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The Oral Microbiome and Its Effects on Human Systemic Diseases

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by

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Dedication

I dedicate this thesis to my family for supporting me with affections and love and their unyielding encouragement for me to pursue the career of my life.

Abstract

In the past decade, scientists and healthcare professionals have gained interest in the microbiome and its function as part of the human body. The two most diverse microbiome environments are in the gut and the oral cavity. While the gut microbiome has been investigated more deeply and continues to be of great interest, the oral microbiome is in comparison a more recent subject with fewer reports on the topic. The purpose of this review paper is to focus on the main human systemic diseases associated with the oral microbiome and to discuss how our understanding of the oral microbiome's effects on various diseases such as oral cancer, gastrointestinal cancer, diabetes, and periodontal disease, has improved.

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Introduction

The microbiota makes up the majority of cells in the human body, with human cells representing only 10% of host cells (Wilson 2008). Symbiotic and commensal microorganisms contribute to pathogen resistance, improve the efficiency of the immune system, and help with different organ functions (He 2014). The human mouth is the second largest and diverse microbial environment in the human body, as it hosts over 700 species of bacteria that reside on the surface of teeth and tissues of the oral mucosa (Kilian 2016). Oral microorganisms can exist in various forms, such as viruses, protozoa, fungi, archaea, and bacteria, which are all represent typical residents of the human oral cavity. As the human mouth is heavily populated by various microorganisms, the oral cavity microbiome is one of the main causes of most dental and periodontal diseases. It is the main reason why people engage in regular oral hygiene practices in order to prevent such diseases, as maintaining clean oral health limits the number of oral microorganisms that could possibly cause dental and periodontal diseases (Wade 2013). As the oral cavity is the primary point of entry to the digestive and respiratory tracts, maladaptation or microbial imbalance in the oral cavity is also associated to oral inflammation, and may lead to systemic diseases in the human body through microbial pathways such as bacteremia (Han and Wang 2013). Oral microbiomes have also proven to present risk factors for human health, such as tumor formation, diabetes mellitus and other bacterial disesases. (He 2014). In this context, the purpose of this review is to further explore the connections between oral microbiome with human health and various systemic diseases.

The oral microbiome and systemic health

Periodontal disease

Periodontal disease can originate from various sources, but the most common source would be a lack of oral hygiene, which could trigger pathogens residing in the periodontal pocket to cause inflammation (Costalonga 2014). To date, the most commonly used database for oral microbiome taxonomy is the Human Oral Microbiome Database (HOMD). It consists of 34,573 quality filtered cloned sequences that also represent possible disease causing triggers of inflammation within the oral cavity (Aas 2005). Differences in species composition of the oral microbiome is a result of differences in dietary habits and available nutrients amongst individuals (Wade 2013). Nutrients play an important role in shaping the symbiosis of the oral microbiome that reside on the non-shedding surfaces of the teeth in the oral cavity. For example, a person on a vegan diet would have a different oral microbiome compared to a person on a carbohydrate-based diet, because the main sources of nutrients would be different.

The trends in oral microbiome changes between preindustrial samples and modern samples would show that the non-pathogenic microbiomes decreased in the modern era, and species that are more pathogenic, such as *S. mutan,* increased highly, which can be correlated with increased periodontal disease. (Adler 2013). It is also prevalent that the environment and host-genetics can show tremendous differences in oral microbiome composition. For example, Eskimo tribes showed a lower rate of periodontal disease occurrence until more western diets were introduced. (Costalonga 2014). In this recent decade, there has been a decrease in oral microbiome diversity among different cultures and races. The main contribution could be due to reduced resistance to protrusion of pathobionts into the microbial environment, which could be caused by a globalized food industry (Adler 2013).

The core original adhesion site for the oral microbiome would be the roots of the teeth. The roots of the teeth include both salivary and serum proteins, such that the colonizing microbiome would adhere to the protein-rich film on the roots. Since the enamel is only composed of salivary film, the non-shedding surface of the roots is more complex compared to the enamel portion of the teeth, which makes the non-shedding surface more suitable for establishment of the oral microbiome for long-term development (Kolenbrander 2010). Thus, the supragingival microbial environment would differ from the subgingival microbial environment. The supragingival microbial environment would form on the salivary film, while the subgingival microbial community would form on protein-rich film, and the subgingival environment would be more anaerobic and more extreme in pH level and temperature. These different factors would contribute to the subgingival microbiome having a greater diversity in the composition of bacterial species compared to the supragingival microbiome. The subgingival microbial environment consists of *Streptococcus ssp.* and *Veillonella* as its most prevalent bacteria (Kumar 2011). The bacteria in the saliva would originate from various oral tissues and mainly from the tongue. The superior surface of the tongue includes mainly *Prevotella* and *Veillonella*, while *Streptococcus* and *Gemella* are more prevalent on the inferior surface. The salivary microbial environment consists primarily of *Prevotella* and *Streptococcus* (Mager 2003).

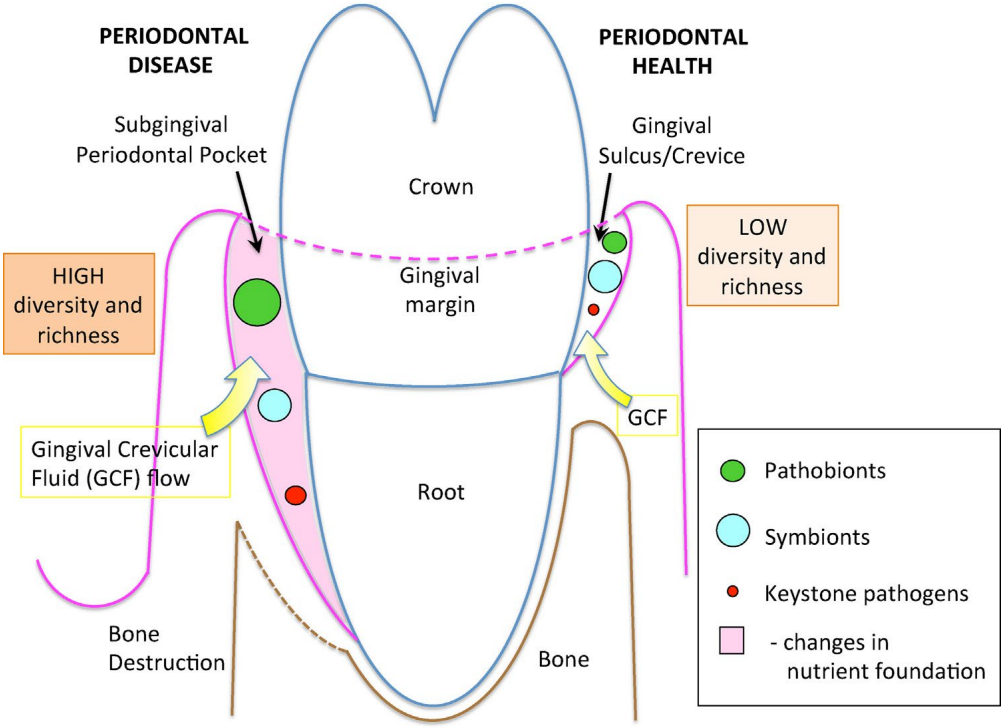
The oral microbial community for healthy individuals is the result of an equilibrium between symbionts and pathobionts, with the resulting microbiome not having a pathogenic effect on the individuals unless a state of dysbiosis occurs. An equilibrium is generally maintained within the microbial environment, but it can be disturbed by various situations (Costalonga 2014). Microbial perturbations caused by pathogens such as *P. gingivalis* can disrupt the equilibrium maintained in the oral microbiome environment. The perturbations would change the original nutrient needs of the community, which can disrupt both symbionts

and pathobionts in the environment (Hajishengallis 2014). The species-specific repression of the host can also alter the quantity of either the symbionts or the pathobionts, which can lead to pathogenic effect. The competition between different microbial species in the host can also cause the disruption of the equilibrium, which can also cause bacteriophagic activity and increase the pathogenic potential within the oral microbiome community (Wang 2013).

Periodontal disease results in complex immunological responses, as innate immunity works to prevent damage to the oral tissue caused by the disruption in periodontal tissue homeostasis. The T helper cells are the primary cells that infiltrate oral tissues in human gingivitis, and the phenotype is derived from the activity of pathogenic cells such as dendritic cells and Langerhans cells (Yamazaki 2003). Changes in environmental homeostasis within the periodontal tissues could be triggered by perturbations in the microbiome as a result of a transition amongst microbial species. During the change, the role of the immune response within the gingiva would also be affected. Indeed, the initial immune response of the gingiva is to recruit and activate neutrophils in order to destroy pathogenic bacteria, although the immune response would also cause chronic infiltration of T, B and plasma cells during the change. Immune cells would become chronically infiltrated, thus causing periodontitis, which would present signs such as vascular proliferation, damaged connective tissues, and alveolar bone destruction (Teng 2003).

It has been clearly identified that the CD4 T cells are the primary contributors to alveolar bone destruction during periodontitis. It has been shown through experiments in mouse models that most periodontitis-affected mice showed induced levels of CD4 T cells during the development of alveolar bone damage (Baker 1999). Other contributors to osteoclastic activity of alveolar bone could be memory B cells and T cells. Both cells have been found to release RANK-ligand, a type II membrane protein of the TNF family that regulates apoptosis and

differentiate osteoclasts to induce osteoclastic action within the bone tissue. Prior to the development of the bone damage near alveolar region, T cells would release a number of cytokines (Takahashi 2005).



The observation that periodontal disease can be caused by more than one pathogen has led to the dysbiosis theory. This theory proposes that a composition shift of low-abundance pathogenic species of bacteria, such as *P. gingivalis*, within the oral microbial community in the periodontal pocket would alter the host microbial environment, which would ultimately enhance the destructive effect of inflammation and result in the breakdown of bone tissue. While *P. gingivalis* is present in low cellular density, it is considered the keystone pathogen for periodontal disease, as it can act as a virulence factor to alter and depress the host immune response (Hajishengallis 2014). The dysbiosis theory is also comprehensive in that it helps to explain how other species of the microbiome can cause periodontal disease. Indeed, *P. gingivalis* is not the only possible causative agent of periodontal disease, as was shown in

mouse experimental models where monocolonization with this pathogen did not initiate any characteristics of periodontitis. (Hajishengallis 2011).

While it has been well accepted that association of *P. gingivalis* with other microbial bacteria would cause periodontal diseases, the specificity of the microbial composition and measurement of progression of the periodontal disease is still unclear (Costalonga 2014).

Oral cancer

Among all American patients diagnosed with oral cancer every year, about 90 percent of the patients have oral squamous cell carcinoma. The survival rate of the squamous cell carcinoma is about 40 percent, which has not been improved over 40 years (Parkin 1999). While tobacco and alcohol usage are considered to be the main contributors to the development of oral carcinoma, many patients with oral cancer have not been exposed to tobacco and alcohol consumption (Schmidt 2004). As oral carcinoma is associated with various routes of infection, the oral microbiome may contribute to the formation of oral squamous cell carcinoma in different forms of pathogenesis through certain viruses and bacteria (Al-Hebshi 2019).

Classically, the majority of causal agents for oral cancer have been found to be viruses, especially the Human papillomaviruses and Human herpesviruses (Al-Hebshi 2019), of which the former are highly associated with oropharyngeal cancer. The high-risk (hr) HPVs are known to be the main cause of oropharyngeal cancer, through the HPV E6 and HPV E7 oncogenes which inhibit the p53 and retinoblastoma (Rb) gene proteins in the posterior third of the tongue, blocking their tumor suppressing action (Johnson 2018). The Epstein-Barr virus is known to be the main contributor to nasopharyngeal cancer, but there is not enough evidence to show that it plays a major role in causing oral cancer (Johnson 2018). A more evident role of Herpes simplex viruses, HSV-1 and HSV-2, was found in contributing to oral squamous cell carcinoma, but the pathogenic mechanisms remain unknown (Al-Hebshi 2019).

In addition to viruses, certain oral bacteria can also influence the pathogenicity of oral carcinoma, and their contribution to oral cancer has emerged recently. Among the members of the oral bacterial community, the two most influential bacteria are thought to *Porphyromonas gingivalis* and *Fusobacterium nucleatum* (Al-Hebshi 2019). *P. gingivalis* can induce the development of carcinoma in various ways, including through activation of JAK1/STAT3 and PI3K/Akt signaling pathways, by blocking caspase-3 and caspase-9 activity (Mao 2007), and by preventing ATP-dependent $P2X_7$-mediated apoptosis (Yilmaz 2008). Both *P. gingivalis* and *F. nucleatum* can downregulate the expression of the p53 tumor suppressor gene as well as upregulate kinases and cyclins to induce the cell proliferation (Al-Hebshi 2019). *P. gingivalis* and *F. nucleatum* can induce the production of pro-inflammatory cytokines, which leads to increased chronic inflammation that could contribute to the development of oral cancer (Andrian 2004, Kostic 2013). Other factors, like production of acetaldehyde, could also play a major role in progression of oral cancer. This metabolic activity is highly associated with other bacterial species of the oral microbiome, such as *Streptococcus spp.* and *Neisseria spp.* (Al-Hebshi 2019).

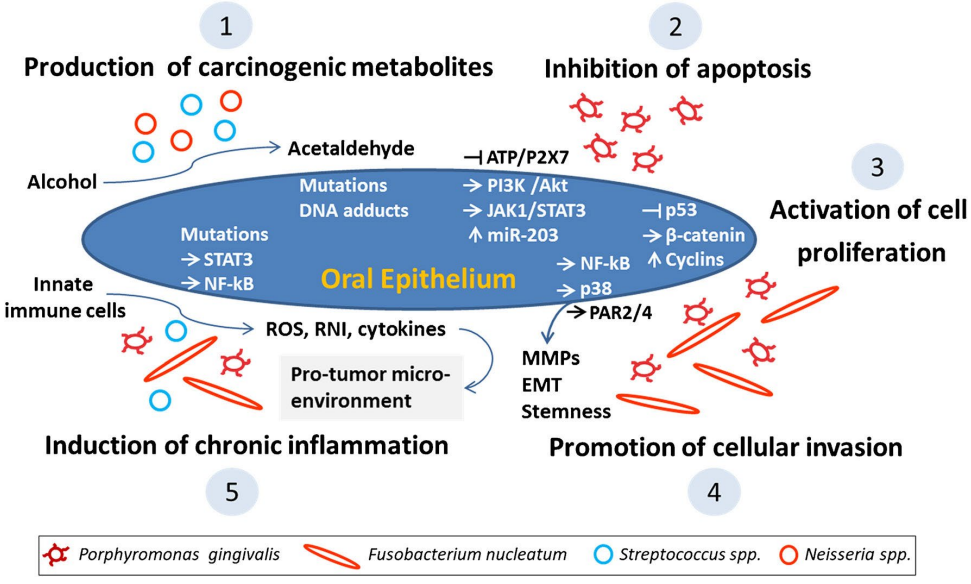


Figure 2. Effect of different bacterial species of the oral microbiome that may induce the progression of oral cancer (Perera 2016).

Variations in bacterial composition can occur during development of oral cancer mainly because different species of bacteria can play a similar function in the community, and thus are able to substitute for each other. This is known as functional redundancy, which can explain the composition differences associated with oral cancer (Tian 2017). Metatranscriptome sequencing has been used to monitor the transcriptional activity and gene expression of the oral microbiome in correlation with oral squamous cell carcinoma. The result from a study showed that the oncogenic bacteriomes had induced primary pro-inflammatory features, such as lipopolysaccharide biosynthesis, high production of peptidases, flagella assembly, and bacterial chemotaxis (Yost 2018). The conceptual model called "passenger-turning-driver" model lays out the function of the oral microbiome in oral cancer, which is not to initiate the disease. The initial intra-tumor microbiome would be more advantageous at combining with the tumor microenvironment to express pro-inflammatory features. The expression would lead to a functioning ("driver") intra-tumor microbiome that would induce the progression of oral cancer through chronic inflammation of the cells (Al-Hebshi 2019).

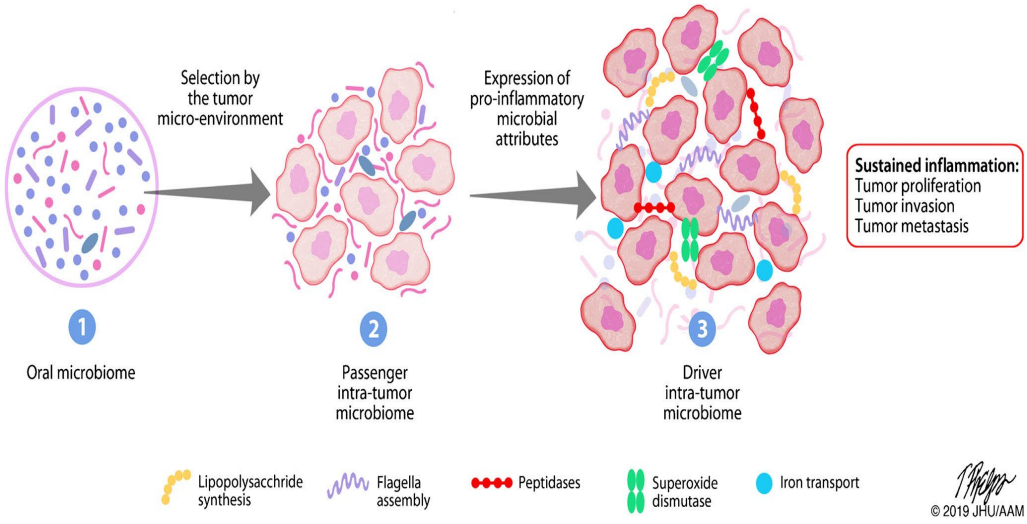


Figure 3. "Passenger-turning-driver" conceptual model that explains the progression of the oral microbiome with the tumor microenvironment. The oral microbiome would not initiate the oral cancer, but it would be selected by the tumor-microenvironment to create pro-inflammatory features. The passenger intra-tumor microbiome would be turned into driver intra-tumor microbiome because of the pro-inflammatory expression, leading to chronic progression of tumors in the oral cavity (Al-Hebshi 2019).

Gastrointestinal cancer

Gastrointestinal cancer risks from oral microorganisms is associated with oral bacteria that promote the development of periodontal disease and tooth loss in the oral cavity, to which other significant factors such as smoking, body mass index, and socioeconomic status can contribute (Meyer 2008). The oral microbiome may have an effect on oral and gastrointestinal cancer risk through two main contributing factors, which are local activation of carcinogens originating from alcohol and smoking. Ethanol is not a strong carcinogen, but oral bacteria are capable of converting ethanol to acetaldehyde, which is a familiar carcinogen in humans, leading to the exposure of the oral and gastrointestinal tract to carcinogenic acetaldehyde. Mutagenic quantities of acetaldehyde can be detected from saliva after consumption of alcohol (Ahn 2012).

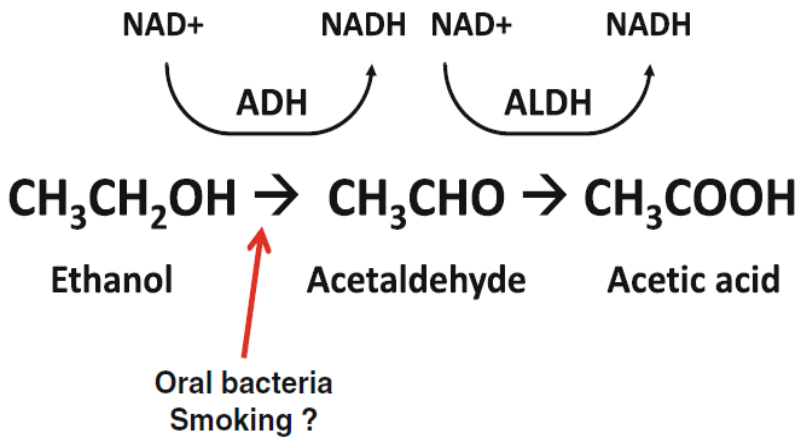


Figure 4. Alcohol metabolism in oral bacteria. Under normal physiological conditions, ethanol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH), then acetaldehyde is further metabolized to acetic acid by aldehyde dehydrogenase (ALDH). Oral bacteria have the capacity to convert ethanol to acetaldehyde, leading to extended acetaldehyde exposure of the oral and gastrointestinal tract following alcohol consumption. This mechanism may be potentiated by smoking (Ahn 2012).

Oral bacteria may also take part in induced activation of carcinogenic nitrosamines from smoking tobacco (Yang 2011). The oral microbiota can activate the nitrosamine in tobacco smoke, nitrosodiethylamine (NDEA), to its hydroxylated product, which is a potent carcinogen in humans. Tobacco smoking can also lead to increased production of acetaldehyde by oral bacteria that could lead to production of both acetaldehyde and nitrosamines.

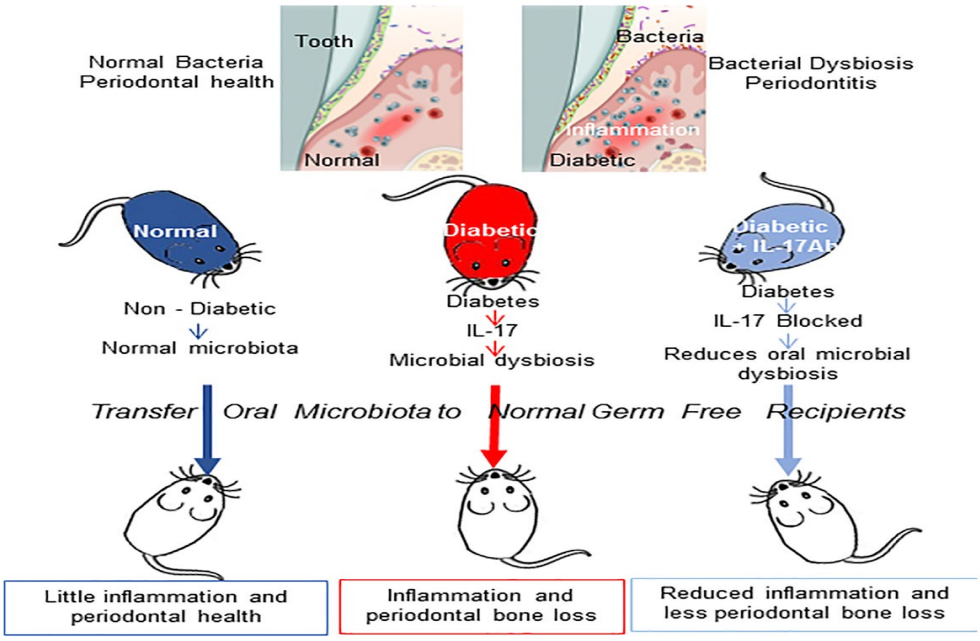
The antiseptic mouthwash chlorohexidine can reduce the levels of salivary acetaldehyde and nitroso-amino acid formation and secretion in saliva and urine. Usage of chlorohexidine prior to ethanol consumption can lead to a 50% decrease in salivary acetaldehyde levels (Homann 1997). The chlorohexidine can also decrease the levels of nitroso-amino acid formation and excretion in saliva and urine by 30% (Shapiro 1991).

Oral microorganisms that can promote gastrointestinal disease also show a strong relation to periodontal disease. Although, the systemic disease is involved with oral microbiome-related carcinogenesis, it is much clearer that the periodontal disease has a greater association with the systemic effects leading to the cancer (Ahn 2012). Successful treatment of periodontal disease caused by oral microorganism that were also found in atherosclerotic plaque have led to a reversal or regression of systemic diseases. The treatment induced endothelial function and decreased inflammatory markers (Tonetti 2007), which could help explain the strong relationship between periodontal disease and gastrointestinal cancer. Oral and gut microbiome structure may be different in the same individual, but oral microorganisms can enter the GI tract (Ahn 2012). In addition, oral bacteria can provide ligands for Toll-like receptors, which are membrane receptors expressed by innate immune cells that bind structural molecules derived from microorganisms, and potentially link inflammatory response down the cell-signaling pathway to other human bacteria. Other evidence supports that immune response

to chronic exposure to bacteria and their toxins may be critical to oral and gastrointestinal carcinogenesis (Pizzo 2010).

Diabetes

Diabetes, which can be of type 1 or type 2, is a clinical disease characterized by hyperglycemia due to either insufficient or deficient secretion of insulin or to reduced insulin function by other factors (Alberti and Zimmet 1998). Diabetes shows a bidirectional relationship with periodontal disease, while the oral microbiome is associated with homeostasis and it affects various pathologic processes (Iwai 2009). Diabetes can also be a risk factor for periodontitis, and it may influence the severity of disease progression. The severity of periodontitis disease would increase heavily in type 1 diabetes and the age would also be a great risk factor for periodontitis (Cullinan 2001). Type 2 diabetes would also increase the risk for periodontitis (Emrich 1991).



As diabetes increases the risk of periodontitis, the risk and severity of tooth loss would also increase among diabetics. A diabetic mouse would exhibit a different oral bacterial composition, which would be more pathogenic compared to disease-free mice. In addition, the treatment of IL-17 antibody has shown to decrease the pathogenicity of the oral microbiome in diabetic mice. The oral microbiota from IL-17-treated donor mice increased the rate of neutrophil recruitment, reduced IL-6. Bone resorption was also reduced. Diabetes-enhanced IL-17 changed the oral microbiota composition in the oral cavity of the recipient mice and became more pathogenic (Xiao 2017).

The composition of subgingival dental plaque in diabetics was found to be different compared to non-diabetic individuals. Sequencing of the 16S rRNA gene was used to identify differences in subgingival microbiota between type 2 diabetics and non-diabetics. Significant differences were observed with diabetics having higher abundance of *TM7, Aggregatibacter, Neisseria, Actinomyces, Capnocytophaga, Gemella, Eikenella, Selenomonas, Fusobacteriu, Veillonella, Streptococus, F. Nucleatum, V. Parvula, Veillonella dispar,* and *E. corrodens* (Casarin 2013). Considering the hyperglycemic state of diabetic hosts and their altered immune response, the subgingival difference between diabetics and non-diabetics could be a potential risk factor for pathogenicity in oral microbiome due to dysbiosis of oral microorganisms in diabetics.

Discussion

The oral microbiome community is diverse and shown to influence multiple systemic diseases. Bacteria can either be a primary cause of certain diseases, or they can help to induce diseases through other mechanisms, such as by prolonging inflammation. Oral related diseases such as periodontal disease and oral cancer could be directly affected by the primary action of the oral microbiota, which would accelerate the onset and progression of these diseases in humans. Other non-oral related diseases such as gastrointestinal cancer and diabetes could also be affected by the microbial environment, by either altering disease progression or prolonging disease-related chronic effects.

Future work

In the future, more biological mechanisms and pathways can be determined through research, including further analyses of the oral microbiota that can be done with clinical data and experimental data. Especially, determining how the oral microbiome would transfer over to affect other system diseases such as GI cancer and diabetes could be deeply researched. More mechanisms need to be identified, since the mechanisms involved in the progression of many of the diseases mentioned in this review remain to be determined. Also, a deeper understanding of the relationship between diseases and the oral microbiome remain to be further explored.

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