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Inflammatory Networks Linking Oral Microbiome with Systemic Health and Disease

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Abstract

The dance between microbes and the immune system takes place in all biological systems, including the human body, but this interaction is especially complex in the primary gateway to the body: the oral cavity. Recent advances in technology have enabled deep sequencing and analysis of members and signals of these communities. In a healthy state, the oral microbiome is composed of commensals, and their genes and phenotypes may be selected by the immune system to survive in symbiosis. These highly regulated signals are modulated by a network of microbial and host metabolites. However, in a diseased state, host-microbial networks lead to dysbiosis and considerable burden to the host prior to systemic impact that extends beyond the oral compartment. Interestingly, we presented data demonstrating similarities between human and mice immune dysbiosis and discussed how this affects the host response to similar pathobionts. The host and microbial signatures of a number of disease states are currently being examined to identify potential correlations. How the oral microbiome interacts with inflammation and the immune system to cause disease remains an area of active research. In this review, we summarize recent advancements in understanding the role of oral microbiota in mediating inflammation and altering systemic health and disease. In line with these findings, it is possible that existing conditions may be resolved by targeting specific immune-microbial markers in a positive way.

Keywords: inflammation, systems biology, cytokines, dysbiosis, resolution, interactome

Introduction

The oral cavity is a complex microbial ecosystem that provides the gateway to the human body. The human oral microbiome contains upward of 2,000 bacterial, archaeal, viral, and fungal species (Sampaio-Maia et al. 2016). The majority of oral microbiota are considered to be commensals, although the oral cavity can also harbor opportunistic pathobionts (Yumoto et al. 2019). There has been increased interest in the role of the microbiome in human disease with the completion of the Human Microbiome Project (Human Microbiome Project Consortium 2012). While the majority of microbiome research has initially focused on the gut microbiome, there has been increasing research into other regions, including the skin, vaginal, and oral microbiomes, as well as recent recognition of oral-systemic axes of crosstalk, including the oral-gut axis (Schmidt et al. 2019; Carr et al. 2020). Within the oral microbiome, there has been significant interest in the role of oral dysbiosis in causing disease. Indeed, dysbiosis of the oral host-microbiome has been associated with local diseases (e.g., dental caries, periodontitis; Belstrøm et al. 2017), oral cancers (Gholizadeh et al. 2016), and systemic disease, including Alzheimer's disease (Laugisch et al. 2018), preterm birth (Cobb et al. 2017), cardiovascular diseases (Mesa et al. 2019), and colorectal, pancreatic, and other cancers (Komiya et al. 2019; Chung et al. 2020).

Growing evidence suggests that dysbiotic inflammation precedes the development of chronic conditions through defective or exacerbated signaling networks. Inflammation is a protective response against infections and injury that ultimately promotes tissue repair and regeneration (Furman et al. 2019). The acute (or homeostatic) phase of the inflammatory response is carefully orchestrated and timed, where upregulation of activation mechanisms also triggers their resolution networks. However, low-grade inflammation that fails to resolve can progress to chronic inflammatory conditions, including periodontal, metabolic syndrome, cardiovascular, nonalcoholic fatty liver, chronic kidney, and autoimmune diseases. The prevalence of chronic inflammatory diseases is rising, representing an important threat to global health, and such diseases are the largest cause of death worldwide when combined, accounting for >50% of mortality (Roth et al. 2018). While the role of low-grade chronic inflammation has been increasingly recognized as being significant in the development of these comorbid noncommunicable diseases, we have yet to fully elucidate the exact inflammatory pathways that trigger or sustain this chronic inflammatory state.

The most common human chronic inflammatory diseases present in the oral cavity are gingivitis and periodontitis, which affect 42% of the US adult population (Eke et al. 2018). There is clear evidence indicating that host-microbiome dysbiosis affect oral diseases, including dental caries, periodontitis, and

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oral cancers (Curtis et al. 2011), with increasing evidence for a role in systemic disease (Konkel et al. 2019; Yumoto et al. 2019). However, the oral cavity maintains a robust microbiome in healthy individuals, and the exact mechanisms that trigger a shift to oral dysbiosis and disease remain unclear. As a mucosal barrier heavily exposed to various environmental stimuli, the oral cavity must maintain immune tolerance to its commensal microbiota and provide immune surveillance against possible microbial threats (Belkaid and Harrison 2017). This critical role of oral cavity immune surveillance has only recently been appreciated (Moutsopoulos and Konkel 2018; Konkel et al. 2019) and sheds light on the novel hypothesis of immune diversity in host-microbial commensalism, in which immune cells are highly heterogeneous. It continues to be debated how exactly changes in the oral microbiome reach the tipping point for disease; however, it is clear that an inflammatory immune response is involved (Curtis et al. 2011; Pan et al. 2019; Yumoto et al. 2019). Further mechanistic research is necessary to elucidate the directionality, to map the immune cell landscape, to understand how inflammation critically mediates the interplay between microbiome dysbiosis and disease, locally and systemically.

There has been recent progress in understanding the role of the oral microbiome in local and systemic disease. However, many unresolved questions remain, including how immune dysbiosis affects microbial community perturbations, whether inflammation is a result or cause of microbial dysbiosis, and whether host-microbial interactions in the oral cavity are similar to other mucosal environments or unique.

In this review, we critically examine the role of the oral microbiome in systemic human health and disease. We review current knowledge of oral homeostasis, inflammation, and its resolution, with emphasis on the role of oral immune dysbiosis in disease. We further focus on exciting new developments in the field, including utilizing multi-omic techniques to better assess the oral microbiome in health and disease and the potential to harness inflammation resolution to treat disease. In the midst of the COVID19 pandemic, the same virus (SARS-CoV-2) causes different diseases. Each individual presents unique levels of inflammation and dysbiotic networks toward the virus can aggravate, leading to death. Research focused on host repose and inflammatory networks is urgently needed.

Oral Homeostasis

In healthy individuals, the oral cavity exists in a carefully balanced state of homeostasis without inflammation (Belkaid and Harrison 2017; Caton et al. 2018). The oral cavity is a highly complex mucosal interface with varied environmental niches, each hosting its own microbial community, including the surfaces of the tongue, cheeks, palate, tonsils, and teeth (where oral biofilms can accumulate), as well as copious amounts of saliva (~750 mL/d in healthy individuals; Curtis et al. 2011). In addition to various microbial communities, immune cells are present in oral tissue, acting in routine surveillance. Neutrophils, monocytes, T lymphocytes (including Th17 cells), and B lymphocytes have been observed in healthy periodontal tissue alone; the transition to diseased tissues results in increased immune cell clonal expansion and abundance due to periphery cell migration from blood, including macrophages and dendritic cells (Graves et al. 2019; Konkel et al. 2019; Pan et al. 2019). The oral cavity is a place of enormous heterogeneity, from tissue composition to the microbiota to human immune cells—with each cell populations and subpopulations containing diverse members and interaction networks suited to particular niches, environments, and functions.

Inflammation and Resolution

Any environmental insult, including bacterial infection, trauma, and chemical cues, has the potential to elicit an inflammatory response (heat, pain, redness, swelling, and loss of function). Acute inflammation is protective for the host against infection or injury, involving an influx of immune cells, as well as migration, priming, cell activation, and synthesis of inflammatory mediators, such as proinflammatory cytokines (Feehan and Gilroy 2019). By nature, acute inflammation returns to homeostasis following resolution. Inflammation resolution is an active cellular process that includes removal of the inflammatory stimuli and involves specialized immunoresolvent mediators (e.g., resolvins, lipoxins, maresins, and protectins). These proresolution mediators bind to specific immune cell receptors as agonists, activating signaling, phagocytosis, and efferocytosis to resolve inflammation and restore tissue integrity and function (Serhan et al. 2008; Freire, Dalli, et al. 2017; Serhan and Levy 2018; Feehan and Gilroy 2019). Understanding the proresolution signals that restore the oral microbiome to its symbiotic (rather than dysbiotic) state may provide novel insights into host and microbial mechanisms of interaction in health and disease.

When cells fail to resolve acute inflammation to restore homeostasis, prolonged dysbiosis and low-grade unresolved inflammation develop, potentially leading to microbial changes in addition to chronic inflammatory disease complications. Chronic inflammation is mainly driven by delayed activity of innate immune cells, continuous challenge, and saturated response from the adaptive immune system. Neutrophils, normally present in periodontal tissues with sentinel capacity, are key immune cells for initial inflammation and its resolution, and neutrophil abnormalities—including impaired adhesion, cytokine signaling, and phagocytosis—are becoming increasingly recognized as being important to chronic inflammatory disease development (Alba-Loureiro et al. 2007; Curtis et al. 2011; Hotamisligil 2017; Serhan and Levy 2018; Feehan, Dalli, and Gilroy 2019). A recent transcriptomics study showed that chronic inflammation in type 2 diabetes correlated with reduced neutrophil gene expression as compared with healthy patients (Kleinstein et al. 2019), similar to observations in gut dysbiosis (Hunt et al. 2008). The main role of neutrophils in the inflammatory response is to clear tissue debris or microbes, which is partially completed by releasing neutrophil extracellular traps (NETs; Silvestre-Roig et al. 2019). NETs are primarily composed of decondensed neutrophil DNA, which is extruded from neutrophils to physically entangle bacteria, releasing antibacterial mole-

cules and eliciting a proinflammatory response (Silvestre-Roig et al. 2019).

Activation of inflammatory pathways is a complex and generalized host response, mediated by various immune cells and signaling molecules such as cytokines. As signaling molecules that are secreted by mononuclear phagocytes, antigen-presenting cells, lymphocytes, and neutrophils, cytokines control the phenotypes seen in the tissue milieu. The most well-established proinflammatory cytokines are in the IL-1, IL-6, and TNF families, which are secreted after pathogen introduction during the oral tissue responses (Pan et al. 2019). These cytokines can act in cascades to broadly activate inflammation further and specifically recruit immune cell subsets, including differentiating T and B cells. The recruitment of immune cells is key to control tissue cells—such as fibroblasts, osteoclasts, and osteoblasts—through activation of a key regulator, the NLRP3 inflammasome, and have been associated with oral and systemic diseases (García-Hernández et al. 2019; Konkel et al. 2019; Pan et al. 2019). Inflammasomes are part of inflammatory complexes that respond to pathogens or cellular damage by maturing proinflammatory cytokines, and inflammasomes represent a key component of the innate immune response (Tsai et al. 2020). As cytokines are secreted by and recruit immune cells, they can act in a feedback loop that amplifies inflammation until resolution halts the process. Importantly in periodontitis, proinflammatory cytokines, along with enzymes, can also result in tissue destruction, while some cytokines, including IL-11 and IL-27, have anti-inflammatory activity, though pro- or anti-inflammatory cytokine activity is often concentration or stimuli dependent (Pan et al. 2019). We have further data indicating that specific cytokine levels are increased in type 2 diabetes, a chronic inflammatory disease, relative to healthy states in humans and mice (Fig. 1). The effects of bacteria on cytokine production and immune modulation have been shown for a variety of inflammatory mediators and bacteria, including *Fusobacterium nucleatum* and *Porphyromonas gingivalis* (Table). Overall, the complex interaction of cytokines, feedback between pro- and anti-inflammatory circuitry, and exactly how this interplay contributes to disease is still emerging.

Figure 1. Dysbiotic inflammation is present in human and murine cytokine levels in disease (type 2 diabetes [T2D]). Original cytokine data are displayed to exemplify dysbiosis in the immune response, placing the host at risk of more aggressive microbial behavior. Mean levels (pg/mL) of 13 cytokines in mice (right side of circle, $n = 5$ healthy, $n = 5$ diabetic) and humans (left side of circle, $n = 5$ healthy, $n = 5$ diabetic). Health, green; type 2 diabetes, orange. Data show similar trends between human and mice cytokine levels, with higher expression among diseased versus healthy subjects. Radar lines mark 25 pg/mL; black bars show standard deviation.

Oral Microbiome and Inflammation

The correlation of oral microbiome dysbiosis with oral disease is well established: selected oral biofilms can lead to gingivitis, periodontitis, and peri-implantitis (Curtis et al. 2011; Freire, Devaraj, et al. 2017). Microbial dysbiosis in periodontal diseases is generally characterized by the oral microbiota being enriched for Gram-negative pathogenic bacteria expressing virulence factors, rather than Gram-positive commensal bacteria (Kirst et al. 2015; Lamont et al. 2018). Sokransky's "red complex" comprises a cluster of oral bacteria with pathogenic behavior (*P. gingivalis, Tannerella forsythia*, and *Treponema denticola*) that have been associated with pathogenic biofilm formation and periodontitis, though the exact triggers of disease conditions remain unclear, as these species have also been found in healthy oral sites at low levels (Byrne et al. 2009; Curtis et al. 2011; Bartold and Van Dyke 2019). Gingivitis and periodontitis involve inflammation of oral tissues; however, while inflammation in gingivitis is reversible, chronic signaling in periodontitis destroys tissues irreversibly (Caton et al. 2018). The mechanisms of progression from oral health to gingivitis to periodontitis and why some individuals never progress to severe forms of the disease remain to be fully elucidated, though evidence clearly indicates a complex network of interactivity between oral bacteria and the host immune system.

Increasingly, links have been established between oral pathogens and oral cancer (Gholizadeh et al. 2016). In particular, *F. nucleatum*, a Gram-negative obligate anaerobe, has been implicated in periodontitis and gingivitis (Teles et al. 2013), as well as in oral cancers (Han 2015; Holt and Cochrane 2017; Yost et al. 2018). More broadly, changes in relative microbial abundance in the oral microbiome, including the decrease of commensal *Rothia* and abundance of *Streptococcus*, have been linked to the development of oral cancer (Schmidt et al. 2014; Zhao et al. 2017). A handful of recent longitudinal studies have tried to assess the oral microbiome role in caries development, including that in the context of head and neck cancer (Xu et al. 2018; Mougeot et al. 2019; Kahharova et al. 2020). These microbial abundances demonstrate that ecologic changes are happening in healthy versus disease states, yet functional and longitudinal studies are needed to capture the metabolic complexity of the immune systems and host-microbiome interactions.

Oral Dysbiosis in Systemic Disease

In addition to its local impact, the role of periodontal disease in systemic disease risk is appreciated for chronic inflammatory diseases, such as diabetes (García-Hernández et al. 2019) and cardiovascular disease (Pietiäinen et al. 2018). Oral microbiota

Table. Examples of Inflammatory Mediators of Microbial-Induced Disease.

Marker	Bacteria	Function	Reference
		Immune activation: exacerbates disease	
IL-1β	*Aggregatibacter actinomycetemcomitans*	Inflammasome cytokine activation. Leukotoxin-induced macrophage cell death.	Kelk et al. (2011)
IL-18	*A. actinomycetemcomitans*	Inflammasome cytokine activation. Leukotoxin-induced macrophage cell death.	Kelk et al. (2011)
Th17	*A. actinomycetemcomitans*	Proinflammatory; immune evasion; promoted Th17 activation and induced atherosclerotic lesions	Jia et al. (2015)
IL-6	*Fusobacterium nucleatum*	FadA adhesin/invasin of *F. nucleatum* is a key virulence factor; implicated in oral infections, adverse pregnancy outcomes, gastrointestinal disorders, etc.	Han (2015)
IL-8	*F. nucleatum*	FadA adhesin/invasin of *F. nucleatum* is a key virulence factor; implicated in oral infections, adverse pregnancy outcomes, gastrointestinal disorders, etc.	Han (2015)
TNF-α	*F. nucleatum*	FadA adhesin/invasin of *F. nucleatum* is a key virulence factor; implicated in oral infections, adverse pregnancy outcomes, gastrointestinal disorders, etc.	Han (2015)
Th1	*Klebsiella pneumoniae, K. aeromobilis*	Proinflammatory; oral *Klebsiella* promoted Th1 proliferation and gut inflammation and disrupted tissue homeostasis (murine)	Atarashi et al. (2017)
IL-1β	*Porphyromonas gingivalis*	Proinflammatory; *P. gingivalis* enhanced expression/secretion; correlated with periodontitis; periodontitis treatment decreased IL-1β levels	Hamedi et al. (2009); Gilowski et al. (2014)
IL-17	*P. gingivalis*	Proinflammatory; produced in response to *P. gingivalis*; increased Th17 cells in mesenteric lymph nodes; aggravated articular injury in arthritis, arthritic bone destruction	de Aquino et al. (2014); Sato et al. (2017)
IL-18	*P. gingivalis*	Proinflammatory; *P. gingivalis* upregulated; stimulated MMP-8 production; leads to inflammatory bone loss	Johnson and Serio (2005); Hamedi et al. (2009)
IL-23	*P. gingivalis*	Proinflammatory; secreted by myeloid antigen-presenting cells in response to *P. gingivalis*; promoted Th17 pathogenicity, suppressed anti-inflammatory IL-10; associated with periodontal tissue damage	McGeachy et al. (2007); Himani et al. (2014)
IL-33	*P. gingivalis*	Proinflammatory; drove differentiation/polarization of myeloid and lymphoid cells; may induce alveolar bone destruction via RANKL	Malcolm et al. (2015); Tada et al. (2016); Tada et al. (2017)
IL-17	*Prevotella nigrescens*	Proinflammatory; produced in response to *P. nigrescens*; increased Th17 cells in mesenteric lymph nodes; aggravated articular injury in arthritis, arthritic bone destruction	de Aquino et al. (2014)
IFN-γ	*Streptococcus mutans*	*S. mutans* induced in the liver to exacerbate colitis/digestive disease	Kojima et al. (2012)
MMP-9	*S. mutans*	Induced MMP-9 expression to exacerbate cerebral hemorrhage in stroke	Nakano et al. (2011)
		Immune protective: promotes health	
MMP-3	*Lactobacillus casei*	Decreased neutrophil elastase and MMP-3 activities in GCF	Staab et al. (2009)
MPO	*L. casei*	Gingival inflammation was lower in the group consuming the probiotic product, as measured by MPO activity after a 4-d period of experimental gingivitis.	Staab et al. (2009)
scFV	*Lactobacillus paracasei*	Synthetic expression of functional scFV antibody binding to the surface of *P. gingivalis*; decreased *P. gingivalis*-related phenotypes	Marcotte et al. (2006)
IL-12	*P. gingivalis*	Anti-inflammatory; role in bacterial clearance; secreted by mononuclear phagocytes/dendritic cells; promoted IFN-γ production/Th1 differentiation; inhibited osteoclastogenesis/bone resorption	Horwood et al. (2001); Johnson and Serio (2005)
IL-37	*P. gingivalis*	Anti-inflammatory; Treg secretion suppressed NK cell function; can suppress osteoclast formation; downregulated in GCF of chronic periodontitis.	Offenbacher et al. (2018); Sarhan et al. (2018)
IFN-γ	*P. gingivalis*	Protective against *P. gingivalis* induced osteoclastogenesis / bone resorption.	Horwood et al. (2001)

Table sorted by immune function (exacerbating or ameliorating disease) and biological factor (marker).
GCF, gingival crevicular fluid; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; NK, natural killer; scFV, single-chain variable fragment; Th, T helper.

may contribute to systemic disease through several routes: 1) by entering the circulatory system via perturbed periodontal tissues (oral-blood axis), leading to bacteremia; 2) through aspiration that can lead to respiratory diseases (oral-vascular axis); or 3) through the oral-gut axis (Schmidt et al. 2019), where dislodged portions of oral biofilms make their way through the digestive system to the gut, protected in the biofilm from the acidic stomach environment (Konkel et al. 2019; Yumoto et al. 2019). These microbial perturbations may be the result of dental procedures or routine activities, such as brushing and flossing (Konkel et al. 2019), though these activities alone are not enough to cause disease in healthy individuals. In

fact, for disease causality, there must be an additional trigger, likely through oral dysbiosis and host inflammatory response interactions.

Several known oral bacteria have been implicated in systemic diseases. The periodontal pathogen *P. gingivalis* has been linked to cardiovascular diseases, lung disease, fetal loss, and rheumatoid arthritis, where local and systemic inflammation is suggested to act as the driving factor (Konkel et al. 2019). *F. nucleatum*, in addition to its role in bridging biofilms and in oral diseases, has been implicated in a range of systemic diseases, including gastrointestinal abscesses (George et al. 2016) and acute appendicitis (Swidsinski et al. 2011), intra-amniotic infection (Gauthier et al. 2011), colorectal cancers (Kelly et al. 2018; Brennan and Garrett 2019; Komiya et al. 2019), and pancreatic cancer (Mitsuhashi et al. 2015; Gaiser et al. 2019).

Oral streptococci are a common human commensal with >100 identified species, which are known to colonize early in life and act in initial microbiome development (Yumoto et al. 2019). However, *Streptococcus* pathogens are also opportunistic and play important roles in oral and systemic disease (Yumoto et al. 2019). Locally in the oral cavity, certain *Streptococcus* species have been associated with health, such as *S. salivarius*, while others were involved in dual health and disease states: *S. sanguinis, S. mitis, S. gordonii*, and *S. oralis* are considered common commensals that have been shown to be involved in initial biofilm formation and are associated with systemic disease risk (Yumoto et al. 2019). Other *Streptococcus* spp. have more clearly defined pathogenic roles: in particular, *Streptococcus mutans* can potentially degrade NETs to escape neutrophils and cause oral disease, from dental caries to cancer, as well as systemic diseases, including sepsis and endocarditis (Liu et al. 2017; Yumoto et al. 2019). Oral streptococci have been further associated with a range of systemic diseases—abscesses, arthritis, cardiovascular diseases, gastrointestinal diseases, and cerebrovascular diseases, among others—indicating their ability to survive, evade the immune system, and thrive throughout the body (Yumoto et al. 2019). Given the complex and often opposing roles of streptococci in health and disease, locally and systemically, it is clear that individual bacterial virulence factors (including adhesins, toxins, and colonization factors) and the host immune response, including inflammation, must play a role in disease development. Such study of specific organisms traditionally utilized defined culture systems to advance molecular knowledge. Unculturable bacteria represent a new field, and to capture the complexity of their immune functions, multi-omics techniques are needed.

Importantly, while periodontal diseases increase the risk of systemic diseases, the reverse is also true (Graves et al. 2019), indicating an ongoing interplay between inflammatory networks that signal through the tissues locally and systemically and that chronic immune dysfunction may also cause microbial dysbiosis (Figs. 2, 3). This dual increased risk between systemic and oral disease may be at least partially explained by the role of unresolved dysbiotic inflammatory networks in the development of a host of chronic inflammatory diseases across the body (e.g., the interplay of periodontitis and diabetes).

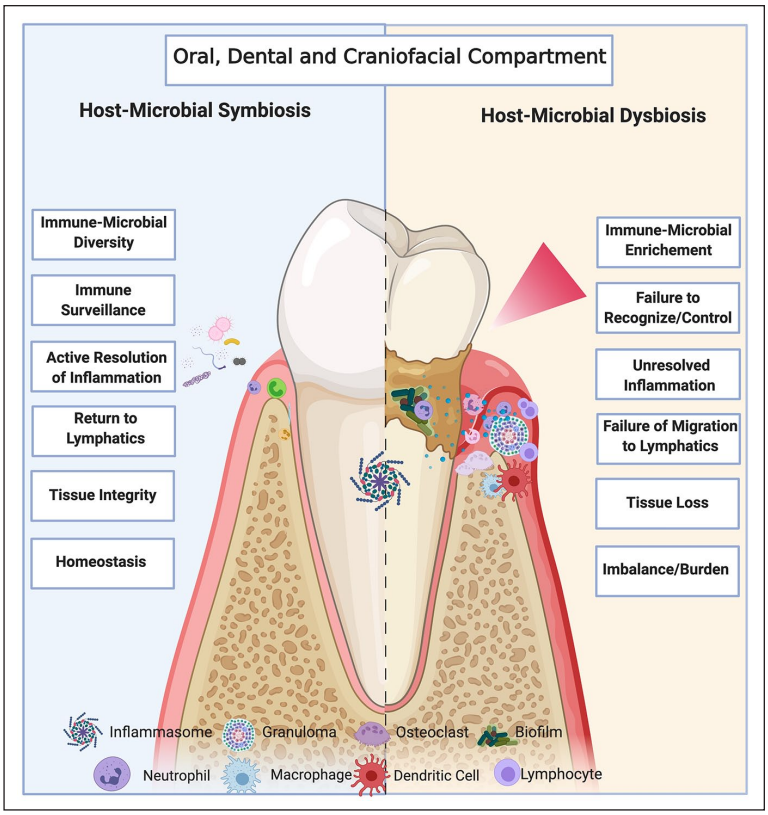

Figure 2. The oral microbiome interacts with host inflammatory networks, with oral dysbiosis inducing local disease. Schematic diagram of oral microbiome inflammatory interactions in health (left panel) and disease (right panel). In a healthy state, the oral microbiome and host immune system exist in a state of symbiosis, with commensal bacteria and sentinel host immune cells (neutrophils, inflammasomes) coexisting in oral tissue. This symbiosis is characterized by a diverse oral microbiome, with any inflammation (due to injury or insult) being acute and actively resolved to restore tissue integrity and homeostasis. However, should microbial dysbiosis occur, there is an enrichment of pathogenic over commensal bacteria and increased immune cell infiltration (neutrophils, macrophages, dendritic cells, other lymphocytes) in oral tissue, which can lead to biofilm and subsequent inflammasome formation. This failure to recognize or control bacterial dysbiosis, with immune cell infiltration, causes chronic low-grade inflammation, which can lead to tissue loss locally and systemic disease more broadly. Image created with BioRender.com.

Advances in Multi-omics Research of the Oral Microbiome

The capacity of multi-omics to expand scientific knowledge across fields is rapidly being appreciated. Interactions between human hosts and their microbiota are complex and require

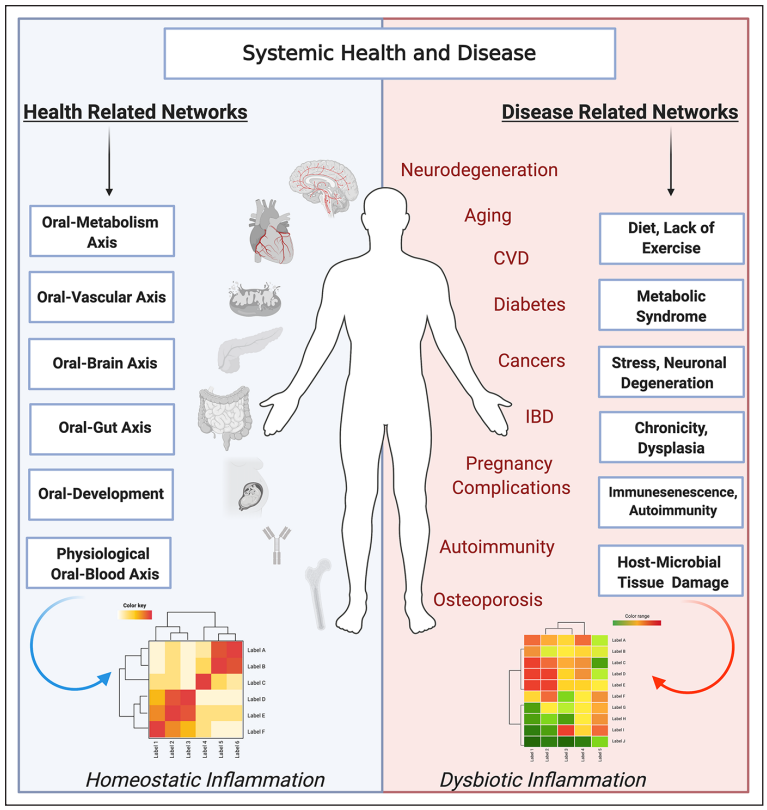

Figure 3. Dynamic interactions of the oral microbiome and host inflammatory networks play a role in oral dysbiosis and the oral impact on systemic diseases. The oral microbiome plays a key role in health and systemic disease. In a healthy state, homeostatic interactions of systemic and oral tissues lead to health. These driving factors affect systemic health through the oral-metabolism, oral-vascular, oral-brain, oral-gut, oral-development, and oral-blood axes. In contrast, oral dysbiosis can act through these axes to activate pathologic inflammatory networks, leading to chronic inflammation and, in conjunction with environmental factors, affecting systemic organs and aggravating systemic diseases, including diabetes, cardiovascular diseases, autoimmune diseases, age-related ailments, lung diseases, cancers, osteoporosis, pregnancy complications, and neurodegenerative diseases. Image created with BioRender.com. CVD, cardiovascular disease; IBD, inflammatory bowel disease.

novel multimodal techniques. Recent multi-omics investigations into periodontal diseases are helping to reveal microbial biofilm composition, including its role in disease-causing microbial dysbiosis and subsequent commensal restoration following dental treatments (Califf et al. 2017). In addition, such multi-omics research with 16S ribosomal RNA sequencing has greatly expanded available knowledge of the bacterial role in oral cancer (Robledo-Sierra et al. 2019).

Identification of bacteria has traditionally relied on laboratory culturing methods (which are limited by bacterial growth in available media and conditions) and sequencing of the bacterial 16S ribosomal RNA through universal primers and polymerase chain reaction. While 16S sequencing has greatly improved bacterial detection over traditional culturing methods, including that for the oral microbiome (Dewhirst et al. 2010), it remains difficult to detect low-abundance species, and it has limited ability to detect complex microbiome community interactions. Advances in sequencing technologies have enabled deep sequencing for more comprehensive bacterial detection in samples (Varoni et al. 2019), including identification of microbial communities in deep periodontal pockets (Curtis et al. 2011) and supragingival plaque biofilms (Espinoza et al. 2018). In addition, binary logistic regression prediction models to detect severe periodontitis provided increased reliability when combining biomarkers from an oral rinse (albumin, MMP-8, chitinase, protease) with a tailored self-reported oral health questionnaire (Verhulst et al. 2019). These noninvasive measures combined with multi-omic molecular measures provide an opportunity to enhance the accuracy of diagnosis and precision medicine and dentistry.

Meta-transcriptomics represents an opportunity to investigate the microbial composition and mRNA expression through microbial profiling at the individual species and community levels. A recent meta-transcriptomics study of the oral microbiome was able to identify an association with *F. nucleatum* and oral squamous cell carcinoma where *F. nucleatum* had higher overall numbers of transcripts in tumor sites (vs. healthy tissue), but microbial communities also expressed clear metabolic signatures in disease (including enrichment of chemotaxis, iron update, and protease activities), regardless of composition (Yost et al. 2018).

Meta-transcriptomics studies have also been recently applied to specific oral cavity regions, including investigating the saliva microbiome in healthy subjects (enriched for carbohydrate metabolism genes) as compared with those with dental disease (dental caries or periodontitis); *P. gingivalis* and *Filifactor alocis* were associated with periodontitis, while *S. mutans* and *Lactobacillus fermentum* were associated with caries, lending evidence to the pathogenic nature of these bacteria (Belstrøm et al. 2017). A study of *S. mutans* global transcriptomics with whole-genome microarrays showed differential gene expression during biofilm dispersal, including that of a key virulence nuclease (*deoC*; Liu et al. 2017). Studies such as these highlight the potential of functional meta-transcriptomics and multi-omics to tease apart the relative contributions of specific microbes, including disease progression and severity. Meta-transcriptomics research also provides functional information about commensal-pathobiont transitions, including expression levels of microbial virulence factors (e.g., O-antigens, leukotoxin, lipopolysaccharides, Fap2) and whether a specific taxon or multiple pathobionts will provide "disease" signals to the niche.

Host-Microbial Interactions: Inflammation and Disease

Microbial biofilms contain not only bacteria but also their products, including polysaccharides and proteins, as well as bacterial and host DNA (Yumoto et al. 2019). This extracellular host DNA (eDNA) is involved in biofilm formation,

maturation, and structural maintenance and has emerged as a potential drug target to treat pathogenic biofilms, as the exact quantity of eDNA is tightly regulated: a certain threshold is necessary for biofilm formation, but extremely high eDNA concentrations will cause the biofilm to collapse or detach (Okshevsky et al. 2015; Yumoto et al. 2019). While eDNA immunomodulation of the oral biofilm and other biofilm regions can ameliorate local microbial dysbiotic phenotypes, further research on its systemic effects are needed (Freire, Devaraj, et al. 2017; Devaraj et al. 2018). It is plausible to hypothesize that detachment of bacteria liberated from oral biofilms could cause secondary site infections through potential mechanisms, including resistomes within the oral-gut axis (Carr et al. 2020). This detached biofilm can be swallowed and affect the gut axis (Schmidt et al. 2019). Unraveling the molecular links of biofilm formation and stabilization with immune evasion is necessary to determine how to best co-opt this dispersion mechanism for the treatment of human disease.

Biofilm formation and eDNA incorporation are not the only mechanism that bacteria use to escape the host immune system. As experts at incorporating and modulating the host response, pathogenic oral bacteria, including *P. gingivalis* and *Aggregatibacter actinomycetemcomitans*, acquired the capability to "copy" host functions through molecular mimicry. For example, *A. actinomycetemcomitans* induced host citrullination, while pathogenic transitions of *P. gingivalis* demonstrated increased expression of citrullinated antigens, leading to autoantibody production via epigenetics in a mouse model (Konkel et al. 2019). The presence of these bacteria mimicking self-antigens has been proposed as being causal in autoimmune diseases such as rheumatoid arthritis, as well as potentially related to development of cardiovascular disease and pregnancy complications, where cross-reactive bacterial epitopes lead to aberrant immune responses (Konkel et al. 2019).

This interaction between bacteria and the host immune response is critical: it is now understood that host variation in inflammatory genes, including IL-17, can increase the risk of periodontitis and systemic diseases (Bedoya et al. 2013; Dutzan et al. 2018; Borilova Linhartova et al. 2019). Furthermore, we have shown evidence for dysregulation of neutrophil gene expression and cytokines in type 2 diabetes as compared with health (Kleinstein et al. 2019). Dissecting interaction between specific signals from bacteria and inflammation is key to understanding the development of chronic inflammatory diseases.

Further understanding the role of inflammation in microbial dysbiosis can provide relevant treatment options. As inflammation resolution is a natural process endogenously, recent research has investigated the possibility of treating inflammatory diseases (oral and systemic) with an exogenous dose of a proresolving small molecule lipid ligand mediator, such as resolvin E1 (Lee et al. 2016; Chiang et al. 2017; Werz et al. 2018). There is compelling evidence that treatment of inflammation with proresolving molecules can actually restore microbial commensalism from dysbiosis (Lee et al. 2016). Yet gaps remain in our mechanistic understanding of how host-microbial dysbiosis is dependent on each environmental compartment. It also remains unclear how inherited, acquired, or triggered dysbiotic resolution signals select for specific microbial and immune networks, acutely and chronically.

Conclusion

The microbiome is composed of a community of organisms that act synergistically and antagonistically. Research suggests that disruptions in the composition, quantity, and function of host-microbial networks result in local and systemic consequences. Evidence that the presence of a particular "keystone pathogen" drives most prevalent chronic oral diseases—rather than ecologic and functional dysbiosis linking local oral, dental, and craniofacial and systemic compartments—has proved questionable (Bartold and Van Dyke 2019). This highlights the limitations of our current knowledge, including the potential for spurious results in host-microbiome research, emphasizing the necessity of robust research and validation of associations. In this review, we have explored the role of inflammatory signals in linking oral microbial and immune dysbiosis to systemic human disease, which we believe acts as a critical component of this process. Chronic, low-grade, and unresolved inflammation has been shown to underlie the development of a variety of chronic inflammatory diseases across the body, including periodontal diseases, and this link is important for investigation. Many questions about the role of the oral microbiome in disease remain to be addressed, including fully elucidating whether disease is caused by community compositional changes, metabolites, or host-microbial networks and whether the oral dysbiosis is a cause or symptom of the underlying deficiency of resolution. Future research of the oral cavity microbiome and systemic axes as a whole (e.g., oral-brain, oral-gut, oral-respiratory, oral-blood vessels; Fig. 3) and specific oral surfaces (including expanded deep sequencing, multi-omics, and longitudinal studies) is critically needed to address the important role of host-microbiome network specificity and heterogeneity in health and disease.

Author Contributions

S.E. Kleinstein, contributed to conception, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; K.E. Nelson, contributed to design, critically revised the manuscript; M. Freire, contributed to conception and design, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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