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The Oral Microbiota Is Modified by Systemic Diseases

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Abstract

Periodontal diseases are initiated by bacteria that accumulate in a biofilm on the tooth surface and affect the adjacent periodontal tissue. Systemic diseases such as diabetes, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) increase susceptibility to destructive periodontal diseases. In human studies and in animal models, these diseases have been shown to enhance inflammation in the periodontium and increase the risk or severity of periodontitis. All 3 systemic diseases are linked to a decrease in bacterial taxa associated with health and an increase in taxa associated with disease. Although there is controversy regarding the specific oral bacterial changes associated with each disease, it has been reported that diabetes increases the levels of *Capnocytophaga, Porphyromonas*, and *Pseudomonas*, while *Prevotella* and *Selenomonas* are increased in RA and *Selenomonas, Leptotrichia*, and *Prevotella* in SLE. In an animal model, diabetes increased the pathogenicity of the oral microbiome, as shown by increased inflammation, osteoclastogenesis, and periodontal bone loss when transferred to normal germ-free hosts. Moreover, in diabetic animals, the increased pathogenicity could be substantially reversed by inhibition of IL-17, indicating that host inflammation altered the microbial pathogenicity. Increased IL-17 has also been shown in SLE, RA, and leukocyte adhesion deficiency and may contribute to oral microbial changes in these diseases. Successful RA treatment with anti-inflammatory drugs partially reverses the oral microbial dysbiosis. Together, these data demonstrate that systemic diseases characterized by enhanced inflammation disturb the oral microbiota and point to IL-17 as key mediator in this process.

Keywords: bacteria, biofilm, dysbiosis, periodontitis, periodontium, inflammation

Oral Microbiome in Health

The microbiome has a significant impact on the host, as germ-free mice have increased immune diseases, such as asthma and inflammatory bowel disease, indicating a dynamic relationship between them (Olszak et al. 2012). The oral microbiome includes bacteria, fungi, archaea, viruses, and protozoa (Dewhirst et al. 2010). The bacterial component is the best understood and is the focus of this review. The formation of dental plaque is affected by the mode of delivery (vaginal or caesarean), breast or bottle-feeding, and proximity to siblings and pets (Dewhirst et al. 2010). Bacteria can be found on all oral tissues, and there is overlap in the bacteria found on each. The most abundant bacteria are *Streptococcus oralis, Streptococcus mitis*, and *Streptococcus peroris*. Bacteria associated with periodontal health include *Streptococcus, Granulicatella, Neisseria, Haemophilus, Corynebacterium, Rothia, Actinomyces, Prevotella*, and *Capnocytophaga* (Segata et al. 2012). A biofilm forms on the tooth surface, initiated by a pellicle that promotes bacterial adhesion, with *Streptococcus* and *Actinomyces* as early colonizers (Socransky and Haffajee 2005). The latter facilitate formation of a multispecies biofilm that is spatially organized and depends on coaggregation among bacterial taxa (Socransky and Haffajee 2005). The subgingival biofilm is typically more anaerobic than the supragingival biofilm (Socransky et al. 1998).

Changes in the Oral Microbiota Caused by Periodontal Disease

In a National Health and Nutrition Examination Study, 47% of US adults had evidence of periodontitis, and 10% to 15% had advanced periodontitis (Kinane et al. 2017). Periodontal diseases are thought to result from opportunistic infections. The specific factors leading to changes in bacteria that cause periodontal diseases are unknown, although it is recognized that nonideal restorations, genetic conditions that alter the host response, and systemic diseases, such as diabetes and rheumatoid arthritis (RA), predispose to disease (Kinane et al. 2017). The relationships between the biofilm and the host immune response are dynamic, and the ecologic interactions between them determine local homeostasis or transition to a state of disease (Dewhirst 2010; Griffen 2012). Inflammation occurs when bacteria or their products encounter leukocytes in the

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epithelium or underlying connective tissue. Bacterial challenge leads to the migration of dendritic cells (DCs) to lymph nodes and gingival epithelium. A loss of DCs in experimental periodontitis or a decrease in DC function through lineage-specific gene deletion increases periodontal inflammation, receptor activator of nuclear factor kappa-B ligand (RANKL) expression, and bone loss (Xiao et al. 2015). Interestingly, reduced DC activity diminishes activation of lymphocytes and formation of antibodies and is linked to increased periodontal disease susceptibility (Xiao et al. 2015).

Periodontitis is associated with a shift in the bacterial community structure and composition (Dewhirst 2010; Diaz 2012; Griffen et al. 2012). A noticeable change in this equilibrium is quantitative, with an increased bacterial biomass with up to a 3-log increase in subgingival bacterial load in periodontitis subjects (Diaz 2012). Qualitative changes also occur as a result of competitiveness among species (Diaz 2012; Griffen et al. 2012), leading to an increase in bacterial taxa that are pathogenic. Thus, the dynamic balance among various bacterial taxa is likely to be instrumental in determining periodontal disease activity. Socransky and colleagues (1998) identified combinations of *Bacteroides forsythus, Porphyromonas gingivalis*, and *Treponema denticola* as being highly associated with clinical measures of periodontal disease. Fine and coworkers (2013) reported that a combination of *Aggregatibacter actinomycetemcomitans, Streptococcus parasanguinis*, and *Filifactor alocis* was associated with bone loss in localized aggressive periodontitis (Fine et al. 2013).

In gingivitis and periodontitis, there is likely to be an alteration in microbial composition or bacterial pathogenicity which is currently referred to as *microbial dysbiosis* (Roberts and Darveau 2015). Unlike many infectious diseases, periodontitis is initiated by bacteria that are likely already present, rather than by the introduction of an exogenous taxa. Putative periodontal pathogens are often found at healthy sites with no evidence of periodontal breakdown (Dewhirst 2010; Diaz 2012; Griffen et al. 2012). The composition of the microbiota is governed by local factors, but systemic factors can also have a significant effect. One mechanism is that systemic inflammatory diseases may increase local inflammation, which alters the expression of inflammatory mediators locally and increases recruitment of leukocytes to the periodontium (see Fig. 1). An alternative hypothesis that was popular in the mid-1900s and has some recent support postulates that an overall increase in microbial biomass, rather than a specific change in composition, may promote periodontitis. This is supported by increased bacterial loads in humans with periodontitis and in mice as they age and develop periodontitis, with increased susceptibility to colonization by periodontal pathogens such as *P. gingivalis* (Wu et al. 2016).

Changes in the Oral Microbiota Caused by Diabetes

Systemic diseases with increased inflammation are frequently linked to increased risk of periodontal disease (Jepsen et al. 2018). Increased levels of periodontal disease, diabetes, systemic lupus erythematosus (SLE), and RA may reflect a common susceptibility, since each has inflammation as a common risk factor. Those individuals with a greater tendency toward inflammation have enhanced susceptibility and risk of periodontitis as well as increased levels of diabetes, SLE, and RA. The increased inflammation in each of these diseases provides a common framework for altering the oral microbiota.

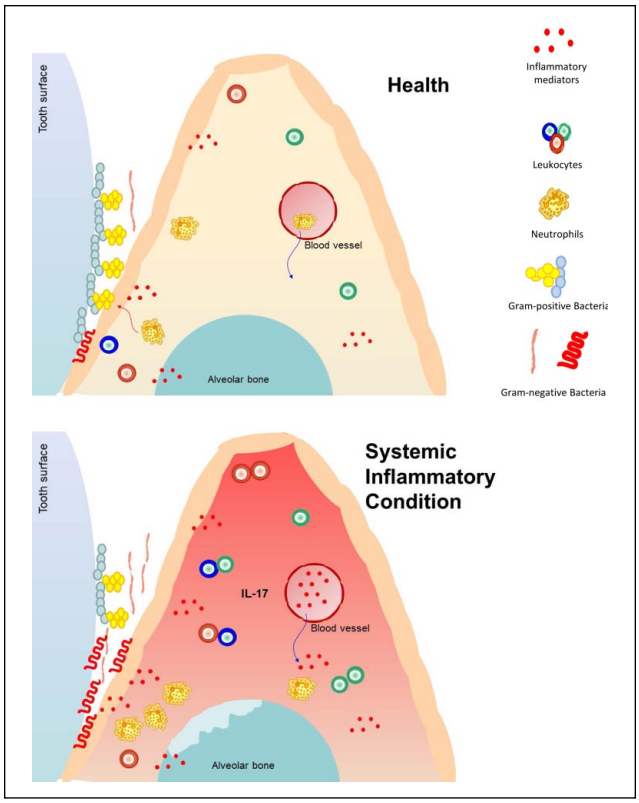

Figure 1. The impact of a systemic health condition on the periodontium and associated microbiota. In periodontal health there is little inflammation and gram-positive, aerobic species predominate. With a systemic inflammatory diseases associated with increased inflammation, there is a subsequent increase in periodontal inflammation, with recruitment of more inflammatory cells favoring colonization by facultative and anaerobic bacteria and gram-negative taxa. The change in bacteria may enhance inflammation.

Systemic diseases have a significant impact on periodontitis, with diabetes mellitus having one of the strongest linkages. Type 1 and type 2 diabetes mellitus (T1DM and T2DM) affect the periodontium in children and adults, with an increase in periodontal inflammation similar to the increased inflammation in other tissues affected by diabetes (Wu et al. 2015). Inoculation of the same bacterial load in the connective tissue of diabetic animals stimulates a greater inflammatory response compared with normoglycemic controls (Naguib et al. 2004). Diabetes potentially affects a number of factors that can enhance inflammation in periodontal tissues, including high glucose levels, increased formation of advanced glycation end products, and enhanced cytokine expression (e.g., tumor necrosis factor [TNF]; Wu et al. 2015). Neutrophils and monocytes/macrophages from diabetic patients express higher levels

of cytokines in response to stimulation and are less effective in bacterial killing (Omori et al. 2008). Diabetes also affects mesenchymal cells in the host, including periodontal ligament cells, osteoblasts, and osteocytes that increase RANKL expression, and reduce coupled bone formation following an episode of periodontal bone loss (Wu et al. 2015). Cause-and-effect relationships have been established showing that blocking advanced glycation endproduct (AGE) signaling reduces inflammatory cytokine levels (including TNF), matrix metalloproteinase expression, and periodontal bone loss (Lalla et al. 2000).

T1DM and T2DM are associated with similar complications, particularly those linked to increased inflammation, such as cardiovascular disease, impaired wound healing, neuropathy, nephropathy, and periodontal disease (Chapple et al. 2013; Wu et al. 2015). T1DM and T2DM increase the inflammatory response to the same bacterial challenge (Naguib et al. 2004; Graves et al. 2005). The increased periodontal inflammation observed in T1DM and T2DM has been implicated in periodontal tissue damage triggered by bacteria that colonize the tooth surfaces. An important question is whether the increased periodontal destruction in diabetic subjects is strictly due to an altered host response, whether there is a change in bacterial pathogenicity that leads to greater inflammation and damage, or both.

A consensus report from the European Federation of Periodontology and the American Academy of Periodontology found no compelling evidence that diabetes has a significant impact on the oral microbiota (Chapple et al. 2013). Thus, human studies examining the impact of diabetes in the oral microbiome have not provided conclusive evidence for a significant change or no change. Similarly, there is no consensus that T1DM induces a specific bacterial change as compared with T2DM. However, some studies do report diabetes-induced alterations in the oral microbiome. Examples of these bacterial changes include 1) increased *Capnocytophaga* in patients with diabetes mellitus (Mashimo et al. 1983); 2) increased *P. gingivalis* and *Tannerella forsythia* (Campus et al. 2005; da Cruz et al. 2008); and 3) increased *Capnocytophaga, Pseudomonas, Bergeyella, Sphingomonas, Corynebacterium, Propionibacterium*, and *Neisseria* in hyperglycemic individuals (Ganesan et al. 2017). Note that these results are often not consistent, as it has been reported that diabetes reduces *Porphyromonas, Filifactor, Eubacterium, Synergistetes, Tannerella*, and *Treponema* genera (Casarin et al. 2012). Thus, previous human studies have not revealed consistent changes in microbial composition, in part because of the limited numbers of bacteria surveyed. It has also been proposed that there are differences in overall oral microbiome in normoglycemic and diabetic subjects rather than between healthy and diseased sites in the same individual (Ganesan et al. 2017). Recent high-throughput analysis suggests that there may be differences between diabetic and normal cohorts, but there is yet no consensus on the changes induced, as shown in Table 1 (Casarin et al. 2012; Aemaimanan et al. 2013; Zhou et al. 2013; Merchant et al. 2014; Sakalauskiene et al. 2014; Castrillon et al. 2015; Demmer et al. 2016). There may be a number of potential reasons for a lack of consensus—including statistical reasons based on large numbers of oral microorganisms yielding false positives; insufficient subject numbers, which may contribute to false negatives; presence of confounding factors, including the degree of hyperglycemia, duration of disease, and medications; technical limitations, such as the lack of unbiased approaches to identify oral bacteria; and a limited number of longitudinal studies.

We carried out a longitudinal study in mice that spontaneously develop diabetes. The diabetes-prone and normoglycemic littermates initially had similar oral microbiomes. Development of hyperglycemia induced a shift in the bacterial composition (Xiao et al. 2017), increasing the levels of Proteobacteria (Enterobacteriaceae) and Firmicutes (*Enterococcus, Staphylococcus*, and *Aerococcus*) associated with pathologic changes (Demmer et al. 2016; Grice et al. 2010). Diabetes also reduced the diversity of oral microbiota as reported in other tissues where diabetes reduces bacterial diversity (Ussar et al. 2016). Interestingly, we have found that aging in mice also reduces oral bacterial diversity, which is accompanied by greater colonization of *P. gingivalis* when exposed to this human pathogen (Xiao et al. 2016).

Studies were undertaken to establish whether diabetes rendered the oral microbiota more pathogenic and to identify the potential mechanisms involved. To accomplish the former, the diabetic oral microbiota was transferred from diabetic hosts to normal germ-free mice and compared with the transfer of bacteria from normoglycemic donors to similar hosts. Transfer from hyperglycemic mice stimulated greater neutrophil infiltration and increased expression of bone-resorbing cytokines (IL-6 and RANKL), enhanced osteoclast numbers, and stimulated more periodontal bone loss than bacteria from normoglycemic controls. Inhibition of IL-17 altered the microbial composition in diabetic mice so that it was more similar to the normoglycemic oral microbiota and reduced the abundance of *Enterococcus* in particular. IL-17 inhibition decreased the capacity of bacteria from diabetic animals to stimulate inflammation and alveolar bone loss in normal germ-free recipients. We propose that chronic inflammation enhanced by diabetes causes microbial dysbiosis that increases bacterial pathogenicity (see Fig. 2). Inhibition of IL-17 could alter the microbiota by reducing inflammation, which in turn affects bacterial growth or colonization. This may occur as a result of reduced formation of substrates generated as a by-product of inflammation or, alternatively, by affecting antibacterial defenses (Curtis et al. 2011). Interestingly, high IL-17 levels are found in humans with periodontitis, and IL-17 induces RANKL (Abusleme and Moutsopoulos 2017). Leukocyte adhesion deficiency in humans results in greater IL-17 production and formation of dysbiotic bacterial communities, thereby identifying IL-17 as a cause of microbial dysbiosis (Abusleme and Moutsopoulos 2017). Similarly, patients with oral lichen planus have increased disease-associated bacterial species and increased IL-17 in saliva (Wang et al. 2014).

Table 1. Major Changes in Bacterial Community Associated with Diabetes, RA, or SLE.

Oral Bacterial Diversity		Oral Bacterial Biomass		Bacterial Changes Associated with Disease		Bacterial Changes Associated with Health	
Human	Animals	Humans	Animals	Humans	Animals	Humans	Animals
Effect of diabetes							
Reduced[a]; no change in alpha diversity[b]	Reduced[c]	Increased[d,e]	No change[c]	Increased 1) facultative bacteria in subjects with periodontitis, 2) anaerobes in subjects with no periodontitis,[a] and 3) disease-associated bacteria[f]	Increased disease-associated bacteria[c]	Reduced health-associated bacteria[a, f]	Reduced health-associated bacteria[c]
Effect of SLE							
Reduced[g]	No data	Increased[g]	No data	Increased disease-associated bacteria[g]	No data	Reduced abundance of health-associated bacteria[g]	No data
Effect of RA							
Increased[h]	No data	Increased[h]	Increased[i]	Increased disease-associated bacteria[h,j]	Increased anaerobes[k]	Reduced abundance of health-associated bacteria[h,j]	Reduced abundance of health-associated bacteria[k]

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
[a]Ganesan et al. (2017).
[b]de Groot et al. (2017).
[c]Xiao et al. (2017).
[d]Anbalagan et al. (2017).
[e]Coelho et al. (2018).
[f]Zhou et al. (2013).
[g]Corrêa et al. (2017).
[h]Corrêa et al. (2018, unpublished results).
[i]Queiroz-Junior et al. (2011).
[j]Zhang et al. (2015).
[k]Corrêa et al. (2016).

In skin wounds, diabetes alters the wound microbiota, which is linked to increased inflammation (Grice et al. 2010). Similarly, the gut microbiota changes with diabetes, which is subsequently altered when diabetes is reversed by bariatric surgery (Sweeney and Morton 2013). Moreover, when IL-17 was inhibited, the oral microbiota shifted in a direction of reduced pathogenicity and to a composition that was more similar to that of normoglycemic control animals (Xiao et al. 2017), suggesting that controlling inflammation increases the likelihood of having a "nonpathogenic" oral bacterial profile. Furthermore, there may be a bidirectional relationship between the gut microbiota and diabetes whereby 1) diabetes alters bacterial composition and 2) changes in bacterial profile enhance susceptibility to diabetes through a butyrate-mediated mechanism. Butyrate-producing bacteria are reduced in individuals with T2DM, and butyrate protects against the development of diabetes (Arora and Bäckhed 2016); thus, reduced production of butyrate may increase risk of diabetes. Oral bacteria may also have an impact on diabetes, although the evidence to support this link is limited. Oral administration of *P. gingivalis* coincides with the development of systemic inflammation and

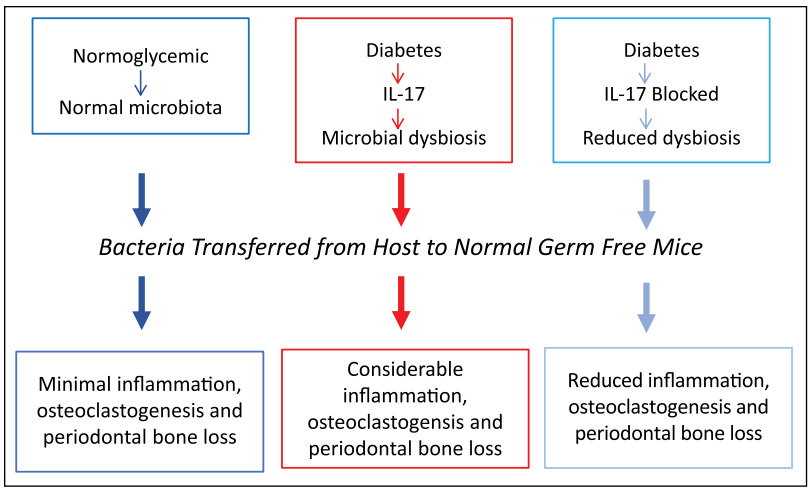

Figure 2. Diabetes induces microbial changes in a murine model. Diabetes increases IL-17 expression, leading to increased periodontal inflammation and a change in bacterial composition that is more pathogenic when transferred to a germ-free host as compared with a transfer from normoglycemic animals. Inhibition of IL-17 reduces the pathogenicity of the diabetic microbiota (for details, see Xiao et al. 2017).

onset of insulin resistance in mice (Arimatsu et al. 2014). The increased systemic inflammation may be linked to a reduction in barrier function in the intestine caused by oral inoculation of *P. gingivalis* (Sato et al. 2017). Oral bacteria may contribute to a bidirectional relationship between periodontal disease and diabetes, whereby changes in the oral microbiota through increased systemic inflammation enhance insulin resistance to promote hyperglycemia (as discussed by Borgnakke et al. 2013).

Changes in the Oral Microbiota Caused by Rheumatoid Arthritis

RA is a systemic autoimmune disease characterized by chronic inflammation (de Smit et al. 2015). Periodontal disease and RA share some pathogenic mechanisms, including enhanced inflammation and bone loss. Increased prevalence of periodontitis is observed in patients with RA (de Smit et al. 2015). There is also evidence that periodontitis can initiate RA by the production of enzymes that form malondialdehyde-acetaldehyde, citrullinated and carbamylated adducts that enhance self-antigenicity to initiate an autoimmune response (de Smit et al. 2015). We and others have shown that experimental arthritis in rodents promotes alveolar bone loss (Ramamurthy et al. 2005; Queiroz-Junior et al. 2011; Corrêa et al. 2016; Kim et al. 2017). Treatment with oral antiseptics that reduce the total oral bacterial load protects against RA-induced periodontal bone loss, indicating a role for oral microbiota (Queiroz-Junior et al. 2011). The data are consistent with a "2-hit" model, in which one hit represents the oral microbiota and the second hit the impact of the systemic disease on the local inflammation. RA may amplify the inflammatory response in the periodontium, which in turn modifies the microbiota (Golub et al. 2006). Chronic systemic inflammation in RA may affect levels of inflammatory cytokines in oral tissues (Mirrielees et al. 2010). RA in rodents increases the expression of inflammatory cytokines in the periodontium, such as TNF-α, IL-1, IL-6, and IL-17 (Queiroz-Junior et al. 2011). RA subjects also show increased salivary concentration of IL-17, TNF-α, and IL-33 (Corrêa et al. 2018, unpublished results) similar to observations in SLE (Corrêa et al. 2017). It is noteworthy that studies examining other diseases showed a link between IL-17 and disturbances in the microbiota, such as LAD-1 (leukocyte adhesion deficiency 1) and oral lichen planus (Moutsopoulos et al. 2014; Wang et al. 2014).

RA alters the oral microbiome qualitatively and quantitatively in animal studies. Mice with RA exhibit higher levels of *Parvimonas micra, Selenomonas noxia*, and *Veionella parvula* (Corrêa et al. 2016). In humans, the RA-associated microbiome is substantially different from that of healthy controls. Anaerobic species such as *Lactobacillus salivarius, Atopobium, Leptotrichia, Prevotella*, and *Cryptobacterium curtum* are enriched in the oral microbiota of RA patients, and health-associated *Corynebacterium* and *Streptococcus* genera are reduced (Scher et al. 2012; Zhang et al. 2015). We also found that RA increases the microbial biomass approximately 1-log and alters the composition with increased numbers of pathogenic bacteria (Corrêa et al. 2018, unpublished results). RA patients without periodontitis have an enrichment in periodontitis-associated bacteria, such as *Prevotella* (e.g., *P. melaninogenica, P. denticola, P. histicola, P. nigrescens, P. oulorum*, and *P. maculosa*), and other pathogenic species (*S. noxia, S. sputigena*, and *Anaeroglobus geminatus*) (Corrêa et al. 2018, unpublished data). In addition, RA subjects have a reduction of health-associated species (*Streptococcus, Rothia aeria, Kingella oralis, Haemophilus*, and *Actinomyces*) (Corrêa et al. 2018, unpublished data). These data are summarized in Table 2.

The microbial composition of the gut in early RA differs from controls, with a reduction of *Bifidobacterium* and *Bacteroides* and an increase in *Prevotella* (Horta-Baas et al. 2017). Similarly, *Prevotella* species are also enriched in the saliva (Zhang et al. 2015) and subgingival microbiota (Corrêa et al. 2018, unpublished) of RA subjects. Interestingly, *Prevotella copri* has a high capacity to induce Th17-related cytokines, and *Prevotella* sp. is associated with Th17-mediated mucosal inflammation (Larsen 2017).

The increased levels of inflammatory mediators in the periodontal tissues of subjects with RA and other diseases may change the ecologic conditions to favor pathogenic bacterial species and promote periodontitis (Abusleme and Moutsopoulos 2017). Inflamed subgingival sites, which exhibit a low redox potential, support a microbial community with higher proportions of obligate anaerobic bacteria (Dewhirst 2010; Diaz 2012; Griffen et al. 2012). Local inflammation enhanced by systemic disease may change the microbial composition toward one that is adapted to an inflammatory environment and more capable of inducing inflammation. The increased inflammation caused by RA coupled with microbial changes may amplify periodontal inflammation and explain the greater susceptibility to periodontitis that we and others have observed in these patients (de Smit et al. 2015). Therefore, changes in systemic and local inflammation may disrupt microbial homeostasis and consequently increase bacterial pathogenicity and periodontal disease susceptibility (see Table 1). Conversely, RA treatment improves periodontal status and affects the oral microbiome (Zhang et al. 2015). Disease-modifying antirheumatic drugs reduce inflammation and the severity of RA, and alter the gut and oral microbiota (Zhang et al. 2015). For example, bacteria that are associated with oral health as *Prevotella maculosa* are increased after RA treatment. These results suggest that controlling inflammation can shift the microbiota to a "healthy status," restoring systemic and oral/periodontal homeostasis.

Oral Microbiota and SLE

SLE is an autoimmune disease characterized by persistent inflammation that leads to tissue damage in multiple organs, including kidneys, lungs, joints, heart, and brain. The etiology of SLE includes genetic and environmental factors (López et al. 2016) and is linked to microbial dysbiosis (Hevia et al. 2014; López et al. 2016; Corrêa et al. 2017).

Table 2. Specific Changes in the Bacterial Community Associated with Diabetes, RA, or SLE.

Genera		
Elevated in Human Diabetes	Elevated in Human SLE	Elevated in Human RA
Capnocytophaga, Pseudomonas, Bergeyella, Sphingomonas, Corynebacterium, Propionibacterium, and *Neisseria*[a]	*Prevotella oulorum, P. nigrescens, P. oris, Selenomonas noxia, Leptotrichia*, and *Lachnospiraceae*[b]	*Lactobacillus salivarius, Atopobium*, and *Cryptobacterium curtum*[c]
Streptococcus, Actinomyces, and *Rothia*[d]		*Leptotrichia* and *Prevotella*[e]
Prevotella, Tannerella, and *Pseudomonas*[f]		*Prevotella* (e.g., *P. melaninogenica, P. denticola, P. histicola, P. nigrescens, P. oulorum, P. maculosa*), *Selenomonas noxia, S. sputigena*, and *Anaeroglobus geminatus*[g]
TM7, Aggregatibacter, Neisseria, Gemella, Eikenella, Selenomonas, Actinomyces, Capnocytophaga, Fusobacterium, Veillonella, and *Streptococcus*[h]		
Reduced in Human Diabetes	Reduced in Human SLE	Reduced in Human RA
Actinomyces, Atopobium, Bifidobacterium, Scardovia, Atopobium, Corynebacterium, and *Rothia*[i]	*Capnocytophaga, Rothia, Haemophilus parainfluenzae*, and *Streptococcus*[b]	*Corynebacterium, Streptococcus*, and *Haemophilus*[c]
Porphyromonas, Filifactor, Eubacterium, Synergistetes, Tannerella, and *Treponema*[h]		*Streptococcus, Rothia aeria, Kingella oralis, Haemophilus*, and *Actinomyces*[g]

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
[a]Ganesan et al. (2017).
[b]Corrêa et al. (2017).
[c]Zhang et al. (2015).
[d]de Groot et al. (2017).
[e]Scher et al. (2012).
[f]Zhou et al. (2013).
[g]Corrêa et al. (2018, unpublished results).
[h]Casarin et al. (2012).
[i]Long et al. (2017).

In the oral cavity, the manifestations of SLE include unspecified oral ulcers (Jensen et al. 1999), xerostomia, hyposalivation (Jensen et al. 1999), and increased periodontal disease (Mutlu et al. 1993; Kobayashi et al. 2003; Corrêa et al. 2017). In a meta-analysis, a 1.76-fold increased risk of periodontal disease in SLE subjects was reported (Rutter-Locher et al. 2017). The increased risk is associated with changes in local and systemic inflammatory pathways, as demonstrated by elevated levels of cytokines (e.g., IL-6, IL-17, and IL-33) in the saliva of SLE patients (Marques et al. 2016; Corrêa et al. 2017; Mendonça et al. 2018). The inflammatory changes have been linked to dysbiosis of the subgingival biofilm in SLE subjects, as described in Figure 1. These observations are based on human studies. However, functional studies linking specific microbiota disturbances and inflammatory pathways with periodontal damage in SLE have not been reported as they have been for diabetes (Xiao 2017).

It was demonstrated that SLE patients have a higher bacterial load as compared with healthy subjects (Jensen et al. 1999; Corrêa et al. 2017) with an altered bacterial composition. High counts of *Lactobacilli* and *Candida albicans* are found in the oral cavity of SLE patients versus controls (Jensen et al. 1999). SLE subjects have reduced microbial diversity with greater proportions of pathogenic bacteria (Corrêa et al. 2017). Bacteria associated with periodontal disease, including *Prevotella oulorum, P. nigrescens, P. oris, S noxia, Leptotrichia*, and *Lachnospiraceae*, are elevated in SLE subjects, even in periodontally healthy sites (Corrêa et al. 2017). In addition, bacteria commonly associated with periodontal health, such as *Capnocytophaga, Rothia, Haemophilus parainfluenzae*, and *Streptococcus*, are diminished in SLE patients with periodontitis. Changes in the microbiota in SLE patients are summarized in Tables 1 and 2. Moreover, the presence of pathogenic bacteria is positively correlated with the level of systemic inflammation, measured by serum C-reactive protein (Corrêa et al. 2017). Overall, a worsening periodontal condition is correlated with systemic inflammation (Corrêa et al. 2017). In line with these findings, periodontal treatment improves the response to conventional therapy in SLE patients with a reduction of disease activity (Fabbri et al. 2014). Increased inflammation may provide a source of nutrients in the form of tissue breakdown products and may alter the environment, favoring the growth of anaerobic bacteria (Hajishengallis 2014). In turn, changes in the microbiota might be important to amplify local inflammation and periodontal tissue damage, worsening the impact of the systemic disease on periodontal health. Taken together, these data highlight the connection between the microbiota and SLE and suggest that reduced inflammation will promote the formation of a less pathogenic oral microbial profile.

Changes in the gut microbiome in SLE patients have been reported and are reflected by increased diversity compared with healthy individuals (Hevia et al. 2014; López et al. 2016). Lupus-prone mice have depleted lactobacilli and an increase in Clostridial species (Lachnospiraceae) associated with an overall increase in bacterial diversity (Zhang et al. 2014; Mu et al. 2017). As a proof of concept, increasing Lactobacillales in the

gut of mice by adding a mixture of 5 *Lactobacillus* strains led to an improvement of SLE severity and prolonged survival (Mu et al. 2017). In line with these results, the relative abundance of Lactobacillales seems to be restored in SLE patients without active disease (Hevia et al. 2014).

Concluding Remarks

Systemic diseases may share common risk factors that lead to an increased inflammatory response when there is an interruption in equilibrium. For example, the host response to oral bacteria may be altered by systemic diseases such as diabetes, RA, SLE, and LAD-1 so that the degree of inflammation induced is greater than it would be in normal conditions. The local periodontal inflammation may in turn alter the competition among bacterial species by affecting nutrient availability or redox potential and/or altering gene expression within a bacterial community. These changes may then enhance the pathogenicity of the microbiota to further activation of the inflammatory pathways. IL-17 and other cytokines may play a pivotal role in this process. Microbial changes observed in systemic diseases generally reduce microbial diversity and shift bacterial composition by increasing taxa that are generally considered to be "bad" and reducing those that are "good" (see Table 1). However, the assignment to "good" and "bad" categories is an oversimplification and needs to be experimentally justified, as recently reported for murine diabetic studies (Xiao et al. 2017). Furthermore, it is widely recognized that several systemic diseases cause increased periodontal inflammation with the assumption that the primary component was a straightforward upregulation of pro-osteoclastogenic factors (Xiao et al. 2016). However, this may be an oversimplification, as the inflammatory changes may induce an amplification loop in which the bacterial component becomes more pathogenic. We propose that a central mechanism for altering the microbiota is increased IL-17. We also recognize that IL-17 operates in concert with other inflammatory cytokines and that an overall dysregulation of these mediators may contribute to host alterations that lead to microbial dysbiosis. This concept and the downstream events that specifically alter the composition or behavior (gene expression) of bacteria need further investigation to render this hypothesis more precise.

Author Contributions

D.T. Graves, contributed to conception, design, and data interpretation, drafted and critically revised the manuscript; J.D. Corrêa, T.A. Silva, contributed to design and data interpretation, 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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References

Abusleme L, Moutsopoulos NM. 2017. IL-17: overview and role in oral immunity and microbiome. Oral Dis. 23(7):854–865.

Aemaimanan P, Amimanan P, Taweechaisupapong S. 2013. Quantification of key periodontal pathogens in insulin-dependent type 2 diabetic and non-diabetic patients with generalized chronic periodontitis. Anaerobe. 22:64–68.

Anbalagan R, Srikanth P, Mani M, Barani R, Seshadri KG, Janarthanan R. 2017. Next generation sequencing of oral microbiota in type 2 diabetes mellitus prior to and after neem stick usage and correlation with serum monocyte chemoattractant-1. Diabetes Res Clin Pract. 130:204–210.

Arimatsu K, Yamada H, Miyazawa H, Minagawa T, Nakajima M, Ryder MI, Gotoh K, Motooka D, Nakamura S, Iida T, et al. 2014. Oral pathobiont induces systemic inflammation and metabolic changes associated with alteration of gut microbiota. Sci Rep. 4:4828.

Arora T, Bäckhed F. 2016. The gut microbiota and metabolic disease: current understanding and future perspectives. J Intern Med. 280(4):339–349.

Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. 2013. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. J Periodontol. 84(4):S135–S152.

Campus G, Salem A, Uzzau S, Baldoni E, Tonolo G. 2005. Diabetes and periodontal disease: a case-control study. J Periodontol. 76(3):418–425.

Casarin R, Barbagallo A, Meulman B, Santos V, Sallum E, Nociti F, Duarte P, Casati M, Gonçalves R. 2012. Subgingival biodiversity in subjects with uncontrolled type-2 diabetes and chronic periodontitis. J Periodontal Res. 48(1):30–36.

Castrillon CA, Hincapie JP, Yepes FL, Roldan N, Moreno SM, Contreras A, Botero JE. 2015. Occurrence of red complex microorganisms and *Aggregatibacter actinomycetemcomitans* in patients with diabetes. J Investig Clin Dent. 6(1):25–31.

Chapple ILC, Genco R; Working Group 2 of Joint EFP/AAP Workshop. 2013. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol. 40 Suppl 14:S106–S112.

Coelho A, Paula A, Mota M, Laranjo M, Abrantes M, Carrilho F, Ferreira M, Silva M, Botelho F, Carrilho E. 2018. Dental caries and bacterial load in saliva and dental biofilm of type 1 diabetics on continuous subcutaneous insulin infusion. J Appl Oral Sci. 26:e20170500.

Corrêa JD, Calderaro DCDC, Ferreira GA, Mendonça SMS, Fernandes GR, Xiao E, Teixeira ALAL, Leys EJ, Graves DT, Silva TATATA, et al. 2017. Subgingival microbiota dysbiosis in systemic lupus erythematosus: association with periodontal status. Microbiome. 5(1):34.

Corrêa JD, Saraiva AM, Queiroz-Junior CM, Madeira MF, Duarte PM, Teixeira MM, Souza DG, da Silva TA. 2016. Arthritis-induced alveolar bone loss is associated with changes in the composition of oral microbiota. Anaerobe. 39:91–96.

Curtis MA, Zenobia C, Darveau RP. 2011. The relationship of the oral microbiotia to periodontal health and disease. Cell Host Microbe. 10(4):302–306.

da Cruz GA, de Toledo S, Sallum EA, Sallum AW, Ambrosano GM, de Cássia Orlandi Sardi J, da Cruz SE, Gonçalves RB. 2008. Clinical and laboratory evaluations of non-surgical periodontal treatment in subjects with diabetes mellitus. J Periodontol. 79(7):1150–1157.

de Groot PF, Belzer C, Aydin Ö, Levin E, Levels JH, Aalvink S, Boot F, Holleman F, van Raalte DH, Scheithauer TP, et al. 2017. Distinct fecal and oral microbiota composition in human type 1 diabetes, an observational study. PLoS One. 12:e0188475

Demmer RT, Breskin A, Rosenbaum M, Zuk A, LeDuc C, Leibel R, Paster B, Desvarieux M, Jacobs DR Jr, Papapanou PN. 2016. The subgingival microbiome, systemic inflammation and insulin resistance: the Oral Infections, Glucose Intolerance and Insulin Resistance Study. J Clin Periodontol. 44(3):255–265.

de Smit MJ, Westra J, Brouwer E, Janssen KM, Vissink A, van Winkelhoff AJ. 2015. Periodontitis and rheumatoid arthritis: what do we know? J Periodontol. 86(9):1013–1019.

Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, Lakshmanan A, Wade WG. 2010. The human oral microbiome. J Bacteriol. 192(19):5002–5017.

Diaz PI. 2012. Microbial diversity and interactions in subgingival biofilm communities. Front Oral Biol. 15:17–40.

Fabbri C, Fuller R, Bonfá E, Guedes LK, D'Alleva PS, Borba EF. 2014. Periodontitis treatment improves systemic lupus erythematosus response to immunosuppressive therapy. Clin Rheumatol. 33(4):505–509.

Fine DH, Markowitz K, Fairlie K, Tischio-Bereski D, Ferrendiz J, Furgang D, Paster BJ, Dewhirst FE. 2013. A consortium of *Aggregatibacter actinomycetemcomitans, Streptococcus parasanguinis*, and *Filifactor alocis* is present in sites prior to bone loss in a longitudinal study of localized aggressive periodontitis. J Clin Microbiol. 51(9):2850–2861.

Ganesan SM, Joshi V, Fellows M, Dabdoub SM, Nagaraja HN, O'Donnell B, Deshpande NR, Kumar PS. 2017. A tale of two risks: smoking, diabetes and the subgingival microbiome. ISME J. 11(9):2075–2089.

Golub LM, Payne JB, Reinhardt RA, Nieman G. 2006. Can systemic diseases co-induce (not just exacerbate) periodontitis? A hypothetical "two-hit" model. J Dent Res. 85(2):102–105.

Graves DT, Naguib G, Lu H, Leone C, Hsue H, Krall E. 2005. Inflammation is more persistent in type 1 diabetic mice. J Dent Res. 84(4):324–328.

Griffen AL, Beall CJ, Campbell JH, Firestone ND, Kumar PS, Yang ZK, Podar M, Leys EJ. 2012. Distinct and complex bacterial profiles in human periodontitis and health revealed by 16S pyrosequencing. ISME J. 6(6):1176–1185.

Grice EA, Snitkin ES, Yockey LJ, Bermudez DM; NISC Comparative Sequencing Program, Liechty KW, Segre JA. 2010. Longitudinal shift in diabetic wound microbiota correlates with prolonged skin defense response. Proc Natl Acad Sci U S A. 107(33):14799–14804.

Hajishengallis G. 2014. The inflammophilic character of the periodontitis-associated microbiota. Mol Oral Microbiol. 29(6):248–257.

Hevia A, Milani C, López P, Cuervo A, Arboleya S, Duranti S, Turroni F, González S, Suárez A, Gueimonde M, et al. 2014. Intestinal dysbiosis associated with systemic lupus erythematosus. MBio. 5(5):1–10.

Horta-Baas G, Romero-Figueroa MDS, Montiel-Jarquín AJ, Pizano-Zárate ML, García-Mena J, Ramírez-Durán N. 2017. Intestinal dysbiosis and rheumatoid arthritis: a link between gut microbiota and the pathogenesis of rheumatoid arthritis. J Immunol Res. 2017:4835189.

Jensen JL, Bergem HO, Gilboe IM, Husby G, Axéll T. 1999. Oral and ocular sicca symptoms and findings are prevalent in systemic lupus erythematosus. J Oral Pathol Med. 28(7):317–322.

Jepsen S, Caton JG, Albandar JM, Bissada NF, Bouchard P, Cortellini P, Demirel K, de Sanctis M, Ercoli C, Fan J, et al. 2018. Periodontal manifestations of systemic diseases and developmental and acquired conditions: consensus report of workgroup 3 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 45 Suppl 20:S219–S229.

Kim D, Lee G, Huh YH, Lee SY, Park KH, Kim S, Kim J, Koh J, Ryu J. 2017. NAMPT is an essential regulator of RA-mediated periodontal inflammation. J Dent Res. 96(6):703–711.

Kinane DF, Stathopoulou PG, Papapanou PN. 2017. Periodontal diseases. Nat Rev Dis Prim. 3:17038.

Kobayashi T, Ito S, Yamamoto K, Hasegawa H, Sugita N, Kuroda T, Kaneko S, Narita I, Yasuda K, Nakano M, et al. 2003. Risk of periodontitis in systemic lupus erythematosus is associated with Fcgamma receptor polymorphisms. J Periodontol. 74(3):378–384.

Lalla E, Lamster IB, Feit M, Huang L, Spessot A, Qu W, Kislinger T, Lu Y, Stern DM, Schmidt AM. 2000. Blockade of RAGE suppresses periodontitis-associated bone loss in diabetic mice. J Clin Invest. 105(8):1117–1124.

Larsen JM. 2017. The immune response to Prevotella bacteria in chronic inflammatory disease. Immunology. 151(4):363–374.

Long J, Cai Q, Steinwandel M, Hargreaves MK, Bordenstein SR, Blot WJ, Zheng W, Shu XO. 2017. Association of oral microbiome with type 2 diabetes risk. J Periodontal Res. 52:636–643.

López P, de Paz B, Rodríguez-Carrio J, Hevia A, Sánchez B, Margolles A, Suárez A. 2016. Th17 responses and natural IgM antibodies are related to gut microbiota composition in systemic lupus erythematosus patients. Sci Rep. 6:24072.

Marques CP, Victor EC, Franco MM, Fernandes JM, Maor Y, de Andrade MS, Rodrigues VP, Benatti BB. 2016. Salivary levels of inflammatory cytokines and their association to periodontal disease in systemic lupus erythematosus patients: a case-control study. Cytokine. 85:165–170.

Mashimo PA, Yamamoto Y, Slots J, Park BH, Genco RJ. 1983. The periodontal microflora of juvenile diabetics: culture, immunofluorescence, and serum antibody studies. J Periodontol. 54(7):420–430.

Mendonça SMS, Corrêa JD, Souza AF, Travassos DV, Calderaro DC, Rocha NP, Vieira ÉLM, Teixeira AL, Ferreira GA, Silva TA. 2018. Immunological signatures in saliva of systemic lupus erythematosus patients: influence of periodontal condition. Clin Exp Rheumatol [epub ahead of print 19 Jul 2018] in press.

Merchant AT, Shrestha D, Chaisson C, Choi YH, Hazlett LJ, Zhang J. 2014. Association between serum antibodies to oral microorganisms and hyperglycemia in adults. J Dent Res. 93(8):752–759.

Mirrielees J, Crofford LJ, Lin Y, Kryscio RJ, Dawson DR 3rd, Ebersole JL, Miller CS. 2010. Rheumatoid arthritis and salivary biomarkers of periodontal disease. J Clin Periodontol. 37(12):1068–1074.

Moutsopoulos NM, Konkel J, Sarmadi M, Eskan MA, Wild T, Dutzan N, Abusleme L, Zenobia C, Hosur KB, Abe T, et al. 2014. Defective neutrophil recruitment in leukocyte adhesion deficiency type I disease causes local IL-17-driven inflammatory bone loss. Sci Transl Med. 6(229):229ra40.

Mu Q, Zhang H, Liao X, Lin K, Liu H, Edwards MR, Ahmed SA, Yuan R, Li L, Cecere TE, et al. 2017. Control of lupus nephritis by changes of gut microbiota. Microbiome. 5(1):73.

Mutlu S, Richards A, Maddison P, Scully C. 1993. Gingival and periodontal health in systemic lupus erythematosus. Community Dent Oral Epidemiol. 21(3):158–161.

Naguib G, Al-Mashat H, Desta T, Graves DT. 2004. Diabetes prolongs the inflammatory response to a bacterial stimulus through cytokine dysregulation. J Invest Dermatol. 123(1):87–92.

Olszak T, An D, Zeissig S, Vera MP, Richter J, Franke A, Glickman JN, Siebert R, Baron RM, Kasper DL, et al. 2012. Microbial exposure during early life has persistent effects on natural killer T cell function. Science. 336(6080):489–493.

Omori K, Ohira T, Uchida Y, Ayilavarapu S, Batista EL, Yagi M, Iwata T, Liu H, Hasturk H, Kantarci A, et al. 2008. Priming of neutrophil oxidative burst in diabetes requires preassembly of the NADPH oxidase. J Leukoc Biol. 84(1):292–301.

Queiroz-Junior CM, Madeira MF, Coelho FM, Costa VV, Bessoni RL, Sousa LF, Garlet GP, Souza Dda G, Teixeira MM, Silva TA. 2011. Experimental arthritis triggers periodontal disease in mice: involvement of TNF-α and the oral microbiota. J Immunol. 187(7):3821–3830.

Ramamurthy NS, Greenwald RA, Celiker MY, Shi EY. 2005. Experimental arthritis in rats induces biomarkers of periodontitis which are ameliorated by gene therapy with tissue inhibitor of matrix metalloproteinases. J Periodontol. 76(2):229–233.

Roberts FA, Darveau RP. 2015. Microbial protection and virulence in periodontal tissue as a function of polymicrobial communities: symbiosis and dysbiosis. Periodontol 2000. 69(1):18–27.

Rutter-Locher Z, Smith TO, Giles I, Sofat N. 2017. Association between systemic lupus erythematosus and periodontitis: a systematic review and meta-analysis. Front Immunol. 8:1295.

Sakalauskiene V, Kubilius R, Gleiznys A, Vitkauskiene A, Ivanauskiene E, Šaferis V. 2014. Relationship of clinical and microbiological variables in patients with type 1 diabetes mellitus and periodontitis. Med Sci Monit. 20:1871–1877.

Sato K, Takahashi N, Kato T, Matsuda Y, Yokoji M, Yamada M, Nakajima T, Kondo N, Endo N, Yamamoto R, et al. 2017. Aggravation of collagen-induced arthritis by orally administered *Porphyromonas gingivalis* through modulation of the gut microbiota and gut immune system. Sci Rep. 7(1):6955.

Scher JU, Ubeda C, Equinda M, Khanin R, Buischi Y, Viale A, Lipuma L, Attur M, Pillinger M, Weissmann G, et al. 2012. Periodontal disease and the oral microbiota in new-onset rheumatoid arthritis. Arthritis Rheum. 64(10):3083–3094.

Segata N, Haake SK, Mannon P, Lemon KP, Waldron L, Gevers D, Huttenhower C, Izard J. 2012. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biol. 13(6):R42.

Socransky SS, Haffajee AD. 2005. Periodontal microbial ecology. Periodontol 2000. 38:135–187.

Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. 1998. Microbial complexes in subgingival plaque. J Clin Periodontol. 25(2):134–144.

Sweeney TE, Morton JM. 2013. The human gut microbiome: a review of the effect of obesity and surgically induced weight loss. JAMA Surg. 148(6):563–569.

Ussar S, Fujisaka S, Kahn CR. 2016. Interactions between host genetics and gut microbiome in diabetes and metabolic syndrome. Mol Metab. 5(9):795–803.

Wang H, Han Q, Luo Z, Xu C, Liu J, Dan H, Xu Y, Zeng X, Chen Q. 2014. Oral lichen planus may enhance the expression of Th17-associated cytokines in local lesions of chronic periodontitis. Clin Oral Investig. 18(6):1647–1654.

Wu Y, Dong G, Xiao W, Xiao E, Miao F, Syverson A, Missaghian N, Vafa R, Cabrera-Ortega AA, Rossa C Jr, et al. 2016. Effect of aging on periodontal inflammation, microbial colonization, and disease susceptibility. J Dent Res. 95(4):460–466.

Wu YY, Xiao E, Graves DT. 2015. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci. 7(2):63–72.

Xiao E, Mattos M, Vieira GHA, Chen S, Corrêa JD, Wu Y, Albiero ML, Bittinger K, Graves DT. 2017. Diabetes enhances IL-17 expression and alters the oral microbiome to increase its pathogenicity. Cell Host Microbe. 22(1):120–128.e4.

Xiao W, Dong G, Pacios S, Alnammary M, Barger LA, Wang Y, Wu Y, Graves DT. 2015. *FOXO1* deletion reduces dendritic cell function and enhances susceptibility to periodontitis. Am J Pathol. 185(4):1085–1093.

Xiao W, Wang Y, Pacios S, Li S, Graves DT. 2016. Cellular and molecular aspects of bone remodeling. Front Oral Biol. 18:9–16.

Zhang H, Liao X, Sparks JB, Luo XM. 2014. Dynamics of gut microbiota in autoimmune lupus. Appl Environ Microbiol. 80(24):7551–7560.

Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D, Wu X, Li J, Tang L, Li Y, et al. 2015. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med. 21(8):895–905.

Zhou M, Rong R, Munro D, Zhu C, Gao X, Zhang Q, Dong Q. 2013. Investigation of the effect of type 2 diabetes mellitus on subgingival plaque microbiota by high-throughput 16S rDNA pyrosequencing. PLoS One. 8(4):e61516.