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The Interplay between Oral Microbes and Immune Responses

Dr. Hanan Selman Hessan Al Gebouri
Assistant Professor, College of Dentistry, University of Babylon

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Annotation: Microbes in the oral cavity play significant roles in maintaining an oral balance. However, a balance disorder of the microbial community, termed dysbiosis, also can lead to the development of diseases through various biological processes. Recent advances suggest that an alteration in oral microbiome with chronic inflammation appears to have a pivotal role in the pathogenesis of several diseases. Damaging interactions from host immune responses to microbial antigens could counteract both oral and systemic diseases. In this review, we have discussed the mechanisms by which oral bacteria interface with host systems in the context of localized and systemic inflammatory pathways. Having a further understanding of these mechanisms may suggest new research opportunities, and potentially decipher new therapeutic targets for a biological-based treatment of oral and systemic diseases.

Keywords: Immune response, oral ecology, oral pathologic conditions, general medical conditions, human physiological well-being.

Introduction

Bacteria in the oral cavity are indispensable for maintaining the balance of oral microbiota. But changes in the population of microbes—known as dysbiosis—may lead to the development of disease via a variety of biological mechanisms. New evidence indicates that a dysequilibrium of oral microbiota coupled with chronic inflammation contribute to the development of several diseases. Interactions initiated by the host's immune responses to microbial pathogens are potentially detrimental to both oral and systemic health. In this review,

The human oral cavity is an extremely complex ecological system, endowed with a variety of highly specialized niches. In health, this oral environment harbors a large and diverse community of microorganisms that include bacteria, fungi, viruses and protozoa, functioning together to maintain oral health. These microbial societies, with their intricate connections, are a front line of defence against invasion from harmful pathogens. However, any disturbance in the resilience of this microbial community can drive immune-mediated inflammation that may in turn lead to tissue destruction. This microbial imbalance triggers a vicious An uninterrupted series of oral disorders includes decay of teeth, inflammatory diseases of the gingivae and periodontium, lesions on mucosa like leukoplakia or oral lichen planus, as well as malignant changes in oral cavity. In addition, the repercussions of this disbiotic microbial community-driven perturbation are not only limited to the oral environment, but they have been associated with a number of) chronic systemic conditions, such as cardiovascular diseases (CVD), type 2 diabetes mellitus (T2D), rheumatoid arthritis, inflammatory bowel disease, Alzheimer's disease, and several types of extraoral malignancies (Hajishengallis. 2015; Acharya et al., 2017; Lamont et al., 2018; Genco Sanz, & 2020).

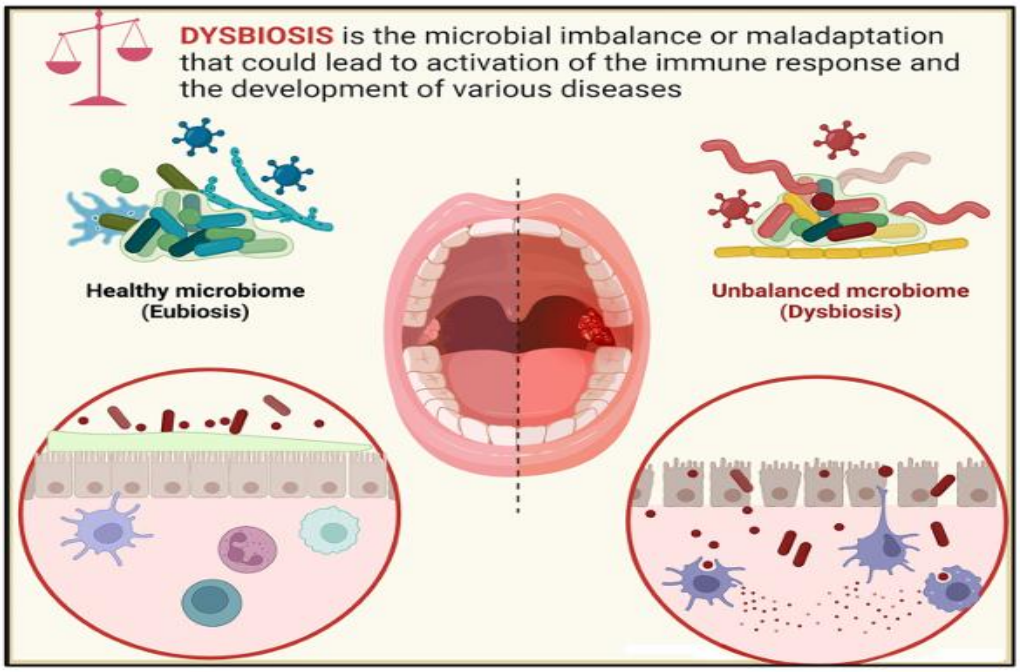

Fig (1): A balanced relationship between host immunity and presence of microbes is key for the maintenance of good health. Disruption of this balance may lead to oral and systemic diseases."

A characteristic feature of the microbial communities in periodontitis is the high biomass and extensive ecological diversity (Hajishengallis. 2014). In addition, host tissue destruction may result from direct biochemistry (eg, the excretion of enzymes and toxins by commensal organisms). Microorganisms trapped in biofilms are potentially able to degrade the collagen

interface between teeth and surrounding bone structures (You et al., 2017; Yousefi et al., 2020), resulting in the formation of infected areas in the oral cavity. In addition to microbial quantity and quality, there is a second mechanism in the development of disease, which includes spreading periodontal bacteria or their products of virulence to the systemic This disseminated blood stream infection is an important factor in the pathogenesis of both local and systemic diseases.

Oral microorganisms can cross the blood-brain barrier and may play a role in the development of distant pathologies (Han & Wang, 2013). For instance, dental microbially induced bacteraemia has been shown to be associated with increased with increased risk of adverse pregnancy outcomes (Saadaoui et al., 2021). Interesting, P.gingivalis has also been found in the cerebral tissue of patients who suffer from Alzheimer's Disease (Dominy et al., 2019). There is a mounting evidence for an active role of oral microbes rather than being bystanders as shared risk factors through multiple immune-mediated mechanisms in the pathways leading to disease. Dysregulated interactions among periodontal microorganisms and the host inflammatory pathways have been demonstrated to mediate initiation and progression of disease through complex biological mechanisms. These microbiotas can also induce local or systemic diseases by promoting the host immune response.

Several pathogenic mechanisms have been suggested to account for these associations. Both host and ectopic colonizers can have a profound impact on immune cells, not only in terms of localization but also in regard to functional profile. For example, the balance between T-helper 17 (Th17) cells and regulatory T cells (Tregs) in inflammatory bowel disease models is influenced by P. gingivalis and Lactobacillus rhamnosus GG through activation of Toll-like receptors TLR4 and TLR2 (Hao et al., 2015). Moreover, both external or local microbial populations can initiate inflammatory signaling or specific immune cell types, driving the onset of diseases. Indeed, oral microbiota have been reported to promote colitis, by inducing inflammasome activation in colonic mononuclear phagocytes and induction of T helper type 17 (Th17) cell migration (Sun et al., 2020).

It should be emphasized that, in periodontal disease, the tissue loss is mainly associated with the host response and not with direct invasion or toxicity of the microorganisms. The immune system acts to defend by preventing microbial invasion of periodontal tissues, although an exaggerated inflammatory response leads to inevitable tissue destruction (Wang K. et al., 2015). The dysbiosis of the oral and local inflammatory responses commonly work together to serve as a self-enhancing vicious circle with one amplifying the other.

Emerging studies also underline the interrelationship between oral and systemic diseases (Zheng et al., 2020). Indeed, periodontitis has been demonstrated to increase serum levels of inflammatory factors including IL-1, IL-6 and acute-phase reactants that can disturb the host metabolic homeostasis and sustain diabetes development (Preshaw et al., 2012). Conversely, systemic infections may induce immune reactions in the bone marrow, such as higher capability of oral pathogen (Yang et al., 2018; Cheng et al., 2021), like neutrophils, monocytes invasion. In addition, systemic factors can free mediators which may additionally perturb oral health. In diabetes, increased IL-17 and the change of oral microbial structure, can lead to an increase in microbial virulence, which promotes oral inflammation (Grassl et al., 2016).

It is still a difficult scientific task to understand the close association between oral microbes and host immune responses. Understanding how oral microbiota interact with or perturb immune reactivity is therefore critical for deciphering how disease states develop. This review is intended to give an overview on how together, oral microbiome and host immune responses both play roles in the development of oral and systemic diseases. Such information is key for the design of preventive interventions and for driving forward new clinical innovations.

The oral cavity is colonised by extrinsic microorganisms, environmental conditions and foreign antigens from birth and a diverse microbial ecosystem develops on the mucosal surfaces of the oral cavity. This early inoculation of the host with microbes is central for sculpting the nascent

immune system of the oral mucosa, and it is involved in the induction of oral immune tolerance by modulating macrophages and ILCs (Abusleme et al., 2013; Kitamoto et al., 2020). These early life events have long lasting implications for later health and disease. Nonetheless, the specific molecular and cellular mechanisms that regulate host–microbiota crosstalk in the oral mucosa during homeostasis are still being elucidated.

In mammals, the oral mucosal tissue is composed of epithelial surfaces and underlying stromal structures, and harbors different immune cells, such as T lymphocytes, neutrophils, innate lymphoid cells (ILCs) and Langerhans cells (LCs) (Jepsen et al., 2018; Kirchner & LeibundGut-Landmann, 2021). Surprisingly, ILCs can be detected pre- and postnatally. T lymphocytes are present within the epithelial lining and the gingival tissues, in humans and animals (Figure 1A). In mice, oral T cells can be further classified into V6, V1 and V4 subsets. The V6 population develops in the oral epithelium in fetal life and expands in a massive fashion after microbial exposure. In contrast, postnatal V1 and V4 populations develop in the gingival tissue (Xiao et al., 2017; Gaffen & Moutsopoulos, 2020).

Within these subsets, V6TCRyd T cells are a major producer of IL-17, an immune modulator that contributes to protection of the oral environment during both infancy and adulthood (Wilharm et al., 2019, Koren et al., 2021). These V6-derived mucosal T helper 17 (T17) cells play a critical role in recruitment of neutrophils into the neonatal oral mucosa in part through IL-17 dependent pathways (Wahaidi et al., 2011).

Neutrophils, similar to T cells, are also resident in oral epithelium prior to birth, and then are expanded, elicited by colonization or IL-17-driven recruitment (Fig. 1B). However, neutrophils are not present in the buccal and gingival epithelia of IL-17 KO but are present in the GF mouse gingiva indicating that neutrophils migration to gingiva is more dependent on IL-17 signaling than presence of the microbes. In contrast, the junctional epithelium of SPF animals contains more cells having the characteristics of neutrophils than does that of GF animals; this difference might be related to TLR2- and TLR4-mediated signaling pathways in health periodontium. TLR2 or TLR4 knock-out mice show a significantly higher presence of neutrophils in the junctional epithelium and marked changes in the oral microbiota (Dutzan et al., 2016; Tordesillas & Berin, 2018).

In humans, we have found ILCs in the oral mucosa of newborn humans (Williams et al., 2021). In murine models, these cells are predominantly found in the oral epithelium basal layers protecting against viral and fungal invaders in uninfected mucosal tissues (Krishnan et al., 2018; Wilharm et al., 2019) (see Figure 1C). DCs as APCs originate from LCs and are present in the stratified squamous epithelia of the skin and oral mucosa. The postnatal mos-IL-12 can recruit these cells with the help of chemokine signals, such as CCL20 and CCL2. Their migration to the mucosa is dependent on presence of microbes, and once residing at this location, LCs contribute to retaining mucosal immune homeostasis and are involved in regulation of tissue damage (Jaitley & Saraswathi, 2012).

In addition to immune cell function, multiple regulatory molecules are needed to maintain stability of the oral epithelium. One of these molecules is the ligand of the TAM family of receptors, Growth Arrest-Specific 6 (GAS6), which is essential for DAMPS-mediated maintenance of innate immune defense in oral tissues (Tsukamoto et al., 2012; Nassar et al., 2017). Colonizing oral microorganisms shortly after birth trigger the up-regulation of GAS6 in gingival epithelium through a MyD88-dependent signaling pathway. The involvement of GAS6 is pivotal for homeostasis of the microbiota; indeed, GAS6-knockout mice display significantly increased gingival inflammation, accompanied by uncontrolled overgrowth of oral bacteria. Addtionally, GAS6 is involved in the immune modulation, as it decreases periodontal inflammation and helps to the balance between Th17 lymphocytes and Tregs. Lack of oral commensal bacteria disturbs immune regulation and causes excessive immune activation and no step down to the inflammation in the oral mucosal milieu.

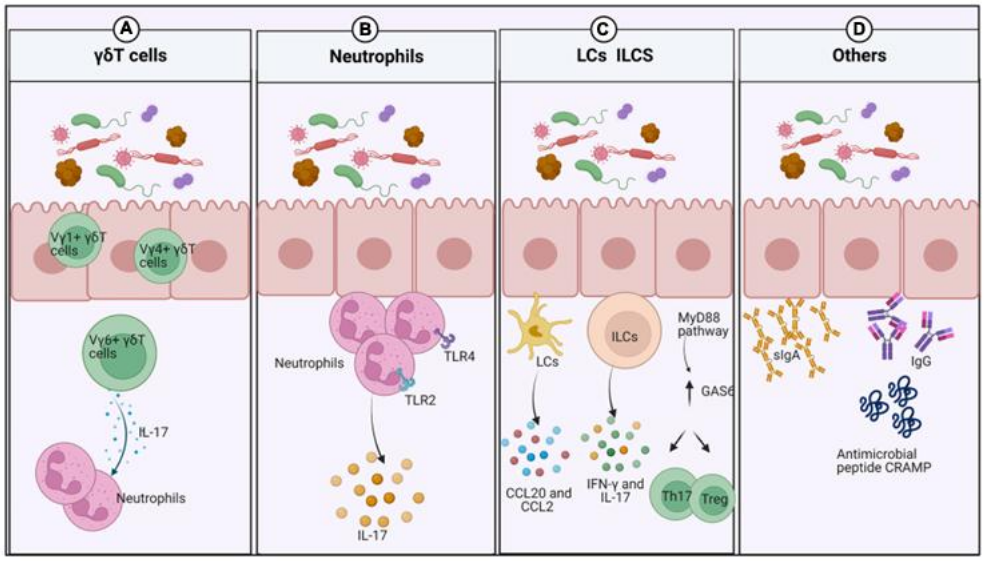

FIGURE 1. Mucosal immune system-physiological coflora interaction in a steady state.

(A) After exposure to extrinsic microbiota, different innate lymphocyte subsets are expanded in the oral mucosa. One of them is represented by γδ T cells that rapidly expand and mediate neutrophil's migration by the release of IL-17.

(B) Neutrophil repertoires expand in the neonatal oral epithelium in response to both IL-17 and local microbial signals, but neutrophil repertoires are maintained in unique tissues like the gingiva through IL-17 signals only.

(C) Oral ILCs produce cytokines, IFN-y, and IL-17 to protect mucosal barriers from fungal and viral insults. The migration of Langerhans cells (LCs) is mediated by chemokines CCL20 and CCL2 towards the mucosa, to maintain mucosal homeostasis and prevent tissue damage as well. Conversely, the gingival epithelial cells also upregulate GAS6 expression when stimulated by bacteria, which permits it to modulate microbial homeostasis and inflammation in gingiva tissues.

(D) Oral microbiotas induce the formation of salivary immune defense factors including sIgA and antimicrobial peptides, which further contribute to mucosal immunity.

In murine neonates, there is a profound oral colonization burden relative to adults. The reduction of oral microbial load is through inducing an elevation of salivary production, this has been shown in mice after the excision Salivary Function and Microbial Impact

Salivary secretion itself, however, is not dependent on colonization as indicated in murine models, especially of the parotid salivary glands. Germ-free (GF) adult mice and specific-pathogen-free (SPF) controls have equivalent rates of salivation (Wahaidi et al., 2011). However, the microbiota has a major impact on the stimulation of salivary antimicrobial factors, including secretory IgA (sIgA), immunoglobulin G (IgG) and antimicrobial peptides, such as CRAMP (Koren et al., 2021; Figure 1D). Of these, sIgA has been identified as playing a role in maintenance of the microbial homeostasis and in preventing dysbiosis in the oral cavity.(Zenobia et al., 2013). The saliva does not only favor bacterial adherence to the oral surfaces, but is also a nutrient-rich medium, which influences the structural dynamics and activity of the oral microbial community (Chang et al., 2019).

Feeding practices have similarly been demonstrated to impact early colonization of oral microbiota in infants. There are different patterns of inoculation between breast- and formula-fed babies. For example, breast-fed babies show higher levels of Gemellaceae, Vogesella Nocardioides Actinobacteria, and Proteobacteria (Duale et al., 2021). On the other hand, Bacteroidetes have a higher prevalence in formula- fed infants (Al-Shehri et al., 2016). Furthermore, immune-modulating elements ID breast milk, for example, cytokines and soluble

receptors have been suggested as factors in oral immune tolerance (Dawod & Marshall, 2019). However, the long-term health consequences of early microbial abundance are unknown, as is the specific role of early oral colonizers in mucosal immune homeostasis.

Recent studies on the oral epithelial–microbial interface in neonatal mice support the concept of distinct host–microbiota interactions during early development potentially shaping the establishment of oral immune homeostasis (Simmerman et al., 2016). Once this fine balance between host and microorganisms is established, however, the system is subject to external and internal stresses that have the potential to end in a failure of oral immune regulation.

The Microbial and Immune Ecosystem in Oral Diseases

Orofacial myofunctional disorders (OMDs) represent a variety of disorders, which primarily involve the oral mucosa and musculature. This spectrum is formed by infectious diseases, pigmentation mucosal abnormalities, ulcerative lesions, and malignant transformation, such as oral squamous cell carcinoma (Lin et al., 2021). The pathogenesis of these disorders may be comprised of various contributing factors, such as immune system dysfunction, bacterial overgrowth, hypersensitivity reactions, hereditary susceptibility, variation in hormone levels, micro traumatism, and psychosocial stressors (Mock et al., 1983; Alrashdan et al., 2016; Vila et al., 2020).

Increasing evidence indicates an association of the oral microbial dysbiosis with the pathogenesis of multiple mucosa diseases (Hu et al., 2019; Yu et al., 2020). Changes in microbial diversity or load can induce immune responses by both innate or adaptive ways and may lead to inflammation-mediated damage (Baek & Choi, 2018; Pellon et al., 2020; Sami et al., 2020). In this section, we discuss the impact of microbial cues on immune regulation in the oral cavity and describe the immune responses that are central to the balance between protection from and progression of oral disease, with specific focus on periodontal disease.

Candida Albicans - Introduction to a warrior fungus Oral-Systemic Immunity and Interactions with Candida Albicans

Oral candidiasis (OC) is a common opportunistic fungal infection generally caused by Candida albicans, which is the most common species of Candida spp. (Akpan & Morgan, 2002; Figure 2A). Oral epithelial cells (OECs) have been considered as the first line of host defense to sense fungal invasion and produce signaling molecules, such as members of the interleukin-1 (IL-1) family and antimicrobial peptides, such as ß-defensins. Following infection, OECs release IL-10, 1ß, as well as IL-36, which activate innate immunity cells, such as IL- 17-producing lymphs (Verma et al., 2018). IL-17 subsequently engages its receptor expressed on OECs to drive downstream expression of antimicrobial effectors like CXC chemokines and granulocyte colony-stimulating factor (G-CSF) to synergistic effect increased mucosal neutrophil recruitment and fungal killing at the mucosal surface (Aggor et al., 2020).

Although it is beneficial to the body, the IL-17/Th17 axis has a two-way nature. Although critical to combating a fungal challenge, a hypertoned IL-17 response may induce host-tissue damage and chronic inflammatory disease such as periodontitis and consequently also alveolar bone loss and in the end periodontal disease (Bunte & Beikler, 2019). The immune response expends other strategies in the defense against fungi. Antibodies and complement proteins attached fungal cell walls to facilitate opsonization and phagocytosis (Wich et al., 2021). In addition, immune cells also secrete hydrolases which help destroy the structural integrity of fungi by degrading their cell wall components (Zhou et al., 2021).

Taken together, host defense against C. albicans is dictated by a sophisticated and precisely balanced immune circuit aimed to maintain mucosal barriers while restraining significant fungal burden.

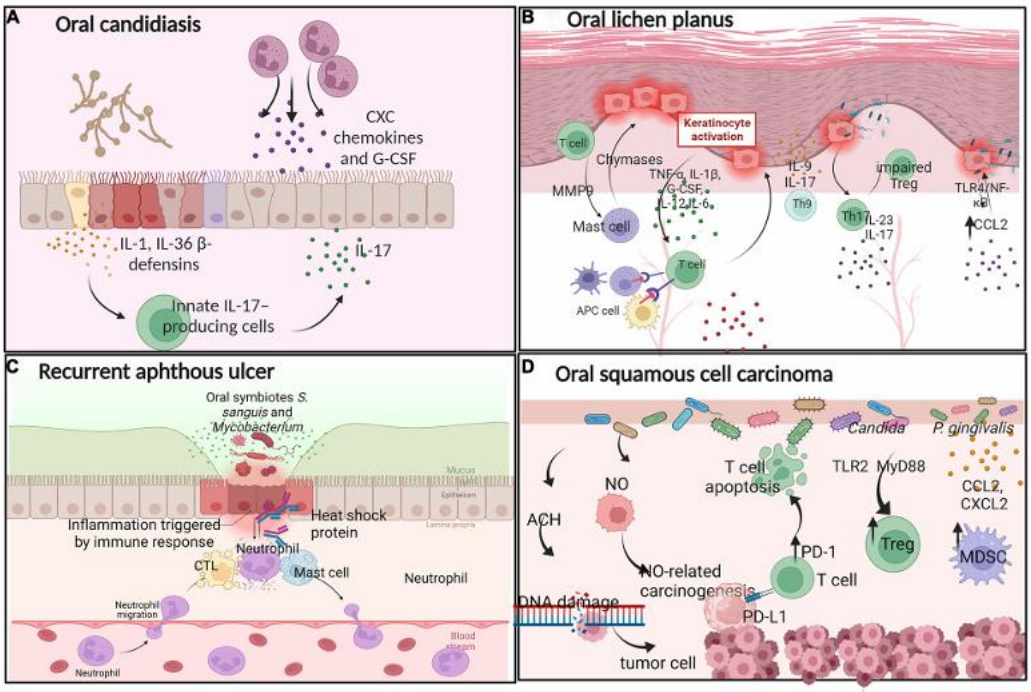

FIGURE 2. Immune-Microbe Responses in Oral Diseases

(A) Oral candidiasis: Candida albicans infectionists induce the production of IL-1, IL-36, and B-defensins, which can stimulate resident and recruited innate immune cells to secrete IL-17. This results in CXC chemokine and G-CSF release with the recruitment of neutrophils and antifungal defense.

(B) OLP: Oral keratinocytes produce several proinflammatory cytokines, which helps in understanding the immunopathological bases of OLP.

(C) RAU: Characterized by immunopathological phenomenon with CTLs, neutrophils, and mast cells.

(D) Oral squamous cell carcinoma (OSCC): Certain oral microorganisms produce ACH and NO, leading to the infiltration of Treg and MDSC into the TME, which may help to promote tumor development.

Recurrent aphthous ulcers (RAU)

RAS [Recurrent aphthous ulcer] is mainly initiated through the activation of cytotoxic T lymphocytes (CTLs) that are stimulated by the infection of microorganisms, inducing damage to the epithelial layer of the mucosa and involving neutrophils and mast cells. After ulcers develop, the compromised oral mucosa is infiltrated with oral microflora, which subsequently enhances focus immune responses. This process over time eventually causes a release of necrotic and fibrinous- laden epithelial debris (Tanacan et al., 2022). In addition, metabolites formed by oral bacteria are known to be harmful to the epithelial structure and tissues, possibly playing a role in the induction of RAU (Hasan et al., 1995). The heat shock 65 kDa protein derived from Streptococcus sanguinis and Mycobacterium tuberculosis is able to cross-react with peptide sequences of OECs to produce autoantibodies against oral tissues and then to develop ulcerative lesions. As such, RAU might originate from a pro/anti-inflammatory cytokine imbalance leading to overactive immune responses toward innocuous oral microbiota and self-antigens. Although some more detailed understanding of RAU is now available, more extensive research is still required.

Oral Squamous Cell Cancer (OSCC)

Oral squamous cell carcinoma (OSCC) is the most common type of oral malignancy, and has

attracted a great deal of oncological interest. There is now a mounting evidence that oral microbial communities are involved in the pathogenesis of OSCC (Figure 2D). Although tobacco use, alcohol consumption, and betel nut chewing continue to be established risk factors, the molecular determinants of malignancy are not well described (Fantozzi et al., 2021). Recent evidence suggests that metabolic changes caused by oral microbes play a role in oncogenesis. For example, some microorganisms produce acetaldehyde (ACH), which is a genotoxic substance that may cause DNA mutations (Yokoyama et al., 2018). Nitric oxide (NO) produced by oral microbial is also involved in carcinogenic pathways (Kakabadze et al., 2020). Immunologic interactions between oral pathogens and the host tissues also affect tumor formation. For instance, Candida species may induce expansion of regulatory T cells (Tregs) through TLR2/MyD88 signaling, leading to mucosal defense defects and augmented fungal burden (Pandiyan et al., 2019). Porphyromonas gingivalis also generates chemokines (CCL2 and CXCL2) enabling MDSCs to infiltrate, which, in turn, promote tumor development (Guo et al., 2021). Moreover, P. gingivalis suppresses T cells through upregulation of PD-L1 expression on which PD-1 receptor binds and triggers T cell apoptosis. This structure promotes cancer cell invasion and chemoresistance. Microbes such as Candida and Fusobacterium nucleatum have similar cancer promoting characteristics. Therefore the oral microbiome regulates tumor cell proliferation and local metastasis. The molecular bases of OSCC will be better delineated as scientific knowledge advances, which will create possibilities for new diagnostics and treatments. Microbial signatures are being investigated as a possible biomarker of oral cancer. Collectively, the involvement of microbial communities in oral cancer includes changes of microbial equilibrium, mucosal colonization and migration, which leads to hyperinflammation, immune suppression, and carcinogenic progression.

Microbiota-Host-Immune Interplay and Systemic Disease

Recent investigations have revealed that local oral infection can lead to secondary pathologic procedures in distant organs by various pathways. Oral bacteria can proliferate in extramucosal transmural sites, where they have been associated with conditions as CVD, respiratory pathologies, IBD, AD, low birth outcomes, and remote neoplasias. This section will elucidate the mechanisms by which periodontal pathogens induce immune cell activation, generating systemic diseases outside the mouth.

Cardiovascular Disease

An increasing number of studies provide evidence that inflammation arising from the oral cavity, mainly from the periodontal region, increases the risk of atherosclerosis and vascular diseases in general (Figure 3 A). Oral environment pathogens might either directly or indirectly provoke vascular harm. The oral epithelial barrier plays an important role in obstructing and preventing bacteria from entering systemic circulation (Xie et al., 2020). P. gingivalis may be translocating through endothelial lining and once there inducing innate immune recognition through TLR/NF-κB pathways. The endothelium activation facilitates monocyte adhesion and perturbs lipid homeostasis, leading to the development of atherogenic plaques. Genetic background also determines the impact of oral infections on immune and lipid responses, reflecting the susceptibility to the development of CMD (Janket et al., 2015). Role of adaptive and innate immune responses in the pathogenesis of periodontal disease and atherosclerosis. For instance during periodontitis, mDCs may infiltrate oral tissues and in atherosclerotic lesions. P. gingivalis promotes mDC maturation with MMP9 release leading to degradation of extracellular matrix, plaque instability and myocardial infarction (Carrion et al., 2012). Furthermore, the gram-negative oral bacteria-derived lipopolysaccharide (LPS) induces proinflammatory events and subsequent formation of cholesterol-laden foam cells in atherosclerotic lesions (Pietiainen et al., 2018). Another route is antibody-induced cross-reactivity whereby Abs against microbial heat-shock proteins or cardiolipin (i.e., anti-ß2 glycoprotein 1 antibodies) also cross-react with host tissues (Choi et al., 2021; Wang C.Y. et al., 2015). In addition, salivary IgA and IgG antibodies specific for oxidized LDL can cross-react with P. gingivalis, suggesting a molecular mimicry in both oral

and vascular inflammation (Akhi et al., 2017). A strong antibody response to both A.

actinomycetemcomitans and P. gingivalis was significantly associated with CV morbidity (Choi et al., 2021). Finally, systemic inflammation, antibody generation and endotoxemia are important mediators through which oral dysbiosis contributes to cardiovascular disease.

Respiratory Infections

Oral bacteria can also spread to the blood stream and even larynx due to aspiration and cause the subsequent respiratory infections. This anatomic pathway is a faster highway to the lungs than to many other organs. There is ample evidence linking oral microbiota with respiratory diseases including pneumonia, chronic obstructive pulmonary disease (COPD), and pulmonary neoplasms. The oral-immune imbalance can lead to the initiation and exacerbation of both oral diseases and respiratory diseases. The same bacteria have been isolated from dental plaque, bronchoalveolar fluid and lung aspirates. In addition, oral hygiene care has been linked to a reduced risk of pneumonia (Pathak et al., 2021). In the COPD lung, the aspiration of the oral flora into the lower airways results in colonization of lower airways by oral and nasopharyngeal pathogens.

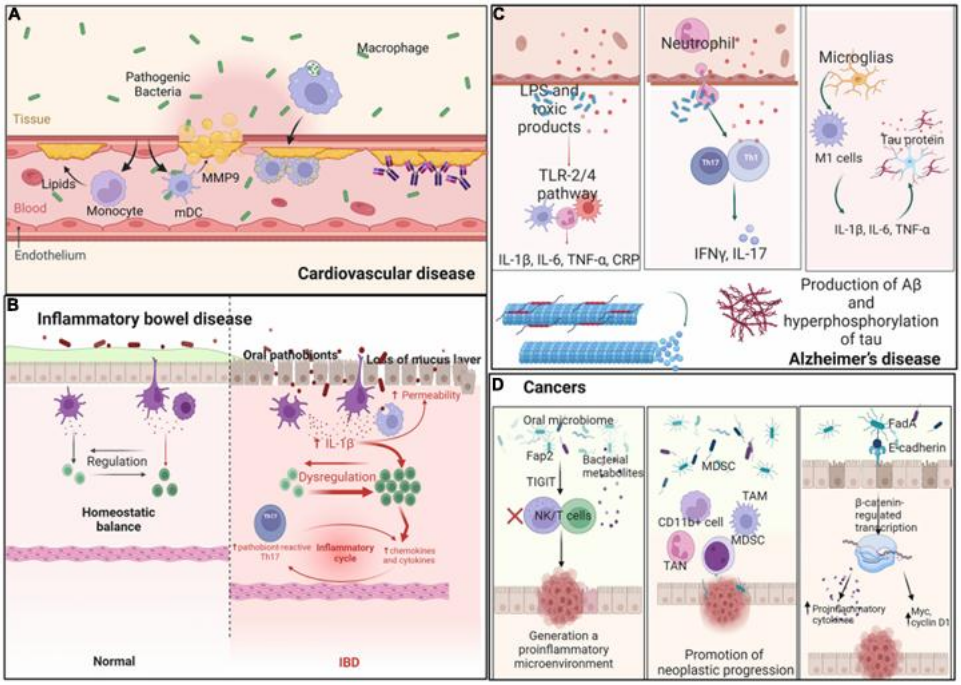

FIGURE 3. Interplay Between Oral Microorganisms and Immune Responses in Remote Organs

Oral pathogens, once displaced from their native environment, can disseminate to distant anatomical sites, where they contribute to the onset of inflammatory disorders.

(A) Cardiovascular Disorders:

Disrupted oral microbial populations facilitate the recruitment of monocytes and myeloid dendritic cells (mDCs), while also promoting the secretion of matrix metalloproteinase-9 (MMP- 9) and lipid molecules. Heat-shock proteins, along with antibodies targeting ß2-glycoprotein I (B2GP1) and oxidized low-density lipoprotein (oxLDL), are implicated in the pathogenesis of myocardial infarction.

(B) Inflammatory Bowel Disease (IBD):

Pathogenic microbes originating in the oral cavity may migrate to the gastrointestinal tract, where they aggravate intestinal inflammation. This is mediated through inflammasome-driven production of interleukin-1β (IL-1β) and the activation of Th17 cells that are reactive to oral-derived microbial antigens, thus intensifying colitis.

(C) Alzheimer's Disease:

Oral microbial invaders stimulate the accumulation of amyloid-ß (Aß) peptides and promote tau protein hyperphosphorylation through engagement of Toll-like receptors TLR-2 and TLR-4. This immune activation results in elevated levels of proinflammatory cytokines such as IL-17 and interferon-gamma (IFN-y), predominantly secreted by T helper cells.

(D) Malignancies:

Certain oral microbes interact with the TIGIT immune checkpoint receptor, leading to a reduction in immune regulatory cells such as myeloid-derived suppressor cells (MDSCs), tumor- associated neutrophils (TANS), and tumor-associated macrophages (TAMs). This immunological disruption fosters oncogenic signaling pathways and sustains a proinflammatory microenvironment conducive to cancer progression.

Aspiration and Pulmonary Complications

Oral secretions entering pulmonary Parenchyma can be seen in aspiration, esp if Oral hygiene is poor. Diseases such as dental caries and periodontitis can disturb the ecological state of the oral cavity, inducing systemic inflammatory reactions responsible for respiratory diseases such as asthma and bronchitis (Mammen et al., 2020). Additionally, respiratory diseases may aggravate oral microbial imbalance and worsen oral diseases, resulting in a vicious cycle of one affecting the other. Further studies are needed to elucidate the bidirectional association of respiratory diseases and the oral microbiome.

IBD (Inflammatory Bowel Disease)

The oral cavity is the initial section of the digestive tube, with its microbial inhabitants playing fundamental functions in the regulation of gastrointestinal homeostasis. Long-term consumption of oral microbes could not only influence gut microbial ecology but also intestinal epithelial permeability, thus possibly contributing to bowel pathology (Hajishengallis, 2015; Figure 3B). Intestinal tissue structural alterations including villous atrophy, basement membrane degeneration and neutrophilic infiltration can also be observed in an experimental model of ligature-induced periodontitis with compromise of the gut barrier (Messora et al., 2013). In some patients with IBD, genetic predispositions could additionally reduce the integrity of in gut mucosa, increasing susceptibility (Merga et al., 2014). Furthermore, we found that treatment with P. gingivalis decreases the expression of major tight junction proteins; occludin. TJP1, supporting observations from ligature- induced models (Nakajima et al., 2015).

In addition to physical injury, the oral flora shapes intestinal immunity. Kitamoto et al. showed that oral pathobionts that accumulated in the gastrointestinal tract in the context of fucosyltransferase deficiency induced IL-1ß secretion through inflammasomes in colonic phagocytes and led to colitis. Furthermore, these microbial strains also promote the priming of Th17 cells in the oral mucosa that home to the inflamed gut. Noteworthy, only the ectopical oral bacteria (not the commensal gut ones) were reported to stimulate these Th17 cells and to cause the induction of inflammation (Kitamoto et al., 2020). Atarashi et al. found that gut-inhabiting oral Klebsiella accelerated Th1 cell expansion in the gut and supplemental administration of IL-18 from TLR4-activated epithelial cells supported this immune boosting. Meanwhile, P. gingivalis was shown to promote the severity of colitis through polarization of the Th17 / Treg ratio through the JAK-STAT pathway and via TCD4 + T cells (Jia et al., 2020). Taken together, these studies suggest that ectopic colonization by oral microbes in the gut may alter the epithelial barrier, immune regulation, and microbial diversity, promoting chronic intestinal inflammation.

Alzheimer’s Disease (AD)

Alzheimer's disease (AD), a neurodegenerative disease, is conventionally characterized by the deposition of amyloid-ß (AB) plaques and hyperphosphorylated tau tangles. A significant evidences is emerging that establishes a link between AD and chronic oral inflammatory diseases,

notably periodontitis (Figure 3C). Dominy et al. found P. gingivalis DNA and gingipains in brain of patients with AD (Dominy et al., 2019). This is in line with theories of oral microbes contributing to AD via multiple modalities. Blood-borne pathogens can cross the blood-brain barrier, releasing LPS and inducing innate immunity through TLR2 and TLR4 signaling (Sansores-España et al., 2021). This leads to upregulation of local pro-inflammatory cytokines such as IL-1ß, IL-6, TNF-α, and CRP, which in turn can induce Aß generation and tau phosphorylation (Singhrao et al., 2015).

In addition, neutrophils, and high IL-17 and IFN-γ were observed in the brain of AD mice, indicating that an immune-related mechanism contributed to neural damage (Sadrameli et al., 2020). Bacterial toxins can also spread through the trigeminal nerve, triggering neuroinflammation by activating microglia. These immune cells can be redirected from an immune regulatory M2 (IL-10 and TGF-β1 secreting) phenotype to a destructive M1 phenotype upon chronic inflammation. The M1 status increases of the production of IL-1β, IL-6, and TNF-α, and the artificial activity of astrocytes with additional potentiation of Aβ generation and tau pathology (Sureda et al., 2020). LPS also induces the production of reactive oxygen and nitrogen species, which drive neuron death and chronic neuroinflammation, two hallmarks of AD pathogenesis.

Number of Adverse Pregnancy Outcomes (APOs)

Several studies have linked gingival inflammation and pregnancy complications. Bacteria migrating to the placenta may coopt with fetal growth and thereby enhanced APOS (Lin et al., 2007; Kaur et al., 2014). Fusobacterium nucleatum is one of the oral species closely associated with these complications and has been found in placentas and fetal tissues. However, other pathogens, such as P. gingivalis, contribute to a high maternal serum level of proinflammatory mediators. These pathogens, their metabolites and the maternal immune response could cause decidual tissue necrosis and fetal damage (Cobb et al., 2017; Liu et al., 2007). Next to more insights into the related microbial species, this knowledge may also result in optimized risk estimation and early diagnosis in pregnant women.

Cancer

The interplay between oral bacteria and host immunity is not restricted to tumorigenesis in the oral cavity. Imbalance (dysbiosis) in the oral microbiome has been associated with tumours in the GI and respiratory tracts. The oral cancer pathogenesis is a consequence of chronic inflammation, aberrant cell cycle and microbial toxin production (Mascitti et al., 2019; Figure 3D). For example, F. nucleatum induces inflammatory chemokines such as CCL20, which create a tumour-permissive microenvironment. Its Fap2 protein interacts with the inhibitory TIGIT receptor to inhibit the NK and T cell activity, and promote the process of CRC (Gur et al., 2015). In addition, F. nucleatum promotes the increase of immunosuppressive cells such as MDSCs, TANs and TAMs (Gholizadeh et al., 2017).

An additional mechanism is by FadA, by adhering to E-cadherin which results in β-catenin activation and upregulation of oncogenes such as Myc, cyclin D1, and also MMPs such as MMP-9 and MMP-13 (Cuellar-Gomez et al., 2021). F. nucleatum also targets the intestinal barrier, which counterac t its colonization (Wu et al., 2019). Increased oral bacteria and their antibodies has been associated with a two-fold increased risk of pancreatic cancer (Li et al., 2020). P. gingivalis can induce the TLR4 pathway in pancreatic tissue, which is overexpressed in pancreatic cancer (Kerr 2015). Elevated salivary counts for oral bacteria and viruses are present in lung cancer subjects. These results indicate microfloral pathways as potential targets for therapeutic intervention. In summary, this data suggest that the systemic effects of oral infections are modulated by immune and microbial interactions with genetics and environment.

Oral Microorganisms and Autoimmunity incidence

There is considerable evidence that oral bacteria may play a role in the development and exacerbation of autoimmune disorders.

Rheumatoid Arthritis (RA):

Figure 4RA is a chronic autoimmune disease which characterized by ACPA generation and bone inflammatory erosion (A). Periodontitis can initiate RA due to the presence of P. gingivalis enzymes like peptidylarginine deiminase that citrullinate host proteins and trigger autoimmunity (Picchianti-Diamanti et al., 2017). In experimental models it was also demonstrated that recruitment of the TLR2 pathway by periodontal pathogens lead to Th17-driven inflammation and that IL-17 influenced osteoclastogenesis stimulating joint erosion (de Aquino et al., 2014). In addition to potentially elevating local cytokine levels further and predisposing obese/prego-RA patients to pathogenic oral microbial overgrowth, systemic RA-related inflammation may also facilitate an environment for worsening periodontitis (Graves et al., 2019).

Systemic Lupus Erythematosus (SLE):

Systemic lupus erythematosus (SLE) is an autoimmune disease that results from autoantibodies against intracellular antigens leading to multi-organ systemic disease. In SLE, patients' diversity of the microorganism is altered in lesions of the periodontium (Aurlene et al., 2020), including an enrichment of anaerobic species such as Prevotella nigrescens, P. oulorum, P. oris, and Selenomonas noxia (Correa et al., 2017). By contrast, facultative anaerobic species like those from the genera Treponema and Selenomonas seem to be implicated less. These balance disorders of microorganisms were likely play an increased role in SLE patients with more severe periodontal disease.

Diabetes Mellitus:

Diabetes The relationship between periodontal disease and diabetes is one of the most significant among the various systemic diseases (Ohtsu et al., 2017; Figure 4B). Advanced glycation end products are high in diabetes patients, causing pro-inflammatory cytokines, such as IL-6 and TNF-a, which are connected to both vascular permeability and inflammatory infiltration. Moreover, hyperglycemia increases oxidative stress via different biochemical pathways, which subsequently results in the activation of MAPK and NF-κB pathways and the release of inflammatory mediators (Huang et al., 2020). High glucose levels also impair immune cell activity, thus providing negative effects over host defense and periodontal support.

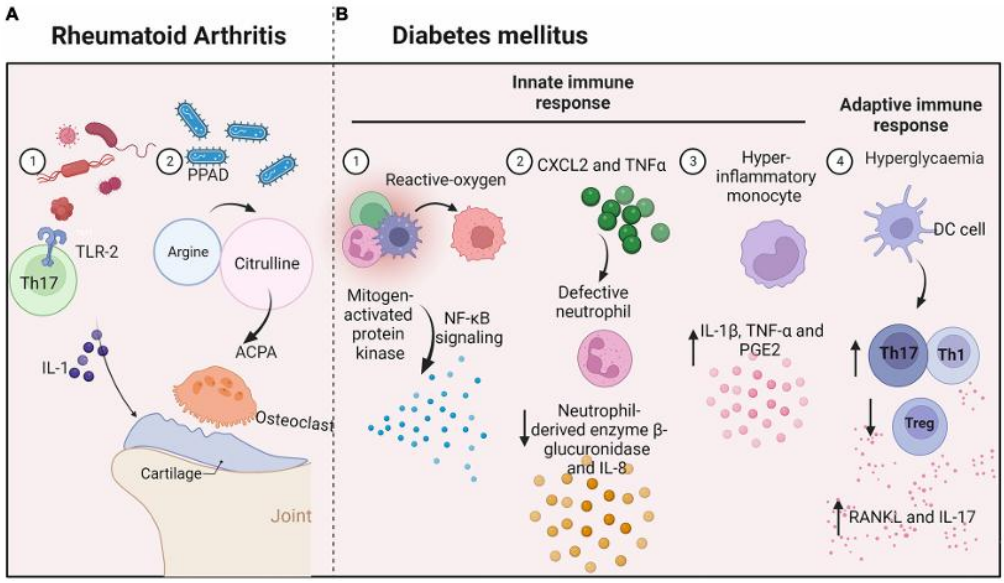

FIGURE 4. The relationship between oral microbiota and immune responses in systemic diseases

(A) Rheumatoid Arthritis:

Pathogenic microorganisms colonizing the periodontal pockets initiate a Th17-type immunological response, mainly modulated by activation of Toll-like receptor 2 (TLR-2) and signaling of interleukin-1 (IL-1). This immunoinflammatory cascade increases the levels of proinflammatory cytokines in the gingival area and enhances the destruction of alveolar bone.

(B) Diabetes Mellitus:

Increased blood glucose concentrations in diabetic patients induce the formation of ROS and depress neutrophil function. Neutrophils from non-functional ones secrete more β-glucuronidase and IL-8. At the same time, monocytes express a pro-inflammatory phenotype with a hyper-responsive state, leading to elevated production of IL-1β, tumor necrosis factor-alpha (TNF-α), and prostaglandin E2 (PGE2). Hyperglycemia also biases T cell differentiation to Th1 and Th17 and inhibits the generation of regulatory T cells (Treg), resulting in an immune imbalance and periodontal destruction.

Neutrophil Dysfunction in Diabetes

In the context of diabetes, neutrophil function is altered leading to lower production of these components including the enzyme ß-glucuronidase and the chemokine IL-8 (Mutua and Gershwin, 2021). Meanwhile, diabetes mellitus also aggravates the activation of neutrophils and increases the production of ROS, which further leads to the damage of periodontal tissue (Zheng et al., 2018). High glucose also enhances NF- KB activity in fibroblasts from the periodontal membranes and induces expression of proinflammatory molecules (e.g., CXCL2 and TNF-α) that can recruit additional neutrophils into the inflamed environment.

Studies have demonstrated that monocytes from patients with type 1 diabetes display a proinflammatory phenotype (Kraakman et al., 2014). Exposure to LPS from periodontal bacteria stimulates these monocytes to generate increased levels of IL-1ß, TNF-a, and PGE2, which may sustain the inflammatory response of neutrophils and macrophages to the bacteria found in dental plaque. Furthermore, diabetes promotes macrophage polarization toward the M1 profile and susceptibility to periodontal destruction.

The adaptive immunity is also involved. Dendritic cell function is also modulated by diabetes, and has the potential to promote a periodontal bone loss through an enhanced Th1 and Th17 populations, or a less Treg cell population present (Graves et al., 2020). Th1 and Th17 cells are important for bone metabolism regulation, and they produce RANKL and IL-17 (the latter at increased levels in patients with diabetic periodontitis). This dysregulation promotes microbial virulence and neutrophilic migration. Remarkably, repression of IL-17 will cause the shift in the composition of the oral microbiota with decreased pathogenicity and will alleviate alveolar bone resorption.

Diabetes also stimulates periodontal ligament, osteoblast, and osteocytes cells to up regulate RANKL expression. In addition, oral infection results in systematic inflammation and might cause insulin resistance in a diabetic mouse model.

Allergic Conditions

Though the causal links between oral microbiota and allergic diseases including asthma, allergic rhinitis or atopic dermatitis have not been definitely identified, oral microbial imbalances are usually related to allergic pathology. For instance, the phylum Proteobacteria is much more abundant in the oral microbiome of atopic dermatitis-affected individuals. Conversely, the relative activity to the peptidoglycan and lysine biosynthesis and to the galactose metabolism is reduced (Li et al., 2019). By contrast, tryptophan metabolic pathway is seemingly enriched in the oral habitat of these patients.

Skin and oral sites show high diversity of microbial structures. Saliva of children with different allergic conditions, such as eczema, food allergy, asthma, and allergic rhinoconjunctivitis, was

found to have more Streptococcus parasanguinis and Gemella hemolysans (Dzidic et al., 2018). Other studies have associated the genera Gemella (including G. sanguinis and G. hemolysans), Streptococcus (including S. mitis/dentisani, S. lactarius, and S. cristatus), and Alloprevotella with development of allergic disease (Matsui et al., 2019).

A decrease in the abundance of commensal oral bacteria and increased salivary IgA levels were demonstrated in a mouse model of food allergy (Ho et al., 2021). Furthermore, peanut allergic individuals also had higher levels of the saliva cytokines IL-4, IL-5 and IL-13 - cytokines that may be associated with the presence of Veillonella species (Mariman et al., 2016).

Future Outlook

This area of research is experiencing a renaissance, as investigators come to appreciate that therapies targeting the oral microbiome as a whole may transcend traditional antibiotics. The modulation of host immune responses is currently one of the most promising ways forward for increasing the effectiveness of treatment and prevention. The intertwining of microbial control with immunity-based therapy suggests that dual action strategy deserves further exploration. Additionally, the starting point immune profiles could be used as predictors of therapeutic response in clinical practice. Ongoing investigation of the relationship between immunomodulation and oral microbiota might offer new perspectives on the treatment of oral and systemic diseases.

Conclusion

The present review summarized the multiple interactions of oral microorganisms and host immune responses in oral and systemic diseases (see supplementary Table). Microbial dysbiosis is not simply a common risk factor, but rather it sets off multiple immune-mediated processes that work in concert to promote both the development and exacerbation of disease. A better understanding of these relationships may guide clinical interventions and provide more focused therapeutic alternatives. As this process unfolds, new molecular mechanisms and immunotherapeutic targets are expected to be identified and our ability to address local and systemic health related issues will be enhanced.

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