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EDITED BY
Aleksander M. Grabiec,
Jagiellonian University, Poland

REVIEWED BY
Anu Goenka,
University of Bristol, United Kingdom
Andrea Santarelli,
Marche Polytechnic University, Italy

*CORRESPONDENCE
Ming Chu
famous@bjmu.edu.cn
Feng Chen
chenfeng2011@hsc.pku.edu.cn

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The interplay between oral microbes and immune responses

Yuan Liu^{1,2}, Wenting Qv³, Yinchao Ma², Yuying Zhang²,
Chong Ding¹, Ming Chu^{2*} and Feng Chen^{1*}

¹Central Laboratory, Peking University School of Stomatology, Beijing, China, ²Department of Immunology, School of Basic Medical Sciences, Peking University, NHC Key Laboratory of Medical Immunology (Peking University), Beijing, China, ³Hunan Polytechnic of Environment and Biology, Hunan, China

Oral microbes play a critical role in maintaining oral homeostasis. Microbial dysbiosis promotes disease pathogenesis through several mechanisms. Recent studies have revealed that microbial imbalance and sustained inflammation are involved in disease progression. The adverse interaction triggered by a host immune response to microorganisms can lead to oral and systemic diseases. Here, we reviewed how oral microbes communicate with hosts during the development of local and distant inflammation. Elucidation of these processes may reveal future directions in this field and the potential targets of novel biological therapies for oral and systemic diseases.

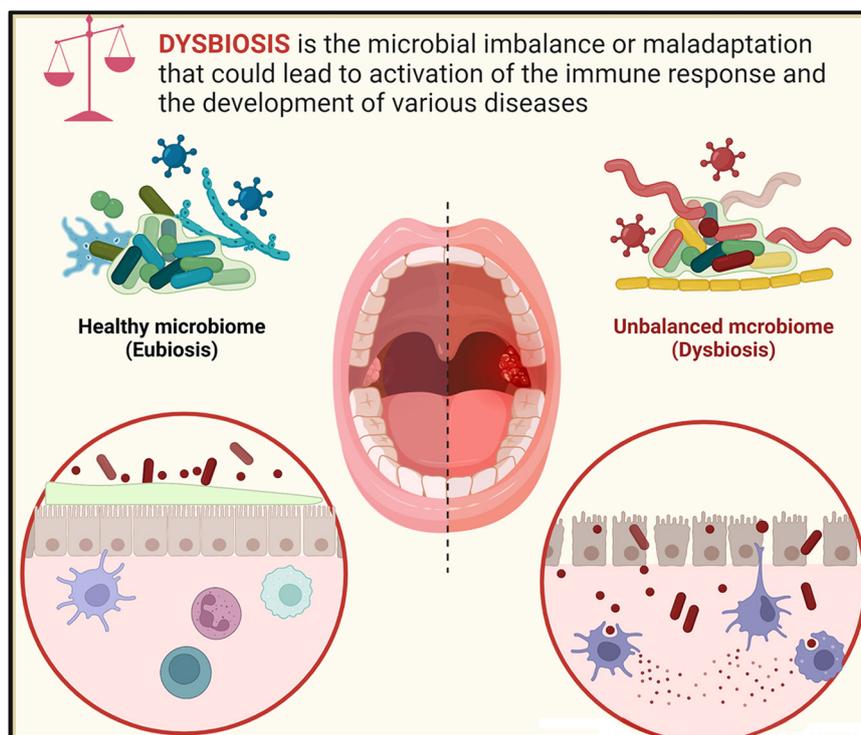
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immune system, oral microbiota, oral diseases, systematic diseases, human health

Introduction

The human oral cavity contains diverse microhabitats. The healthy oral microbiota consists of rich communities of bacteria as well as fungi, viruses, and protozoa. Oral microbes and their interactions help protect the human body against invasion by undesirable organisms. When the microbial balance has been disturbed, inflammatory responses lead to tissue destruction, inducing an unremitting positive feedback loop of oral diseases, including dental caries, periodontal diseases, mucosal diseases (e.g., leukoplakia, lichen planus), and oral cancer, and even several chronic systemic disorders such as cardiovascular disease (CVD), diabetes, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), Alzheimer's disease (AD), and other cancers (Hajishengallis, 2015; Acharya et al., 2017; Lamont et al., 2018; Genco and Sanz, 2020).

In general, imbalanced microbes (dysbiosis) promote diseases through several mechanisms. First, increased microbial loads can induce an inflammatory response. For example, microbes in periodontal pockets are highly associated with periodontal disease (Diaz, 2012), with a 3-log increase in the microbiota load in periodontitis subjects.



GRAPHICAL ABSTRACT

The balance between microbial and immune activities maintains systemic homeostasis. Breaking this balance leads to oral and systemic diseases.

High microbial biomass and community diversity are central features of periodontitis-associated oral microbes (Hajishengallis, 2014). In addition, damage may result from the direct action of microbial enzymes and toxins released by microbiota. Biofilm-forming microbes can destroy the collagen attachment between tooth and bone (You et al., 2017; Yousefi et al., 2020), ultimately causing infectious oral disease. In addition to the increases in microbial biomass and diversity, another mechanism is that periodontal pathogens or virulence factors released by oral microbes circulate through vessels and

across the blood–brain barrier, which can induce distant disease (Han and Wang, 2013). For example, bacteremia induced by oral microbes increases the risk for adverse pregnancy outcomes (Saadaoui et al., 2021). Moreover, *Porphyromonas gingivalis* has been identified in the brains of AD patients (Dominy et al., 2019).

Accumulating evidence indicates that oral microbes are not simply a common risk factor, but multiple microorganism-induced immunological mechanisms are a key point to disease processes. Imbalanced interactions between the periodontal microbiota and the inflammatory response of the host are responsible for promoting some diseases *via* complex and diverse mechanisms.

Microbiota can induce the local or ectopic disease through activation of the host immune system. Several mechanisms have been proposed for this association. The local or ectopic microbiome can directly affect the proportion and composition of immune cells. For example, *P. gingivalis* and *Lactobacillus rhamnosus* GG regulate the balance of T-helper (Th)17 cells and T-cell regulators (Tregs) in colitis *via* Toll-like receptor (TLR)4 and TLR2 (Hao et al., 2015). Moreover, local or ectopic microbiota may release inflammatory cytokines or stimulate particular immune cells, leading to disease. For example, the oral microbiota promotes colitis *via* activation of the inflammasome in colonic mononuclear phagocytes and induction of migratory

Abbreviations: ACPAs, Anti-citrullinated protein antibodies; AD, Alzheimer's disease; APCs, Antigen-presenting cells; APOs, Adverse pregnancy outcomes; b2GP1, B2-glycoprotein 1; COPD, Chronic obstructive pulmonary diseases; CTLs, Cytotoxic T lymphocytes; IBD, Inflammatory bowel disease; ILCs, Innate lymphoid cells; LCs, Langerhans cells; GAS6, Growth arrest specific 6; G-CSF, Granulocyte colony stimulating factor; GF, Germ-free; LPS, Lipopolysaccharide; mDCs, Myeloid DCs; MDSCs, Myeloid-derived suppressor cells; MyD88, Myeloid differentiation primary response gene 88; OC, Oral candidiasis; OECs, Oral epithelial cells; OLP, Oral lichen planus; OMD, Oral mucosal disease; OSCC, Oral squamous cell carcinoma; oxLDL, Oxidized-LDL; RAU, Recurrent aphthous ulcer; RA, Rheumatoid arthritis; Receptor activator for nuclear factor- κ B ligand (RANKL), SLE, Systemic lupus erythematosus; slgA, Secretory immunoglobulin A; TAM, TYRO3–AXL–MERTK; TAMs, Tumor-associated macrophages; TANs, Tumor-associated neutrophils; Th17, Type 17 T helper; tjp-1, Tight junction protein 1; TLR, Toll-like receptor; Tregs, T regulatory cells.

Th17 cells (Sun et al., 2020). Furthermore, tissue destruction in periodontal disease is caused by the host immune response rather than directly by microorganisms or their toxic products, as the host body prevents microorganisms from invading and damaging periodontal tissue. Thus, tissue destruction is an inevitable side effect of an exaggerated host inflammatory response (Wang K. et al., 2015). Microbial dysbiosis and local inflammation can enter a vicious cycle, each increasing the severity of the other.

In addition, recent studies have identified the reciprocal importance of periodontal disease in potentiating systemic disease states (Zheng et al., 2020). For example, periodontitis causes increased serum levels of interleukin (IL)-1 β , IL-6, and acute-phase proteins, which might alter the ecological environment and thus support diabetes (Preshaw et al., 2012). Conversely, systemic infections can be detected in the bone marrow, where the process of increasing neutrophil and monocyte infiltration is initiated to fight oral infection (Yang et al., 2018; Cheng et al., 2021). Moreover, some systemic diseases cause the release of factors that worsen oral disease (Grassl et al., 2016). For example, diabetes enhances IL-17 levels and alters the oral microflora, increasing its pathogenicity.

The study of oral microbes and their relationship with the immune system is complex. Elucidating the interactions among oral microorganisms and their cooperation with the host is key to understanding disease progression. This review comprehensively presents an overview of oral and systemic diseases mediated by the interplay between dysbiosis of the oral microbiota and aberrant immune responses. This is important to provide novel insights to support effective prevention and meaningful guidance for future clinical applications.

Interplay of the oral mucosal immune system with the microbiota under normal conditions

The oral cavity is exposed to external microbiota, foreign antigens, and environmental threats starting at birth, leading to colonization of the oral mucosa by diverse microbes. Microbial colonization modulates the early development of the immune system in oral mucosal tissues, as well as the development of oral tolerance through the regulation of macrophages and innate lymphoid cells (Abusleme et al., 2013; Kitamoto et al., 2020). These early life events have critical impacts on later health and disease. However, the intricate mechanisms involved in host-microbiota interactions in the oral mucosa under normal conditions are just beginning to be revealed. The mammalian oral mucosa contains various epithelial and stromal cells, along with resident leukocytes, such as $\gamma\delta$ T cells, neutrophils, innate lymphoid cells (ILCs), and Langerhans cells (LCs) (Jepsen et al.,

2018; Kirchner and LeibundGut-Landmann, 2021). These innate lymphocytes are recruited before and after birth.

In mice and humans, $\gamma\delta$ T cells reside in the oral epithelium and gingiva (Figure 1A). They can be divided into $V\gamma 6^+$, $V\gamma 1^+$, and $V\gamma 4^+$ subsets in mice. The $V\gamma 6^+$ subset is located in the oral epithelium during embryogenesis and expands rapidly upon exposure to the microbiota, while the $V\gamma 1^+$ and $V\gamma 4^+$ subsets are recruited to the gingiva after birth (Xiao et al., 2017; Gaffen and Moutsopoulos, 2020). $V\gamma 6^+$ $\gamma\delta$ T cells in both the neonatal epithelium and adult mice are the major source of IL-17, a cytokine that plays a key role in oral immunity (Wilhelm et al., 2019; Koren et al., 2021). These $V\gamma 6^+$ $\gamma\delta$ T17 cells mediate the recruitment of neutrophils to the neonatal oral epithelium in an IL-17-dependent manner (Wahaidi et al., 2011).

Neutrophils are present prenatally in the oral epithelium, similar to $\gamma\delta$ T cells, and expand with exposure to the microbiota or transient recruitment by IL-17 (Figure 1B). However, they have also been detected in the gingiva of germ-free (GF) mice, but not in the buccal and gingival epithelium of *IL-17^{-/-}* mice, suggesting that they are recruited to the gingiva in a manner dependent on IL-17 rather than microbes. Conversely, more neutrophils are present in the junctional epithelium of specific-pathogen-free (SPF) mice than in GF mice (Tordesillas and Berin, 2018; Koren et al., 2021). The contributions of TLR2 and TLR4 signaling in healthy periodontal tissue may account for that finding. Significant increases in the numbers of neutrophils in the junctional epithelium and significant changes in oral microbial composition have been observed in TLR2- and TLR4-deficient mice (Dutzan et al., 2016; Tordesillas and Berin, 2018).

Innate lymphoid cells are present in the oral mucosa of human infants (Williams et al., 2021). Furthermore, oral ILCs reside in the basal layers of the epithelium in mice and protect the uninfected epithelium of the oral mucosa against viral and fungal invasion (Krishnan et al., 2018; Wilhelm et al., 2019; Figure 1C).

In mice, LCs, special antigen-presenting cells (APCs) of stratified squamous epithelia such as the skin and mucosa, are recruited by CCL20 and CCL2 to the epithelium postnatally depending on the local microbiota, where they maintain mucosal homeostasis and prevent tissue destruction (Jaitley and Saraswathi, 2012).

In addition to innate lymphocytes, GAS6 and a ligand in the TAM receptor family also play a fundamental role in homeostasis maintenance by the oral epithelium (Tsukamoto et al., 2012; Nassar et al., 2017). A few weeks after birth, oral microbes induce GAS6 expression in the gingival epithelium *via* a MyD88-dependent signaling pathway, while upregulated GAS6 expression maintains microbial homeostasis, as *GAS6^{-/-}* mice exhibit elevated inflammation of the oral mucosa with an expansion of the oral microbiota. Moreover, GAS6 downregulates gingival inflammation, and a lack of GAS6 impairs the balance between Th17 cells and Tregs in the gingiva.

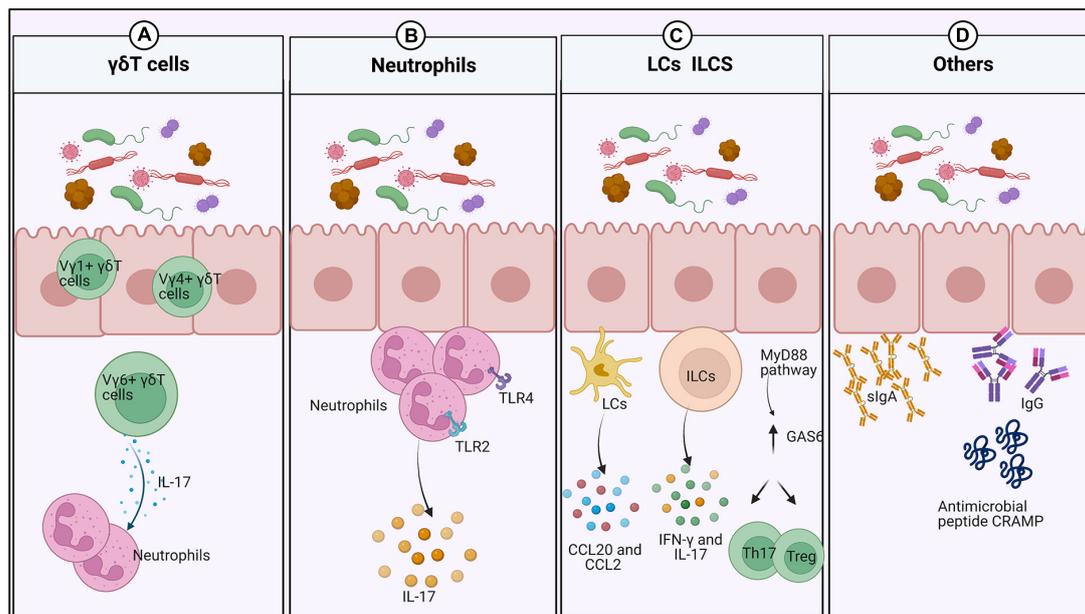


FIGURE 1

Interplay between the oral mucosal immune system and the microbiota under normal conditions. (A) After exposure to the external microbiota, numerous innate lymphocytes expand into the oral mucosa. $\gamma\delta$ T cells increase rapidly in abundance and recruit neutrophils by producing IL-17. (B) Neutrophils increase in response to the local microbiota and IL-17 in the neonatal epithelium, but depend only on IL-17 in the gingiva. (C) Oral ILCs produce IFN- γ and IL-17 to protect the oral mucosa from viral and fungal infection. LCs are recruited by CCL20 and CCL2 to maintain mucosal homeostasis and prevent tissue destruction. In response to oral microbes, expression of GAS6 is upregulated in the gingival epithelium to maintain microbial homeostasis and downregulate gingival inflammation. (D) The oral microbiota promotes the induction of salivary antimicrobial components such as IgA and antimicrobial peptides.

The oral microbial load is significantly higher in murine neonates than in adults. The decrease in oral microbial abundance is mediated by the upregulation of saliva production, which has been demonstrated in mice whose parotid salivary glands were surgically removed. However, the capacity to generate saliva flow is not affected by the microbiota, as the rates of saliva production are similar in adult GF and SPF mice (Wahaidi et al., 2011). The microbiota has a major impact on the induction of salivary antimicrobial components such as sIgA, IgG, and the antimicrobial peptide CRAMP (Koren et al., 2021; Figure 1D). Notably, sIgA plays a protective role in regulating and maintaining the normal oral microbiota to prevent microbial dysbiosis (Zenobia et al., 2013). Saliva can promote the attachment of certain bacteria and serve as a microbial nutrient source to affect the composition and activity of the oral microbiota (Chang et al., 2019). In addition, feeding methods also affect infant microbiota, and the microbial colonization patterns differ between breast-fed infants and formula-fed infants. There was a higher prevalence of *Gemellaceae*, *Vogesella*, *Nocardioideis* (Duale et al., 2021), *Actinobacteria*, and *Proteobacteria* in breast-fed babies, while the phylum *Bacteroidetes* were more prevalent in formula-fed infants (Al-Shehri et al., 2016). Moreover, breast milk-derived cytokines and soluble receptors enhance oral tolerance development (Dawod and Marshall, 2019). It also remains to be

seen if the higher relative abundance of some microbes in early life has oral health consequences in later life.

The relationship between oral bacterial colonization and the establishment of a healthy homeostatic mucosal immune system is not well understood. Recently, unique interactions between the epithelium and microbiota in the oral cavity of murine neonates have been studied, providing clues about the foundation of oral homeostasis (Simmerman et al., 2016). After the fragile balance between the host immune system and oral microbiota is established, it can be broken down by various endogenous and exogenous factors.

Interactions between oral microbes and immune cells in oral diseases

Orofacial myofunctional disorder (OMD) is a general term for a series of diseases that mainly affect the oral mucosa and soft tissues. It includes infectious diseases, mucosal spot disease, mucosal ulcer lesions, and oral cancer (Lin et al., 2021). Many factors are associated with the pathogenesis of OMD, including immune disorders, microbial infections, allergies, genetic susceptibility, hormonal imbalance, mechanical damage,

and stress (Mock et al., 1983; Alrashdan et al., 2016; Vila et al., 2020). Recent studies have shown that imbalanced oral microbiota may lead to the development of oral mucosal diseases (Hu et al., 2019; Yu et al., 2020). Fluctuations in the mucosal microbiota may cause inflammation through interactions with both innate and adaptive immune responses (Baek and Choi, 2018; Pellon et al., 2020; Sami et al., 2020).

Herein, the host immune regulation mechanisms involved in the interactions between periodontal disease and host immune defenses are summarized to elucidate the immune mechanisms employed against the initiation and propagation of oral diseases.

Oral infectious diseases represented by oral candidiasis

Oral candidiasis (OC) is one of the most common fungal infections caused by *Candida albicans*, which is the most common *Candida* species (Akpan and Morgan, 2002) (Figure 2A). Oral epithelial cells (OECs) act as “first responders” to *C. albicans* infection and activate damage-associated immune effectors, including IL-1-family cytokines and β -defensins. *C. albicans*-induced IL-1 α/β and IL-36 activate innate IL-17-producing cells (Verma et al., 2018). IL-17 binds to its receptor on OECs, inducing the release of antimicrobial effectors, including CXC chemokines and granulocyte colony-stimulating factor (G-CSF). These effectors promote a neutrophil response and direct fungicidal activity to maintain barrier integrity (Agor et al., 2020). However, the Th17/IL-17 response is double-edged, as it also contributes to immunopathology and aberrant IL-17/Th17 responses, driving the pathogenesis of periodontitis and consequent bone and tooth loss (Bunte and Beikler, 2019). Moreover, the immune attack can be modified in various ways to destroy fungal pathogens. For example, immune cells secrete molecules such as antibodies and complementary compounds that bind to fungal wall components and enhance phagocytosis (Wich et al., 2021). Host-derived immune cells release enzymes to destroy the integrity of the fungal cell wall (Zhou et al., 2021). Thus, the interaction between mucosal immunity and *C. albicans* involves numerous interconnected host immune regulation mechanisms.

Oral mucosal patch striae diseases represented by oral lichen planus

Oral lichen planus (OLP) is a chronic autoimmune, T cell-mediated inflammatory disease of the oral mucosa (Nosratzahi, 2018; Figure 2B). When infection occurs in the oral cavity, OLP-mediating antigens recruit T cells to the target oral mucosa, where they direct an immune response that culminates in keratinocyte cell death and

long-term disease. Oral keratinocytes release a multitude of proinflammatory cytokines, including TNF- α , IL-1 β , G-CSF, IL-12, and IL-6, to recruit T cells. Activated APCs including dendritic cells (DCs), macrophages, mast cells, and activated oral keratinocytes activate T cells, produce the primary OLP immune response (El-Howati et al., 2022), in which cytotoxic CD8⁺ T cells drive keratinocyte apoptosis through the release of cytotoxins and CD4⁺ Th1 T lymphocytes maintain a pro-inflammatory state (Enomoto et al., 2018). Moreover, mast cells produce chymases, which damage the epithelial basement membrane directly or indirectly through the activation of MMP-9 (Wang et al., 2018). Some other Th subsets are involved in the development of OLP. Th17 cells secrete elevated levels of IL-17 and IL-23, while Th9 cells secrete IL-9 and IL-17 in OLP lesions, where these cells are thought to play key roles in oral immunity (Wang et al., 2017). Some evidence indicates that the proportion of peripheral Th17 cells and pro-inflammatory cytokine IL-17 levels are significantly elevated in patients with OLP (Xie et al., 2012; Wang et al., 2017). Pro-inflammatory cytokine IL-17 increases the proportion of functionally impaired CD4⁺CD25⁺ regulatory T cells in OLP patients, ultimately leading to OLP (Zhou et al., 2016).

Furthermore, oral bacteria within tissues provide insights into the pathogenetic mechanism of OLP. CCL2 is overproduced in oral keratinocytes and induced by lipopolysaccharide (LPS) via TLR4/NF- κ B signaling; increased CCL2 expression is positively associated with the OLP disease score, and thus may sustain or exacerbate the chronic inflammation of OLP (Zeng et al., 2018; Osorio-Osorno et al., 2020). The above evidence suggest that the pathogenesis of OLP includes antigen-specific and non-specific mechanisms. Antigen-specific mechanisms involve T-cell activation following antigen presentation and apoptosis of oral keratinocytes. Non-specific mechanisms consist of the overproduction of CCL2, the activation of MMP-9, and mast cell degranulation. Thus, a complex immune cell relationship exists during the process of OLP.

Ulcerative lesions of the oral mucosa represented by recurrent aphthous ulcer

Recurrent aphthous ulcer (RAU) is a chronic, inflammatory ulcerative disease of the oral mucosa, the pathogenesis of which remains unclear. Recent studies have provided compelling evidence that local immune dysfunction is closely associated with the occurrence of RAU (Saikaly et al., 2018; Figure 2C).

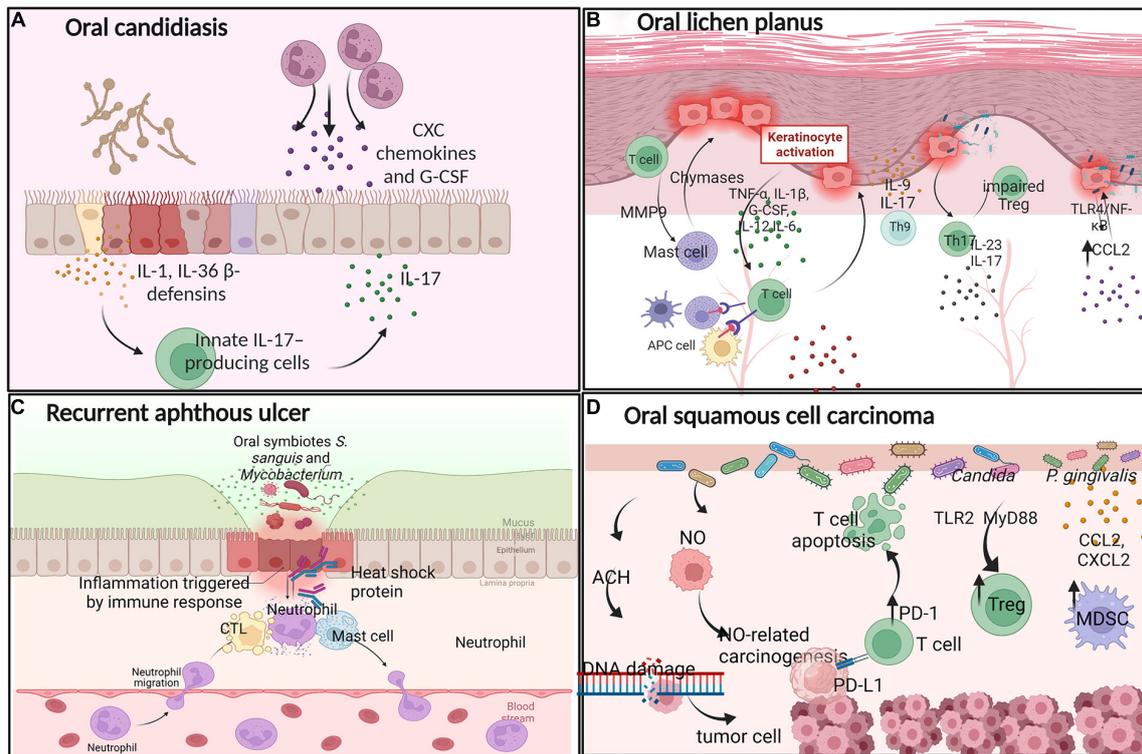


FIGURE 2

Interactions between oral microbes and immune cells in oral diseases. **(A)** Oral candidiasis: *C. albicans*-induced IL-1, IL-36, and β -defensins activate innate IL-17-producing cells to release CXC chemokines and G-CSF, promoting a neutrophil response. **(B)** Oral lichen planus: Oral keratinocytes release a multitude of proinflammatory cytokines, providing insights into the pathogenetic mechanism of OLP. **(C)** Recurrent aphthous ulcer: Driven by CTLs, neutrophils, and mast cells. **(D)** Oral squamous cell carcinoma: Some oral microbes produce ACH and NO, recruiting Treg and MDSCs to the tumor microenvironment to support oral cancer development.

Recurrent aphthous ulcer is driven mainly by microbe-infected cytotoxic T lymphocytes (CTLs) destroying the mucosal epithelium, neutrophils, and mast cells. After ulceration, oral microbes penetrate the ulcerative oral mucosa to further trigger specific immune responses. Eventually, the inflammatory process results in the exudation of fibrinous and necrotic mucosal cells (Tanacan et al., 2022). In addition, metabolites produced by oral microbes damage the oral epithelial structure and may trigger the development of RAU (Hasan et al., 1995). A 65 kDa heat-shock protein produced by *Streptococcus sanguinis* and *Mycobacterium tuberculosis* can cross-react with peptides in OECs, producing anti-oral mucosa antibodies and promoting oral ulcers.

Hence, RAU may be driven by an imbalance of proinflammatory and anti-inflammatory cytokines, which leads to excessive immune activation of oral autoantigens and non-pathogenic microorganisms. Although the specific pathogenesis of RAU has been described, it requires further in-depth exploration.

Oral cancer represented by oral squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is the most prevalent and commonly studied malignant tumor of the oral cavity. Mounting evidence indicate that oral microbes are associated with the occurrence of OSCC (Figure 2D). Although smoking, drinking, and betel nut use are common risk factors for OSCC, the factors driving the malignant transformation process are poorly understood (Fantozzi et al., 2021). Emerging evidence suggest links between several types of metabolic damage and oral cancer. For example, some oral microbiota produces acetaldehyde (ACH), which causes DNA damage (Yokoyama et al., 2018). Bacteria release NO, contributing to NO-related carcinogenesis (Kakabadze et al., 2020). Previous research has revealed that the immunopathology of the oral microbiota is associated with the development of oral cancer. For example, *Candida* infection increases the proportion of Tregs through the TLR2/MyD88 pathway, increasing the fungal burden and disrupting mucous membrane immunity (Pandiyan et al., 2019). *P. gingivalis* expresses chemokines such as CCL2 and

CXCL2 to recruit myeloid-derived suppressor cells (MDSCs) and promote tumor progression (Guo et al., 2021). Furthermore, *P. gingivalis* induces T cell inhibition via activation of PD-L1 binding to PD-1, which leads to apoptosis of T cells. Thus, *P. gingivalis* increases the invasiveness of oral cancer cells and their resistance to chemotherapeutic agents. *Candida* and *Fusobacterium nucleatum* have similar characteristics. Thus, the oral microbiota is involved in regulating the local growth and diffusion of cancer cells. As research progresses, oral squamous cell carcinoma will certainly become increasingly clear, improving treatment options for OSCC. Oral microbes have been proposed for use as a diagnostic indicator of oral cancer.

Altogether, the mechanisms of oral microbiota-induced carcinogenesis include microbial dysbiosis, colonization, and translocation of oral microbiota that lead to an excessive inflammatory reaction, immunosuppression of host, and promotion of malignant transformation. Here, we described the impact of oral microbial abnormalities on carcinogenesis and introduced new ideas for effective prevention of tumors.

Interactions between oral microbes and immune cells in distant organs

A growing body of literature may become increasingly clear that localized inflammatory lesions may initiate secondary inflammatory infections or disease in distant organs through various modes of transmission. Oral microorganisms can ectopically colonize various tissues, leading to several conditions, including CVD, respiratory tract infection, IBD, AD, adverse pregnancy outcomes, and distant tumors. Here, we discuss how periodontal bacteria activate lymphocytes and cause comorbidities that disseminate to extraoral tissues.

Cardiovascular disease

An increasing number of studies suggest that periodontal inflammation and oral microorganisms are associated with elevated and accelerated risks of atherosclerosis and cardiovascular disease (CVD) (Figure 3A). The mechanism through which periodontal pathogens induce atherogenesis could be direct or indirect. The integrity of the oral mucosal basal layer is essential to ensuring that oral bacteria remain outside of the circulatory system (Xie et al., 2020). *P. gingivalis* is essential to ensure that it directly invades endothelial cells and stimulates numerous innate immune cell types through the TLR-NF- κ B signaling pathway. Activated vascular endothelial cells recruit monocytes and elevate circulating lipids, thereby inducing atherogenesis. Furthermore, host genetics regulates lipid-related transcriptome affecting cardiometabolic diseases

(CMDs) and controls the differentiation of innate immune cells activated in oral infections. Thus, genetics creates a complex relationship among oral infections (Janket et al., 2015).

Indirect interactions among periodontal pathogens in CVD include both innate and adaptive immune responses. For example, myeloid DCs (mDCs) infiltrate the oral submucosa via periodontitis and in atherosclerotic plaques. *P. gingivalis* enhances immature mDC differentiation and causes them to secrete high levels of MMP9 and other indicators of extracellular matrix destruction, plaque rupture, and myocardial infarction (Carrion et al., 2012). Oral gram-negative bacteria increase local levels of proinflammatory LPS molecules, thereby promoting inflammation-induced lipid accumulation in macrophages and ultimately leading to macrophage cholesterol accumulation and foam cell formation (Pietiainen et al., 2018). Another mechanism involves several antibodies recognizing host antigens and modulating their function (cross-reactivity). For example, antibodies are produced against the microbial heat-shock protein (Choi et al., 2021) or cardiolipin (targeting b2-glycoprotein 1, b2GPI) (Wang C.Y. et al., 2015). Saliva contains IgA and IgG antibodies binding to oxidized low-density lipoprotein (oxLDL), which show cross-reactive binding to *P. gingivalis*, and may participate in immune reactions involved in atherosclerosis and periodontal disease through molecular mimicry (Akhi et al., 2017). The third mechanism occurs with immune system recognition of periodontal bacteria as antigens. A strong combined IgG response to *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* is associated with prevalent CVD (Choi et al., 2021). In summary, endotoxemia and systemic antibody responses are possible mediators linking oral dysbiosis to increased risk for CVD.

Respiratory tract infection

Oral microbiota can enter the blood circulation or colonize the whole respiratory system through the airways, which have long been recognized as a reservoir for infection of the whole respiratory system. Thus, oral microbes have easier access to the respiratory system than to other organ systems. Various lines of evidence draw links between oral microbes and pneumonia, chronic obstructive pulmonary diseases (COPD), lung cancer, and other respiratory diseases. On one hand, oral microbial dysbiosis leads to oral and respiratory diseases, while on the other hand, oral diseases and respiratory diseases worsen oral microbial dysbiosis.

Research has demonstrated that the same pathogens can be isolated from dental plaque, bronchoalveolar lavage fluid, and lung aspirates. In addition, patients tend to have a significantly lower risk for pneumonia when they receive periodontal treatment (Pathak et al., 2021). Moreover, oral and upper respiratory tract microbes have been detected in the lungs of COPD patients, likely due to the aspiration

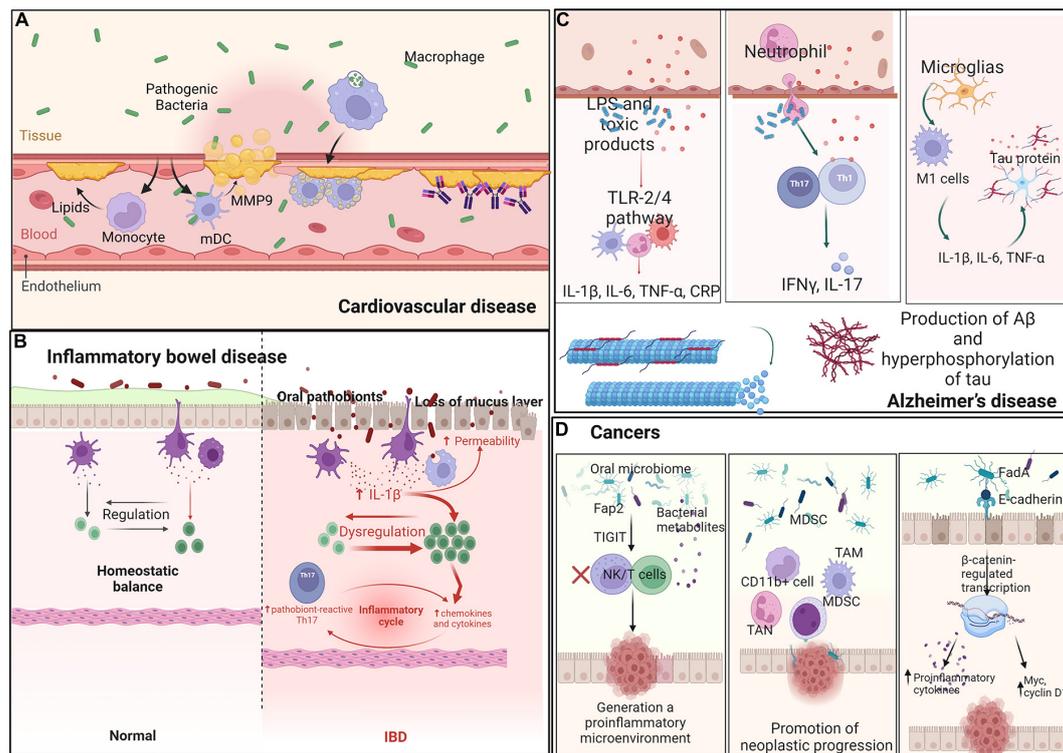


FIGURE 3

Interaction between oral microbes and immune cells in distant organs. Ectopic oral pathogens travel through other parts of the body, triggering inflammatory diseases. **(A)** Cardiovascular disease: Oral microbiota recruit monocytes and mDCs and secrete MMP-9 and lipids. Heat-shock proteins and antibodies against b2GP1 and oxLDL promote myocardial infarction. **(B)** Inflammatory bowel disease: Oral pathobionts translocate to the gut and promote colitis through induction of inflammasome-dependent IL-1 β secretion and oral pathobiont-reactive Th17 cells. **(C)** Alzheimer's disease: Oral pathobionts increase the production of A β and hyperphosphorylation of tau via the TLR-2 and TLR-4 signaling pathways, thereby increasing the levels of IL-17 and IFN- γ produced by Th-cells. **(D)** Cancer: Oral microbes engage the TIGIT receptor of immune cells, decreasing the abundances of MDSCs, TANs, and TAMs and increasing oncogene expression to generate a proinflammatory microenvironment.

of oral secretions into the lungs. Periodontitis or caries can alter the oral microbiota and induce systemic inflammation, leading to asthma and bronchitis (Mammen et al., 2020). In turn, respiratory diseases cause oral microbial dysbiosis and oral diseases and can further exacerbate respiratory diseases in a vicious cycle. Future studies are needed to unravel the interactions between oral microorganisms and respiratory diseases.

Inflammatory bowel disease

The oral cavity is the entry point of the gastrointestinal tract, and oral microorganisms are essential drivers of the balance between health and disease. Large quantities of oral bacteria are constantly swallowed, affecting gut microbiota composition and leading to changes in gut epithelial permeability that can lead to bowel disease (Hajishengallis, 2015; Figure 3B). Messora et al. found that a ligature-induced periodontitis model showed changes in intestinal structure, such as defects of the villi,

basal lamina degeneration, neutrophil infiltration into the small intestine, and direct damage to the intestinal barrier (Messora et al., 2013). Some IBD patients may have genetic factors leading to the weakening of the mucosal barrier, which increases susceptibility to disease (Merga et al., 2014). Moreover, in another study, the administration of *P. gingivalis* downregulated the levels of tight junction protein 1 and occludin in the small intestine (Nakajima et al., 2015), consistent with the ligature-induced periodontitis model.

Apart from direct damage to the bowel barrier, oral flora indirectly regulates the immune system to promote the development of bowel disease. Kitamoto et al. showed that amassed oral pathobionts are ingested and translocated to the gut, where they promote colitis through the induction of inflammasome-dependent IL-1 β secretion in colonic mononuclear phagocytes. Moreover, oral microbes support the generation of oral pathobiont-reactive Th17 cells in the oral cavity, which then migrate to the inflamed gut. Translocated oral pathobionts, but not gut-resident microbes, activate Th17 cells of oral origin and initiate the development of colitis

(Kitamoto et al., 2020). Atarashi et al. found that ectopic gut colonization by oral *Klebsiella* species increased the abundance of Th1 cells. The *Klebsiella*-induced Th1 cell response and secretion of IL-18 by TLR4-activated colonic epithelial cells appeared to amplify the Th1 cell response. Jia et al. explored the relationship between *P. gingivalis* and IBD, in which *P. gingivalis* exacerbated colitis by activating CD4⁺ T cells and upregulating the Th17/Treg ratio via the JAK-STAT signaling pathway (Jia et al., 2020), leading to bowel disease.

Taken together, these studies show that ectopic colonization by several oral bacteria may injure the intestinal epithelial barrier, disrupt the host immune system, and eventually alter gut microbiota composition, mainly characterized by decreased diversity along with disruption of immunoregulation and aggravation of chronic intestinal inflammation.

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition classically characterized by two hallmark pathologies: amyloid- β (A β) plaque deposition and neurofibrillary tangles of hyperphosphorylated tau. There is a strong correlation between AD and oral disease, particularly chronic periodontal diseases (Figure 3C). Dominy et al. reported the presence of *P. gingivalis* DNA and gingipain antigens in the brains of AD patients (Dominy et al., 2019). Moreover, several models explain the pathology of AD based on oral microbiota.

Periodontitis promotes AD through common pathophysiological pathways. Crossing of the blood-brain barrier, entry into brain tissue, and secretion of LPS by microbiota may occur in AD (Sansores-Espana et al., 2021). Moreover, organisms associated with the periodontal disease produce LPS and toxic products that spread from the ulcerated periodontal pocket into the systemic circulation, initiating classical innate immune signaling pathways via the TLR-2 and TLR-4 mechanisms. Then, the production of pro-inflammatory mediators in the brain, including IL-1 β , IL-6, TNF- α , and C-reactive protein (CRP), ultimately increases the production of A β and hyperphosphorylation of tau, thus leading to neurodegeneration (Singh et al., 2015). Furthermore, peripheral neutrophils have been found in the brains of AD mouse models along with increased levels of IL-17 and interferon-gamma (IFN- γ) produced locally by Th cells (Sadrameli et al., 2020), supporting the hypothesis that chronic inflammation is a strong risk factor for the progressive development of neurodegenerative dementia.

Moreover, bacteria or their virulence factors have been suggested to spread from periodontal tissues to the brain through the trigeminal nerve. Such molecules could induce neuroinflammation mediated by the activated pro-inflammatory microglial phenotype. Under inflammatory conditions, microglia differentiate toward a modulator

phenotype or M2, which is characterized by secretion of IL-10 and TGF- β 1. When this inflammatory state becomes persistent, M2 shifts to the pro-inflammatory M1 phenotype. M1 cells increase the levels of IL-1 β , IL-6, and TNF- α and modify the function of astrocytes, which increase their secretion of pro-inflammatory cytokines, generating A β and hyperphosphorylation of tau (Sureda et al., 2020). Moreover, LPS promotes the release of reactive oxygen and nitrogen species such as superoxide ions, iNOS, and NO. Then, vital neurons are destroyed and chronic inflammation occurs, with consequences for the development of disease.

Adverse pregnancy outcomes

A systematic review reported associations between periodontitis and adverse pregnancy outcomes (APOs). Translocation of bacterial pathogens to the placental barrier results in the restriction of fetal growth and APOs (Lin et al., 2007; Kaur et al., 2014). The most prevalent cultivable oral species associated with APOs is *F. nucleatum*, which has been detected in a wide variety of placental and fetal tissues. Other oral pathogens, such as *P. gingivalis*, can induce an approximately two-fold increase in the level of circulating proinflammatory cytokines. Thus, the hematogenous spread of periodontal pathogens, their byproducts (Cobb et al., 2017), and various mediators (Liu et al., 2007) of inflammation generated by the maternal or fetal immune responses cause decidual necrosis. Identification of the species or subspecies involved in APOs will improve early and accurate diagnosis and identification of individuals at risk.

Cancer

Interactions between oral microbes and the immune system are thought to affect tumor development outside the oral cavity. Oral dysbiosis has been linked not only to head and neck cancer but also to the development of other tumors. Oral microbiota can induce carcinogenesis through the following three mechanisms: by promoting chronic inflammation, eventually leading to oncogene activation and angiogenesis; by affecting cell proliferation and inhibiting cellular apoptosis; and by producing carcinogenic substances. A published review summarized selected carcinogenesis mechanisms associated with oral microbes (Mascitti et al., 2019; Figure 3D).

Oral microbes are thought to influence the development of tumors in the gastrointestinal tract through various mechanisms. For example, LPS and cell extracts of *F. nucleatum* increase levels of inflammatory cytokines and chemokines, such as CCL20, generating a proinflammatory microenvironment. Fap2 protein engages the TIGIT receptor of immune cells, inhibiting NK and T cell activities and

generating a proinflammatory microenvironment that supports colorectal carcinoma progression (Gur et al., 2015). *F. nucleatum* increases the abundance of CD11b⁺ myeloid cells, MDSCs, tumor-associated neutrophils (TANs), and tumor-associated macrophages (TAMs), promoting neoplastic progression (Gholizadeh et al., 2017). Moreover, binding of FadA to E-cadherin activates β -catenin-regulated transcription, which increases the expression of transcription factors to increase levels of proinflammatory cytokines and oncogenes, such as Myc and cyclin D1, and stimulates cell proliferation (Cuellar-Gomez et al., 2021). Activation of p38 leads to the secretion of MMP-9 and MMP-13, supporting cell invasion. Moreover, *F. nucleatum* attaches to host colorectal cancer cells and impairs intestinal barrier function, which might induce intestinal colonization by oral microbes (Wu et al., 2019).

The oral microbe has additionally been linked to pancreatic carcinogenesis. Elevated numbers of certain oral bacteria and the presence of serum antibodies against certain microbial species are associated with a two-fold higher risk for pancreatic cancer (Li et al., 2020). *P. gingivalis* triggers an innate immune response that involves recognition by TLR4, resulting in the release of pro-inflammatory cytokines. TLRs appear to play a role in pancreatic cancer development; their expression is explicitly higher in human pancreatic cancer (Kerr, 2015). Levels of oral bacteria are significantly elevated in the saliva of lung cancer patients. These mechanisms may provide novel targets and strategies for therapeutic intervention.

In summary, these results support the hypothesis that the interaction between the pathogenesis of periodontitis and disease in distant organs involves a complex interplay between immune-inflammatory responses and dysbiotic microbiota under the influence of environmental and genetic factors. Thus, clarification of the systemic effects of oral microorganisms would contribute to the goal of using the oral cavity to diagnose and treat non-oral diseases.

Interconnections between oral microbes and immune cells in autoimmune diseases

Evidence is emerging that oral organisms can increase the risk for or severity of autoimmune diseases. The relationship between periodontopathic microbiota and autoimmune diseases has been explored in recent years.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease that may reduce life expectancy. It is characterized by the presence of anti-citrullinated protein antibodies (ACPAs) and with clinical signs of enhanced inflammation and bone

loss (Figure 4A). Evidence indicates that periodontitis can lead to RA through the production of *P. gingivalis* peptidyl-arginine-deiminase enzyme, in which the amino acid arginine is converted into citrulline, initiating an immune evasion response and the production of ACPAs (Picchianti-Diamanti et al., 2017). Recent studies have shown that periodontal pathogens directly promote experimentally induced autoimmune arthritis through induction of a TLR2- and IL-1-driven Th17 response, which leads to osteoclast differentiation and bone erosion (de Aquino et al., 2014). In turn, chronic systemic inflammation in RA may affect levels of inflammatory cytokines in the oral cavity (Graves et al., 2019), including TNF- α , IL-1, IL-6, and IL-17. Increased levels of inflammatory mediators in the periodontal tissues of subjects with RA and other diseases may alter local ecologic conditions to favor pathogenic microbial species and promote periodontitis.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by the production of autoantibodies against nuclear and cytoplasmic antigens, affecting several organs. The diversity of microorganisms in periodontitis lesions is reduced in SLE patients (Aurlene et al., 2020), and microbial components differ between periodontitis and healthy periodontal tissue, indicating that SLE influences microbial diversity. Specifically, the proportion of anaerobic microorganisms (Correa et al., 2017), such as *Prevotella nigrescens*, *Prevotella oulorum*, *Prevotella oris*, and *Selenomonas noxia*, is elevated in the periodontal area of SLE patients. Meanwhile, the proportions of aerobic representatives of *Prevotella*, *Selenomonas*, and *Treponema* are lower. In turn, the influence of the subgingival microbiota in SLE patients aggravates the severity of periodontitis.

Diabetes mellitus

Systemic diseases have significant impacts on periodontitis, with diabetes mellitus having one of the strongest linkages. Diabetes is associated with increased prevalence, severity, and progression of periodontal diseases (Ohtsu et al., 2017; Figure 4B). For example, advanced glycation end-products increase IL-6 and TNF- α levels, leading to increased vascular permeability and the recruitment of inflammatory cells, thereby stimulating increased resorption. Moreover, high levels of glucose increase the levels of reactive oxygen species generated through both enzymatic and non-enzymatic pathways (Huang et al., 2020), leading to activation of mitogen-activated protein kinase and NF- κ B signaling and the release of multiple inflammatory factors.

Hyperglycemia directly disrupts immune responses through impacts on immune cell function. For example,

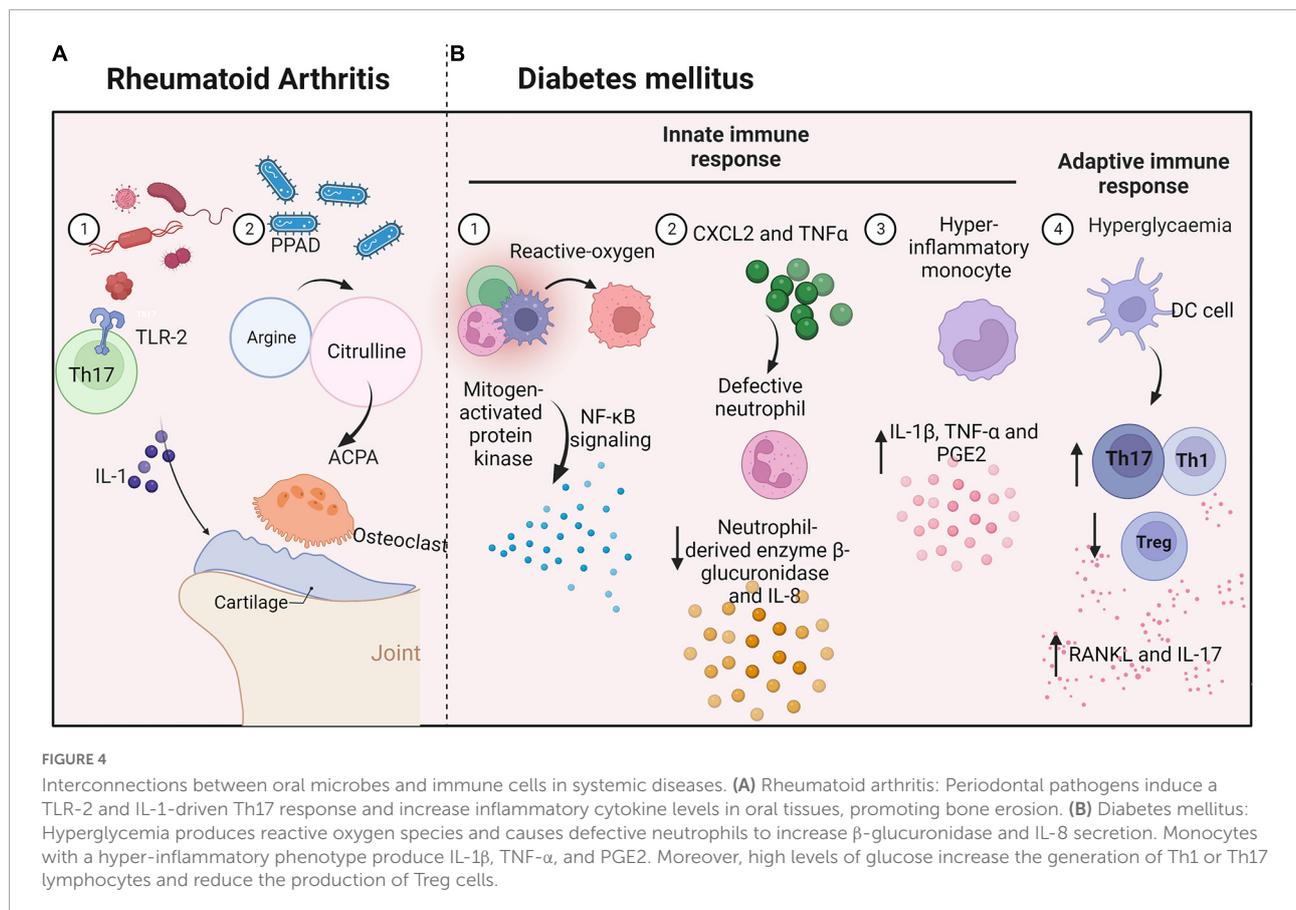


FIGURE 4

Interconnections between oral microbes and immune cells in systemic diseases. (A) Rheumatoid arthritis: Periodontal pathogens induce a TLR-2 and IL-1-driven Th17 response and increase inflammatory cytokine levels in oral tissues, promoting bone erosion. (B) Diabetes mellitus: Hyperglycemia produces reactive oxygen species and causes defective neutrophils to increase β -glucuronidase and IL-8 secretion. Monocytes with a hyper-inflammatory phenotype produce IL-1 β , TNF- α , and PGE2. Moreover, high levels of glucose increase the generation of Th1 or Th17 lymphocytes and reduce the production of Treg cells.

a neutrophil function is defective in diabetes, reducing levels of the neutrophil-derived enzyme β -glucuronidase and the chemokine IL-8 (Mutua and Gershwin, 2021). In turn, diabetes activates neutrophils and increases levels of reactive oxygen species, damaging the periodontium (Zheng et al., 2018). Diabetes increases NF- κ B activity in periodontal ligament fibroblasts, increasing the expression of CXCL2 and TNF α , and leading to the recruitment of more neutrophils. A study demonstrated that monocytes from patients with type 1 diabetes mellitus have a hyper-inflammatory phenotype (Kraakman et al., 2014). The cells respond to LPS from periodontal bacteria by producing significantly higher levels of IL-1 β , TNF- α , and PGE2, possibly prolonging the responses of neutrophils and monocytes/macrophages to plaque bacteria. Moreover, diabetes increases M1 macrophage polarization, increasing susceptibility to periodontal disease.

Diabetes also affects the adaptive immune response, leading to periodontitis. Diabetes can modulate dendritic cells, driving periodontal bone loss through increased abundances of Th1 or Th17 lymphocytes or a reduction of Treg cells (Graves et al., 2020). Th1 and Th17 cells regulate bone resorption and produce cytokines such as RANKL and IL-17, which are elevated in periodontitis patients with diabetes,

increasing the pathogenicity of the oral flora, and leading to further recruitment of neutrophils. When IL-17 is inhibited, the microbial community shifts reflected in decreases in both pathogenicity and alveolar bone loss. Diabetes causes periodontal ligament cells, osteoblasts, and osteocytes to increase RANKL expression. Oral disease is associated with the development of systemic inflammation and the onset of insulin resistance in mice.

Allergic disease

Although there are no known associations between the relative abundance of oral microbial species and asthma, allergic rhinitis, or atopic dermatitis, an imbalance of the oral flora is generally related to allergic diseases. For example, Proteobacteria is significantly enriched in the oral cavity of atopic dermatitis patients, while pathways for peptidoglycan biosynthesis, lysine biosynthesis, and galactose metabolism are decreased in abundance (Li et al., 2019). By contrast, the pathway for tryptophan metabolism is enriched in the oral cavity of allergic dermatitis patients. Interestingly, the microbes of the skin and oral cavity are relatively variable. A study that assessed the bacterial composition of saliva samples from children

with allergic diseases (Dzidic et al., 2018), including eczema, gastrointestinal allergy, asthma, and allergic rhinoconjunctivitis found that *Streptococcus parasanguinis* and *Gemella hemolysans* were more prevalent in those children, while the genera *Gemella* (including *G. sanguinis* and *G. hemolysans*), *Streptococcus* (including *S. mitis/dentisani*, *S. lactarius*, and *S. cristatus*), and *Alloprevotella* were associated with allergy development (Matsui et al., 2019). In a murine food allergy model, the diversity of oral commensal bacteria was reduced, and the salivary IgA level was significantly elevated (Ho et al., 2021). Moreover, IL-4, IL-5, and IL-13 levels in saliva are elevated in subjects with peanut allergy, which may be associated with *Veillonella* species (Mariman et al., 2016).

Future perspective

The review has experienced a renewed interest with the recognition that other than traditional therapies which alter oral microbial composition to cure disease, such as the use of antibiotics, the perspectives on immune response modulation are present, which develop prevention and treatment strategies for improving the efficacy. These two effects combined may beneficially affect disease treatment and this combined therapeutic strategy requires intensive research. Moreover, baseline immune cells are a good predictor of clinical response in patients before and after treatment. Studies of the immunotherapy of oral microbiome's effect on the immune response to oral and systematic diseases are worth pursuing.

Conclusion

This review provides an overview of the complex interactions triggered by the host immune response to the microorganisms in oral and systemic diseases (Supplementary Table). We note that microbial dysbiosis is not simply a common risk factor but triggers multiple microorganism-induced immunological mechanisms to promote disease onset and progression. Elucidation of the interactions will provide more meaningful guidance for future clinical applications. Research in this area is flourishing and in the coming years, more mechanisms and immunotherapies will be revealed.

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Author contributions

YL, WQ, YM, and YZ respectively summarized part of this review. YL and CD finalized the manuscript. FC and MC provided professional instruction. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmicb.2022.1009018/full#supplementary-material>

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