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ORAL MICROBIOME AND ITS AFFECT ON HUMAN SYSTEMIC DISEASES

by

Hee Chang Shin
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 found in the gut and the oral cavity. While the gut microbiome has been investigated more deeply and continues to be a 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 highlight the main human systemic diseases associated with the oral microbiome and to discuss how our understanding of the oral microbiome’s effect on various diseases such as oral cancer, gastrointestinal cancer, diabetes, and periodontal disease with diseases has improved.
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Introduction

The microbiota makes up 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 most diverse microbial environment in the body, as it hosts over 700 species of bacteria that reside on the surface of teeth and soft tissues of the oral mucosa (Kilian 2016). Oral microorganisms can exist in various forms such as viruses, protozoa, fungi, archaea and bacteria residing in human oral cavity. Human mouth is heavily colonized by various microorganisms and the microbiomes in the oral cavity is the main cause of the most dental and periodontal diseases. It is the main reason of people engaging in regular oral hygiene practices in order to prevent such diseases. It would be crucial for individuals to maintain clean oral health in order to limit the number of oral microbiomes in the oral cavity that could possibly cause dental and periodontal diseases (Wade 2013). Oral cavity is primary point to enter digestive and respiratory tract. The maladaptation or microbial imbalance in the oral cavity is linked with oral inflammation and may lead to systemic diseases in 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, diabetes mellitus and cardiovascular diseases. (He 2014). In this context, the purpose is to further understand the correlation between oral microbiome with human health and various systemic diseases.
**Oral microbiome and systemic health**

**Periodontal disease**

Periodontal disease can originate from various sources, but the most common source would be not maintaining clean oral health, which could trigger pathogens residing in the periodontal pocket to cause inflammation (Costalonga 2014). Today, the most common database of taxonomy for oral microbiome is HOMD (Human Oral Microbiome Database). It consists of 34,573 filtered cloned sequences that also represent possible diseased sites of inflammation within the oral cavity (Aas 2005). Different species of the oral microbiome is diversified upon the received nutrients and dietary habits of the individuals (Wade 2013). Nutrients would shape the symbiosis of the oral microbiome housing on the non-shedding surfaces of the teeth in the oral cavity. For example, a person with vegan diet and another person with carbohydrate-based diet would have different oral microbiome environment since the main nutrient is different and each microbiota would correlate differently according to the main source of nutrient.

The trends in the change of oral microbiome compared 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 correlate to increased periodontal disease. (Adler 2013). It is also prevalent that the environment and host-genetics can show tremendous difference in oral microbiome composition. For example, Eskimo tribes showed lower rate of periodontal disease occurrence until more western diet was introduced. (Costalonga 2014). In 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 globalized food industry (Adler 2013).
The core site of original adhesion site of oral microbiome would be in the roots of the teeth. The roots of the teeth are composed of both salivary and serum proteins and the original microbiome would adhere to the protein-rich film on the roots. The non-shedding surface of the roots are more complex compared than the enamel portion of the teeth since the enamel is only composed of salivary film, which make the non-shedding surface more suitable for the oral microbiome to anchor for long-term development (Kolenbrander 2010). As mentioned, the supragingival microbial environment would differ from the subgingival microbial environment. The supragingival microbial environment would form on the salivary film, but the subgingival microbial community would form on protein-rich film, and the subgingival environment would be more anaerobic and extreme in pH level and temperature. The different factors contributing to the subgingival microbiome would have variation in the composition of species of bacteria compared to the supragingival microbiome, which the subgingival microbial environment has *Streptococcus ssp.* and *Veillonella* as the 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 consists mainly of *Prevotella* and *Veillonella*, but the inferior surface is more prevalent of *Streptococcus* and *Gemella*. The salivary microbial environment shows most prevalent of *Prevotella* and *Streptococcus* (Mager 2003).

The oral microbial community for healthy individuals has an equilibrium of symbionts and pathobiont, which the microbiome would not cause pathogenic effect on the individuals. The equilibrium is generally maintained within the microbial environment, although, it can be disturbed by various situations (Costalonga 2014). The microbial perturbation caused by pathogenic microbiome such as *P. gingivalis* can disrupt the equilibrium maintained in the oral microbiome environment. The perturbation would change the need of the original nutrient in the community, which can disrupt both symbionts and pathobionts in the environment (Hajishengallis 2014). The specie-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).

The periodontal disease has complex immunological response and innate immunity prevents the oral tissue damage caused by the disruption of periodontal tissue homeostasis. The T helper cells are the primary cells of the cellular infiltrate in human gingivitis, which the phenotype is derived from pathogenic antigen presenting cells such as dendritic cells and Langerhans cells (Yamazaki 2003). Change of environment homeostasis within the periodontal tissues could be triggered by the perturbation of microbiome or unclear transition of the microbial species. During the change, the role of immune response within the gingiva would also change. The initial immune response of the gingiva is to recruit and activate the neutrophils in order to destruct the pathogenic bacteria. Although, during the change, the immune response would cause chronic infiltrate of T, B and plasma cells. The immune cells would be chronically infiltrated and cause periodontitis, which would present signs such as vascular proliferation, damaged connective tissues, and alveolar bone destruction (Teng 2003).

It is clearly identified that the CD4 T cells are the primary contributors of alveolar bone destruction during the periodontitis. It has been shown through the murine samples that most of the mouse with periodontitis 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 the memory B cells and T cells. The memory B cells, and T cells have been identified to release RANK-ligand, type II membrane protein in TNF family that regulate apoptosis and differentiate osteoclasts, to induce osteoclastic action within the bone tissue.
Although, the Th cells would release set of cytokines before the development of alveolar bone damage (Takahashi 2005).

![Figure 1: Difference between microbial diversity and richness between periodontal health and disease. (Costalonga 2014)](image)

**Figure 1.** Difference between microbial diversity and richness between periodontal health and disease. (Costalonga 2014)

Periodontal disease caused by more than one pathogen, which recently derived into dysbiosis theory. The theory proposes that the 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 that could enhance the destructive inflammation and bone destruction. *P. gingivalis* exist in low quantity but is defined as the keystone pathogen for periodontal disease, which can act as a virulence factor to alter and depress the host immune response (Hajishengallis 2014). The case of dysbiosis theory work with multiple species of microbiome since the mice sample showed that the monoclonization of *P. gingivalis* would not initiate any characteristics of periodontitis. (Hajishengallis 2011).
Even though, it is prevalent that the P. gingivalis associated with other microbial bacteria would cause the 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 the main contributors to the developmental 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 such as viruses and bacteria (Al-Hebshi 2019).

Classically the majority of carcinogens for oral cancer are known to be viruses, especially Human papillomaviruses and Human herpesviruses (Al-Hebshi 2019). Human papilloma viruses are highly associated with oropharyngeal cancer. The high-risk (hr) HPV$s$ are known to be the main cause of the oropharyngeal cancer, where the HPV E6 and HPV E7 oncogenes inhibit the p53 and Rb (retinoblastoma) gene proteins in the posterior third of the tongue to block the tumor suppressing action of the p53 and Rb gene proteins (Johnson 2018). Epstein-Barr virus was known to be the main contributor for the nasopharyngeal cancer, but there are not enough evidence to show that the Epstein-Barr virus plays the major role causing oral cancer (Johnson 2018). The more evident role of Herpes simplex viruses HSV-1 and HSV-2 were found contributing to oral squamous cell carcinoma, but pathogenic mechanism is unknown (Al-Hebshi 2019). Along with the viruses, there are oral bacteria that also influence the pathogenicity of the oral carcinoma.
The interest in oral bacterial contribution to oral cancer has been emerging recently. Among the bacterial community in oral microbiome, the two bacteria that are thought to be most influential are periodontal bacteria Porphyromonas gingivalis and Fusobacterium nucleatum (Al-Hebshi 2019). *P. gingivalis* induce carcinoma in various ways including activation of JAK1/STAT3 and PI3K/Akt signaling pathways, blocking the caspase-3 and caspase-9 activity (Mao 2007), and preventing the ATP-dependent P2X7-mediated apoptosis (Yilmaz 2008). Both *P. gingivalis* and *F. nucleatum* downregulate the amount of p53 tumor suppressor gene and upregulate kinases and cyclins to induce the cell proliferation (Al-Hebshi 2019). *P. gingivalis* and *F. nucleatum* induce the production of pro-inflammatory cytokines, which will lead 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, which 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 in the oral microbiome that may induce the progression of oral cancer through various mechanisms. (Perera 2016)
Variations in bacterial composition occur in 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 the 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 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 oral microbiome with the tumor microenvironment. The oral microbiome would not initiate the oral cancer, but it would be advantageously chosen by the tumor-microenvironment to create pro-inflammatory features. The passenger intra-tumor microbiome would be turned into driver intra-tumor microbiome after the pro-inflammatory expression, thus leading to chronic progression of tumors in the oral cavity (Al-Hebshi 2019).
**Gastrointestinal cancer**

Gastrointestinal cancer risk from oral microorganism is associated with the oral bacteria that leads to the development of periodontal disease and tooth loss in the oral cavity, which these relationships tend to consider significant factors such as smoking, body mass index, and socioeconomic status (Meyer 2008). Oral microbiota may affect oral and gastrointestinal cancer risk through two main contributing factors, which are local activation of alcohol and smoking carcinogens. Ethanol is not a strong carcinogen, but the oral bacteria are capable to convert the ethanol to acetaldehyde, which is a recognized human carcinogen, leading to carcinogenic acetaldehyde exposure to oral and gastrointestinal tract. Mutagenic quantity of acetaldehyde can be detected from saliva after consumption of alcohol (Ahn 2012).

![Diagram of alcohol metabolism](image)

**Figure 4.** Oral bacteria in alcohol metabolism. Under normal physiological conditions, ethanol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH), and acetaldehyde is further metabolized to acetic acid by aldehyde dehydrogenase (ALDH). Oral bacteria have the capacity to convert ethanol to acetaldehyde, a genotoxin, leading to extended acetaldehyde exposure of the oral and gastrointestinal tract, following alcohol use, and possibly 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 activates the tobacco smoke
nitrosamine, nitrosodiethylamine (NDEA) to hydroxylated product, which is strongly carcinogenic to human. Tobacco smoking can also lead to increased production of acetaldehyde by oral bacteria, potentially contributing to both production of acetaldehyde and nitrosamines.

The antiseptic mouthwash chlorohexidine can reduce the presence of salivary acetaldehyde level and nitroso-amino acid formation and secretion in saliva and urine. Usage of chlorohexidine prior to ethanol consumption lead to 50% decrease in salivary acetaldehyde level (Homann 1997). The chlorhexidine also decreased the level of nitroso-amino acid formation and excretion in saliva and urine by 30% (Shapiro 1991). The oral microorganisms leading to gastrointestinal disease show 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 greater association with the systemic effects leading to the cancer (Ahn 2012). The successful treatment of the periodontal disease caused by oral microorganism found in atherosclerotic plaque, have led to reversal effect of the systemic diseases. The treatment induced the endothelial function and decreased inflammatory markers (Tonetti 2007), which explain the strong correlation between periodontal disease and gastrointestinal cancer. Oral and gut microbiome structure may be different in the same individual, but oral microbiome can enter the GI tract (Ahn 2012). In addition, the oral bacteria can provide ligands for toll-like receptors at target membrane receptors. The toll-like membrane receptors are on innate immune cells that bind structural molecules derived from microorganisms and potentially link inflammatory response down the cell-signaling pathway to other human bacteria. More evidence is forming that immune response to chronic exposure to bacteria and its toxins may be the critical portion in oral and gastrointestinal carcinogenesis (Pizzo 2010).
Diabetes

Diabetes is also known as type 1 or type 2 diabetes, which is a clinical disease characterized by hyperglycemia due insufficient or deficient secretion of insulin or reduced insulin function by other factors (Alberti and Zimmet 1998). Diabetes show a bidirectional relationship with periodontal disease and oral microbiome is associated with homeostasis and affects various pathologic processes (Iwai 2009). Diabetes can also be a risk factor for periodontitis, and it may induce the severity of the 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 increase the risk for periodontitis since type 2 diabetes is also a great risk factor for periodontitis (Emrich 1991).

Figure 5. Graphical abstract of difference shown between normal, diabetic, and diabetic IL-17 absent mice associated with oral microbiome (Xiao 2017).

As the diabetes increase the risk of periodontitis, the risk and severity of tooth loss would also increase among the diabetics. The oral microbiota from a diabetic mouse would cause a shift in oral bacterial composition, which would make the oral microbiota of diabetic
more pathogenic compared to the disease-free mice. In addition, the treatment of IL-17 antibody has shown to decrease the pathogenicity of the oral microbiota in diabetic mice. The oral microbiota from IL-17-treated donors increased the rate of reduced neutrophil recruitment, reduced IL-6 and less bone resorption. 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 were shown different compared to the non-diabetics. The 16S rRNA sequencing was used to observe the difference in subgingival microbiota between type 2 diabetics and non-diabetics. Significant difference was observed by showing diabetics presenting higher abundance of *TM7, Aggregatibacter, Neisseria, Actinomyces, Capnocytophaga, Gemella, Eikenella, Selenomonas, Fusobacteriu, Veillonella, and Streptococcus, F. Nucleatum, V. Parvula, Veillonella dispar,* and *E. corrodens* (Casarin 2013). Considering the hyperglycemia in subgingival microorganism and altered immune response, the subgingival difference between diabetics and non-diabetics could be the 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 be related to multiple systemic diseases. The microbial bacteria can be a primary cause to a certain disease, but it can also help to induce multiple diseases through various ways such as prolonging the inflammation or triggering series of effects that would lead to a progression of a disease. An oral related disease such as periodontal disease and oral cancer could be directly affected by the primary action of the oral microbiota, which would aid to cause the diseases in human. Other non-oral related diseases such as gastrointestinal cancer and diabetes would be affected by the microbial environment that could alter the progression of the diseases or prolong the chronic effect related to the diseases.
**Future work**

More methodology and pathway can be determined through research and further analysis of oral microbiota can be done through 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 methods could be identified since many of mentioned diseases lack specific methods of progression and deeper progression relationship between the diseases and oral microbiome.
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