without periodontitis (hazard ratio, 1.66; 95% confidence interval, 0.44-6.27).

Accumulating evidence demonstrates that microbes have a more potent role in gastrointestinal carcinogenesis than previously thought. In particular, various members of the oral microbiota have been linked to cancers of the gastrointestinal tract.

### 2.2.1 | Gastrointestinal microbiome

**Gastric microbiome**

Despite being considered sterile for many years due to the low pH of the gastric lumen, it is now known that the stomach possesses a very specific microbiome. This gastric microbiome is mainly composed of *Streptococcus*, *Veillonella*, *Prevotella*, *Fusobacterium*, and *Rothia* genera, and more than 65% of these species have been previously described as oral commensal bacteria. Colonization by *Helicobacter pylori* leads to dramatic changes in the gastric microbiome, including a higher abundance of Proteobacteria, Spirochaetes, and Acidobacteria and a decreased abundance of Actinobacteria, Bacteroidetes, and Firmicutes. *H. pylori* infection can cause chronic gastritis, peptic ulcer, atrophic gastritis, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma. Still, the interaction between the bacterium and gastric microbiota in the pathogenesis of these conditions has to be fully elucidated.

Regarding the contribution of oral pathogens to gastric cancer, very little has been studied so far. Yuan et al. reported very low levels of *P. gingivalis* in stomach samples; the authors tested the survival rates of the bacteria in acidic buffers and concluded that the bacteria cannot survive in highly acidic environments, such as the stomach. On the other hand, *F. nucleatum* was recently detected in higher abundance in gastric cancer tissues than in normal tissue. Recently, Boehm et al. demonstrated that *F. nucleatum* is associated with lower long interspersed nuclear element-1 DNA methylation in gastric cancer tissues. Thus, more studies are needed to establish whether oral bacteria have tumorigenic effects in the context of gastric cancer. Recently, Nieminen et al. found the presence of the *T. denticola* dentilisin protease in all gastric cancer tissues tested, indicating that the bacterium may have an important role in gastric cancer. However, more studies are still needed to determine the contribution of all these oral bacteria to gastrointestinal carcinogenesis.

**Intestinal microbiome**

The human intestinal microbiome comprises about 10^{13} microbial species, including bacteria, viruses, fungi, and other members, which play a significant role in normal human physiology, by contributing to metabolism and digestion, gut homeostasis, and tissue development. In this chapter, we will focus on the large intestine microbiome and its association with colon cancer.

Among all species found in the large intestine, *F. nucleatum* seems to be increasingly reported in gut infections, such as intestinal abscesses and acute appendicitis. Castellarin et al. was one of the first groups to point out that *F. nucleatum* infection is prevalent in colorectal cancer. Subsequently, metagenomic and transcriptomic studies have demonstrated an enrichment in Fusobacteria species, specifically *F. nucleatum* in colorectal cancer, compared with adjacent normal tissues. Further, *F. nucleatum* accelerates colorectal cancer cell growth and progression in vitro and in vivo. The bacterium also seems to suppress anti-tumor immunity by inhibiting immune natural killer cells. All these findings support that *F. nucleatum* can colonize and is enriched in colorectal cancer, and it may also play a major role in tumor growth and survival. Similar to the mechanism proposed by Kamarajan et al. for oral squamous cell carcinoma, Sun et al. demonstrated that *F. nucleatum* induces colorectal cancer proliferation through toll-like receptor 4 and myeloid differentiation primary response 88 protein activation and upregulation of micro-ribonucleic acids 18a and 4802.

On the other hand, Abed et al. questioned the ability of *F. nucleatum* to reach the colon from the oral cavity; thus, the authors hypothesized that a bacteremia may be responsible for the presence of the bacterium in the colon and rectum. In brief, transient bacteremia is a common finding during periodontal disease, in which periodontal pathogens are able to reach the circulatory system via
the periodontitis-infected sites. It has been reported that bacterial loads reach up to $10^6$ bacteria per milliliter of blood. Within the circulatory system, these bacteria would have access to other tissues, wherein they could colonize and infect. To test this hypothesis, Abed and colleagues intravenously injected mice with *F. nucleatum* and found significantly higher counts of the bacteria on colorectal tumors than in adjacent normal sites. The authors found that a fusobacterial fatty acid–binding protein mediates *F. nucleatum* binding to tumor cells by binding $\alpha$-galactose-beta(1-3)-N-acetyl-$\beta$-galactosamine, a polysaccharide overexpressed in colorectal cancer, whereas fatty acid–binding protein 2–deficient bacteria show reduced $\alpha$-galactose-beta(1-3)-N-acetyl-$\beta$-galactosamine binding. Although this finding is very interesting from the standpoint of demonstrating bacteremia in gastrointestinal cancer, one must also consider the possibility of cancer-enhanced permeability and retention effects. The enhanced permeability and retention effect, first reported by Matsumura and Maeda in 1986, indicates that there is a greater accumulation and prolonged circulation of macromolecules in cancer tissues than in normal tissues due to the enhanced permeability of blood vessels inside the cancer tissues. Although this effect has been demonstrated for macromolecules and nanoparticles, Fang et al demonstrated that bacteria can be taken up by tumors through the enhanced permeability and retention effect, and the effect can be enhanced with the use of nitroglycerin, a known vasodilator. Thus, *F. nucleatum* accumulation within cancer tissues can be mediated by active processes of bacterial internalization and/or by an enhanced permeability and retention effect. This hypothesis could be tested by performing the same procedure proposed by Abed et al but comparing the amount of heat-treated vs live bacteria found in tumor tissues. The enhanced permeability and retention effect hypothesis would be rejected if significantly fewer heat-treated bacteria are found in tumors sites compared with live bacteria.

Recently, Nieminen et al found the presence of *T. denticola* dentilisin in half of the colon cancer tissues tested, indicating that the bacterium may play a role in colon cancer. However, more tests are necessary to determine its contribution.

### 2.3 Lung cancer

Lung cancer is the leading cause of new cancer cases annually and annual cancer deaths worldwide, leading to more than 2.09 million new cases and more than 1.7 million deaths in 2018. Lung cancer is expected to cause almost 230,000 new cancer cases and more than 135,000 deaths in 2020 in the United States.

Associations between periodontal disease and lung cancer have been suggested in the literature. In 2003, Hjøiøl et al demonstrated that general lung cancer presented the strongest correlation with periodontal disease, among the most fatal cancers; the study found a 1.97-fold increase risk for lung cancer in patients with periodontitis. In 2016, a meta-analysis of five different cohort studies, evaluating more than 320,000 patients, demonstrated that individuals with periodontal disease had a 1.24-fold increased rate of general lung cancer. Also, the study pointed out that women with periodontitis have higher risks of developing lung cancer than men do.

Interestingly, Yan et al were the first study to demonstrate that salivary bacteria (ie, *Capnocytophaga*, *Selenomonas*, *Veillonella*, and *Neisseria* genera) were significantly altered in patients with both squamous cell and adenocarcinoma lung cancer compared with control patients. The authors even validated this *Capnocytophaga* and *Veillonella* genera alteration as a potential biomarker for lung cancer. Similarly, Zhang et al also found an increased abundance in *Veillonella* and *Streptococcus* genera in non–small cell lung cancer patients, compared with healthy patients. Additionally, the authors also found *Fusobacterium*, *Prevotella*, *Bacteroides*, and *Faelcalibacterium* genera decreased in non–small cell lung cancer patients, compared with healthy patients.

#### 2.3.1 Lung microbiome

Although the lungs were also regarded as sterile for a long time, several recent studies demonstrated the presence of a lung microbiome. This microbiome seems to be comprised of *Acinetobacter*, *Pseudomonas*, *Ralstonia*, *Prevotella*, *Veillonella*, and *Streptococcus* genera. Microbial species from the oral cavity are thought to migrate from the oral cavities to the lungs via microaspiration, as they are more similar to oropharynx microbiota than nasopharynx microbiota. There is also a fine balance between microaspirated species and microbial elimination via mucociliary clearance, cough, or host immune defense processes. Despite the similarities and a direct impact by the oral microbiome, the lung microbiome has been characterized as a distinct microbiome, with a higher abundance of *Thermi* and Cyanobacteria phyla than in other human microbiomes. Nevertheless, a precise description of the lung microbiome and the influence of the oral microbiome on the lung microbiome is still lacking as the field is just emerging.

Similar to the oral microbiome, lung microbiome dysbiosis seems to be correlated with the emergence of respiratory diseases, such as severe asthma and lung cancer. There is emerging evidence that the lung microbiome seems to play an important role in lung cancer progression. For example, patients with unspecified lung cancer have lower microbial diversity than nonmalignant controls do, with *Thermus* and *Legionella* genera being more abundant in advanced and metastatic lung tissues. Also, a cohort study with 64 patients evaluated differences in the lung microbiome of smokers vs nonsmokers. They found a relatively lower abundance of Bacteroidetes and Proteobacteria phyla in smokers than in nonsmokers, with no significant changes, suggesting that smoking may have a more pronounced effect on the microbiota of the head and neck area than on that of the lower respiratory tract. Nevertheless, data on the impact and mechanisms of the lung microbiome on lung cancer pathogenesis remain limited.

Despite advances in the field, some studies used either sputum or bronchoalveolar fluid collection during bronchoscopy, risking a potential contamination of the samples with oral bacteria, since
collection instruments pass through the naso or oropharynx first before reaching the lungs.\textsuperscript{188,189,193} Thus, avoiding the use of these collection methods is essential to effectively evaluate the lung microbiome.

### 2.4 Other cancer types

Periodontal disease has been recently associated with other cancer types, such as prostate, breast, and uterine cancer. However, more studies are still needed to determine whether this association is true, and, if so, to determine the possible underlying mechanisms.

#### 2.4.1 Prostate cancer

Periodontal disease has been associated with prostate cancer.\textsuperscript{20,194-196} For instance, Hujoel et al\textsuperscript{20} reported a 1.81-fold increased risk for prostate cancer in patients with periodontal disease, compared with patients without it. This was the highest fold risk from all the cancers studied. Recently, the presence of oral bacterial DNA (ie, \textit{P. intermedia}, \textit{P. gingivalis}, and \textit{T. denticola}) was found in prostatic secretion of patients with periodontitis.\textsuperscript{197} Interestingly, patients with periodontitis and prostate inflammation had greater levels of prostate-specific antigen than those with either disease alone did; and periodontal treatment decreased prostate-specific antigen levels in those patients with both conditions, improving prostate inflammation symptoms.\textsuperscript{198,199} These data support the concept of a bacteremia mechanism whereby oral pathogens would colonize and infect the prostate. This infection would, then, lead to a chronic inflammatory response in the prostate, which, in turn, would induce neoplastic transformations; growing evidence implicates chronic prostate inflammation as one of the main contributors for prostate cancer.\textsuperscript{20,196,200,201} Specifically, Simons et al\textsuperscript{20} provided direct evidence that bacterial-induced prostate inflammation accelerates prostate cancer progression and sheds light on how changes in the prostate microenvironment caused by prostate inflammation may accelerate tumor progression.

#### 2.4.2 Breast cancer

Literature is still inconsistent with regard to associations between periodontitis and breast cancer. For instance, in 2011, a longitudinal prospective study in Sweden with more than 3000 subjects between 30 and 40 years of age reported that chronic periodontitis patients were 2.3 times more likely to be diagnosed with general breast cancer than those with healthy gums were.\textsuperscript{23} However, the conclusions were limited by the fact that the authors did not clinically examine some of the patients for periodontitis, but instead used missing molars as a proxy to distinguish patients with or without periodontitis. Since caries can also lead to tooth loss, periodontitis may have been overestimated in these patients. Similarly, Sfreddo et al\textsuperscript{202} reported that women diagnosed with periodontitis had two to threefold more chances of having invasive ductal breast carcinoma than healthy patients did, even after adjusting for confounding variables. In this study, patients were subjected to full-mouth periodontal examinations to diagnose periodontitis. Recently, a meta-analysis study with more than 1.5 million participants investigated the association between periodontitis and general breast cancer and found a 1.2-fold increased risk for general breast cancer in periodontitis cases compared with controls.\textsuperscript{203} Interestingly, no significant association was found among patients with periodontitis and history of periodontal therapy and general breast cancer. If this association is accurate, this report suggests that periodontitis therapy can decrease the higher risk of having general breast cancer. In contrast, Mai and coworkers\textsuperscript{204,205} evaluated 1337 postmenopausal women and found no significant association between the incidence of invasive general breast cancer and either alveolar bone loss or presence of periodontal pathogens. Hujoel et al\textsuperscript{20} also reported no significant association between periodontitis and higher risk of general breast cancer (hazard ratio, 1.32; 95\% confidence interval, 0.74-2.28). Thus, more studies are needed to determine whether the association between periodontitis and breast cancer is true and, if so, to determine the possible underlying mechanism.

Although the association between periodontitis and breast cancer is unclear, Parhi et al\textsuperscript{206} recently tested whether an \textit{F. nucleatum} bacteremia could lead to tumorigenesis and increase the aggressiveness of triple-negative breast cancer in mice. The authors observed a 100-fold increase in abundance in bacteria 24 h after the intravenous injection of the bacterium within triple-negative breast cell line (AT3) tissues compared with normal tissues. They reported that \textit{F. nucleatum} colonizes the triple-negative breast tumor tissue, accelerates tumor growth and progression, and inhibits tumor immune-modulator cells, such as T, B, and natural killer cells, thus indicating that \textit{F. nucleatum}, via a bacteremia, can reach the breast tumor tissue and induce tumor growth and progression. However, an enhanced permeability and retention effect is also possible, and it is not known whether this bacterial accumulation is driven by the bacterium itself or by an enhanced permeability and retention effect.

#### 2.4.3 Uterine cancers

Few studies have examined the correlation between periodontitis and uterine cancer. In a study by Arora et al\textsuperscript{207} that examined twins (to control for confounding factors), periodontitis was positively associated with increased risk of uterine corpus cancer (hazard ratio, 2.20). Interestingly, Han et al\textsuperscript{208} demonstrated that intravenous tail vein injection with \textit{F. nucleatum} led to uterine bacterial colonization, proliferation, and intrauterine infection. Nevertheless, this result may be due to the tail vein draining more to the uterus than other tissues, thus resulting in higher uterine colonization of the bacterium than in other tissues. In his context, gingival inoculation may be more suitable to replicate periodontal bacteremia and evaluate whether uterine colonization by periodontal pathogens is, indeed, possible.
Interestingly, though, recent reports have detected periodontal pathogens on placental tissue associated with multiple adverse pregnancy outcomes,208-212 and preliminary data from our group using an in vivo polymicrobial periodontal disease model described by Gao et al213 show higher counts of periodontal pathogens in the mouse uterus than in control mice. These data indicate that uterine colonization by periodontal pathogens is, indeed, possible. However, further studies are still necessary to better understand how periodontitis may be associated with uterine cancer and whether *F. nucleatum* intrauterine infection can lead to uterine cancer.

### 3 | POTENTIAL THERAPEUTICS FOR ORAL DYSBIOSIS-RELATED CANCERS

#### 3.1 | Antimicrobial peptides

Antimicrobial peptides are peptides composed of 12-100 amino acids with a cationic net charge and amphiphilic characteristics. These peptides are produced by most organisms (from bacteria to humans) as primary defense molecules that target a broad spectrum of pathogens.214,215 In this sense, antimicrobial peptides s can be used as antimicrobials to treat dysbiotic microbiomes, thus possibly preventing the formation of dysbiosis-related cancers. For instance, Shin et al216 demonstrated that nisin, an antimicrobial peptide produced by the bacteria *Lactococcus lactis*, can effectively inhibit and kill periodontal disease pathogens, including *T. denticola*, *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans*, and *P. intermedia*, without affecting normal human oral cells, such as primary periodontal ligament, gingival fibroblasts, and oral keratinocyte cells. Similarly, Radaic et al19 recently demonstrated that nisin is able to revert the diversity levels of in vitro human saliva–based dysbiotic oral biofilms back to control levels, promoting healthier oral biofilms.

Although their main role is in defending against pathogens, several antimicrobial peptides have been reported to selectively target human tumor cells.215 As far as we know, our group was the first to highlight the potential of antimicrobial peptides in cancer treatment in vivo.217 To date, we have demonstrated that nisin inhibits pathogen-induced oral squamous cell carcinoma migration, invasion, tumorsphere formation, and angiogenic sprouting, and it promotes oral squamous cell carcinoma apoptosis in vitro while reducing overall tumor size and prolonging survival in vivo.71,217-219 Importantly, nisin had no cytotoxic effects on normal human oral keratinocytes, periodontal ligament cells, gingival fibroblasts, and osteoblasts.216,218 Magainin 2, an antimicrobial peptide isolated from the African frog *Xenopus laevis*, has antitumor activity against a human lung cancer cell line,220 cytotoxic and antiproliferative effects on bladder cancer cells, and has no effect on normal human fibroblasts.221 LL-37, an antimicrobial peptide produced in humans, promotes caspase-independent calpain-mediated apoptosis in an acute T cell leukemia cell line and mediates mitochondrial depolarization and caspase-independent apoptosis in an oral squamous cell carcinoma cell line.222 However, LL-37 had no effect on a human keratinocyte cancer cell line, indicating possible tissue-specific effects.223 Interestingly, LL-37 is a highly expressed antimicrobial peptide in normal mucosa, especially in lung, breast, and colon tissues.215 However, LL-37 was downregulated in colon cancer tissues due to DNA methylation of the cathelicidin antimicrobial peptide gene promoter, which facilitates colon cancer growth.224 This suggests a possible role for LL-37 in colon tumorigenesis and cancer progression.

These studies illustrate the ability of antimicrobial peptide to specifically bind to and affect tumors, but not normal tissue. This is thought to be related to antimicrobial peptide binding to phosphatidylserine lipids on the outer membranes of tumor cells, which are often not present on normal cells. Briefly, normal cell membranes exhibit an asymmetry in the lipids forming their outer and inner layers; neutral lipids, such as phosphatidylcholines and sphingomyelins, are primarily located in the outer leaflet of the membrane bilayer, whereas most phosphatidylserine molecules are located in the inner leaflet of the membrane.215,225 Then, due to the effect of inflammatory cytokines, oxidative stress, and acidity, tumors lose this membrane asymmetry, thus displaying most of their phosphatidylserine molecules on the outer layer of the cell membrane.215,226,227 Other proposed mechanisms include decreased levels of cholesterol in cancer cells that facilitate antimicrobial peptide binding and cancer cell apoptosis228; electrostatic attraction between other negatively charged components of cancer cells and antimicrobial peptides, facilitating binding and selective disruption of cell membrane229,230; and the ability of antimicrobial peptide to selectively interact with ion channels.217,221 However, all these mechanisms may occur concurrently, contributing more to a set of mechanisms constituting the action of antimicrobial peptides on tumors.

Use of nano-sized drug delivery systems is a potential strategy to improve the delivery of drugs, peptides, and genes into host cells.214,222-234 These systems are able to increase their load potency, area under the curve, and peak serum concentration, decrease the time to reach the maximum serum concentration, and reduce load toxicity and food interactions.214,222 Recently, our group delineated the state of the art for nano-sized drug delivery systems of antimicrobial peptide delivery, focusing specifically on bacteriocins, and we found throughout the literature that associations of antimicrobial peptides with nano-sized drug delivery systems seem to be beneficial, since the delivery systems were able to significantly increase microbial inhibition compared with free bacteriocin.214 Similar effects were found by Goudarzi et al235 for nisin and Niemirowicz et al236 for LL-37. The previous studies demonstrate the increased efficacy of nisin on gastrointestinal, hepatic, and leukemia cancer cell lines after loading the bacteriocin in polyactic acid-polyethylene glycol-polyactic acid nanoparticles; the latter demonstrate that immobilization of LL-37 on the surface of magnetic nanoparticles significantly increases antitumor activity of LL-37 against colorectal adenocarcinoma cell lines (DLD-1 and HT-29) compared with free antimicrobial peptide. These examples illustrate the potential use for antimicrobial peptide–loaded nano-sized drug delivery systems.
to enhance antimicrobial peptide capabilities for cancer treatment. However, very little has been tested in the field.

Although activity is found for antimicrobial peptides in cancer, the particular mechanisms by which these molecules mediate their actions are still poorly understood. For more details on antimicrobial peptides and cancer, please refer to Tornesello et al. 215

### 3.2 | Probiotics

The term "probiotic" was first coined by Lilly and Stillwell 237 in 1965 to distinguish it from the term "antibiotics" and thus define substances produced by protozoa that were able to support the growth of other microorganisms. In 1998, the term was refined by Guarner and Schaarfsma 238 as live cultures of microorganisms, which confer a health benefit to the host when administered in adequate amounts. Since then, these definitions have been adopted by the World Health Organization to define probiotics. 239,240

Probiotics have gained attention owing to their ability to modulate cancer proliferation and apoptosis in vitro and in vivo, turning them into potential chemotherapeutic alternatives. 240,241 For instance, Thirabunyanon and Hongwittayakorn 242 showed that into potential chemotherapeutic alternatives. For instance, Thirabunyanon and Hongwittayakorn 242 showed that *Pedriococcus pentosaceus* FP3, *Lactobacillus salivarius* FP25, *Lactobacillus salivar *ius* FP35, and *Enterococcus faecium* FP51 promote antiproliferative effects and induction of apoptosis in a colon cancer cell line (Caco-2) in vitro. The mechanism by which these bacteria promote their anticancer effect may be due to short-chain fatty acid production, mainly butyric and propionic acids. Appleyard et al 243 demonstrated that pretreating rats for 1 week with VSL#3, a commercial highly concentrated probiotic preparation containing eight live freeze-dried bacterial species normally found in the human gastrointestinal microbiome, including strains of *Lactobacillus*, *Bifidobacterium*, and *S. salivarius* subsp *thermophilus*. 244 prevented the development of colitis-associated colon dysplasia.

Recently, our group reported that a nisin-producing *L. lactis* probiotic can modulate in vitro human-based dysbiotic oral biofilms toward health. 19 Specifically, we demonstrated that *L. lactis* can modulate cancer-related bacteria (ie, *F. nucleatum* and *T. forsythia*) levels back to control levels, thus promoting a healthier oral biofilm. In this context, a nisin-producing *L. lactis* probiotic has the potential to prevent several types of cancer, as described in this review, by specifically inhibiting these cancer-related pathogens.

Interestingly, nano-sized drug delivery systems were used to successfully deliver probiotics into cancer cells. Zheng et al 245 encapsulated *Clostridium butyricum* spores into chemically modified dextran and administrated nano-sized drug delivery system to mice. Interestingly, the spore-loaded nano-sized drug delivery system was specifically found enriched in colon tumor sites after oral administration. Inside the tumors, *C. Butyricum* cells were reconstituted and they fermented the dextran encapsulation, producing short-chain fatty acid in the process and reducing tumors up to 89%. The nano-sized drug delivery system was also able to increase gut microbiome richness, by increasing the abundance of short-chain fatty acid-producing bacteria.

Although probiotics show promise in preventing and treating cancer, their mechanism of action is still largely unknown. Part of their mechanism of action is thought to be an ability to modulate pathogenic bacteria, the local pH, harmful enzymes, proinflammatory cytokine levels, production of short-chain fatty acid, and degradation of potential carcinogens. 241 For more details on how probiotics are a promising tool for the prevention and treatment of cancer and other diseases, please refer to Nguyen et al, 240 Shin et al, 249 and Górska et al 241; for more details specifically about probiotics in gastrointestinal cancer, please refer to Javanmard et al. 246

### 3.3 | Epigenetic drugs

The fact that epigenetic mechanisms are reversible makes them attractive targets for new treatment models in both cancer and inflammatory diseases, garnering significant research interest. 247-249 The term "epidrugs" was coined by Ivanov et al 250 and used to describe drugs that inhibit or modulate disease-associated epigenetic proteins, thereby ameliorating, curing, or preventing the disease. The discovery of specific bromodomain and extraterminal motif protein inhibitors acting as acetylated histone mimetics (ie, I-BET151, and (+)-JQ-1) 251 has not only allowed for therapeutic targeting of bromodomain and extraterminal motif proteins in cancer, but also provided insight into contributions of bromodomain-containing proteins in the pathogenesis of inflammatory disorders that are associated with an altered epigenetic landscape. 252 Bromodomain and extraterminal motif protein inhibitors suppress lipopolysaccharide and cytokine-induced expression of inflammatory cytokines and chemokines in monocytes and macrophages in vitro and in vivo, and they protect mice from lethal endotoxic shock and sepsis. 253,254 Inhibition of bromodomain and extraterminal motif proteins also ameliorates inflammation and resulting pathology in animal models of several inflammatory diseases, including rheumatoid arthritis, graft-vs-host disease, and multiple sclerosis. 254-256 There are two studies to date that demonstrate that the bromodomain and extraterminal motif protein inhibitor (+)-JQ-1 ameliorates gingival inflammation and alveolar bone destruction in *P. gingivalis*-induced experimental periodontitis in mice. 247,249 In this model, the therapeutic effects of bromodomain and extraterminal motif protein inhibition were attributed to diminished inflammatory cytokine production by macrophages and reduced osteoclast formation. However, despite extensive efforts toward understanding bromodomain protein function in health and disease, little is still known about the role of bromodomain and extraterminal motif proteins in the pathogenesis of periodontitis. Thus, there is a need to investigate to what extent xenobiotic exposure can influence epigenetic signatures in the human body, and how epigenetic variability in disease-related genes can be translated into individual differences in drug pharmacokinetics, toxicity, and responsivity.
Epigenetic modifications within periodontal tissues that are influenced by dysbiotic biofilms and the effects of environmental exposures lead to an infectious-inflammatory condition and trans-generational changes in the genome stability that drive disease progression and a favorable landscape for cancer development. Therefore, epigenomic approaches will enable a better understanding of the epigenetic mechanisms regulating the dynamics of complex diseases. The next challenge will be to perform integrated basic and clinical studies in order to comprehensively explore epigenetic regulatory pathways as markers of disease and potential therapeutic targets.

Lastly, targeting super-enhancer regions could be a useful strategy to return whole sets of disease-related genes back to normal physiologic levels. Epigenetic modifications associated with the regulation of human immunodeficiency virus-1 latency may also be interesting targets that hold promise for the discovery of novel drug targets.

4 | SUMMARY

Oral microbial dysbiosis emerges as a result of an unbalanced oral microbial state that is capable of promoting diseases in the host. This unbalanced state is the most accepted paradigm for explaining the initiation and progression of periodontal disease, and it is thought to be driven by an enrichment of pathogens, including *P. intermedia*, *F. nucleatum*, *P. gingivalis*, *T. forsythia*, and *T. denticola*.

Although findings are still emerging for breast and uterine cancer, periodontitis has been positively associated with an increased risk for specific subtypes of head and neck, gastrointestinal, lung, and prostate cancers. In all these cancers, oral bacteria are present and positively associated with tumor growth and progression.

Finally, antimicrobial peptides, probiotics, and epidrugs show significant promise for cancer treatment, since they have a dual therapeutic potential in treating the tumors and tumor microenvironment directly (antimicrobial peptides, probiotics, epidrugs) and modulating the oral dysbiosis state back to health (antimicrobial peptides and probiotics).

ACKNOWLEDGMENTS

This work was supported by funding from the AAP Sunstar Innovation Grant and NIH R01 DE025225 grant to YLK and from the 2019 IADR/Philips Oral Healthcare Young Investigator Research Grant to AR. All original figures in this article were created with BioRender.com.

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How to cite this article: Radaic A, Ganther S, Kamarajan P, Grandis J, Yom SS, Kapila YL. Paradigm shift in the pathogenesis and treatment of oral cancer and other cancers focused on the oralome and antimicrobial-based therapeutics. Periodontol 2000. 2020;87:76–93. https://doi.org/10.1111/prd.12388