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The Potential of Dental Nano-Robots in Oral Healthcare

Ji-Won Yoon
Bachelor of Science, State University of New York at Albany, Albany, NY. USA

***Abstract*—** *Man inevitably maintains symbiosis with bacteria. As long as good bacteria control pathogenic bacteria, the body remains healthy. When pathogenic bacteria dominate the oral cavity, dental diseases occur. It was difficult to determine the number of pathogenic bacteria in real time. When periodontitis occurs, only Indirectly, It may be guessed that the number of pathogenic bacteria increased at that time. However, with the application of nanotechnology, the number of pathogenic bacteria in the oral cavity can be monitored in real time. A major advantage of nanorobots could help keep teeth healthy by controlling the member of pathogenic bacteria*.

***Keywords*—** *Pathogenic Microbiome. Good Microbiome. Nanorobot. Symbiosis, Dysbiosis*.

I. INTRODUCTION

Bacteria that exceed the number of human cells live on the surface of the human body. These bacterial populations in the human body are called “resident flora” and play a role in protecting the human body by preventing the invasion of foreign bacteria [1]. A typical example is "good bacteria", which is said to be an enteric bacterium [2]. Intestinal bacteria exist in the intestine and make vitamin K, which plays an important role in hemostasis [3]. The microbiome of the gut performs extremely important functions for the normal development and functioning of the human body. These functions include the synthesis of vitamins, the decomposition of chemicals and nutrients, the support of fat metabolism, the outcompeting of pathogens, the promotion of angiogenesis and the maintenance of homeostasis and the development of the immune system [4]. There are oral flora formed by more than 700 species in the oral cavity [5]. These bacterial flora coexist with the living body and play a defensive role, but if the balance of the bacterial species that make up for some reason is lost, it is linked to disease [5]. This loss of balance in the flora is called dysbiosis [6]. The two major diseases in the oral cavity, cavity and periodontal disease, are also caused by dysbiosis [6]. Usually, if you do a daily toothbrush, you will rarely have tooth decay. It can be said that the toothbrush prevents disbiosis, which increases the number of bacterial species that can dissolve teeth [6]. Similarly, in periodontal diseases, it is important to prevent toothbrushes from changing the bacteria between the teeth and gums into highly pathogenic ones [7]. These are very different from diseases that are caused by common pathogens such as influenza [7]. If it is a normal pathogen, it will become ill when bacteria enter, and if the pathogen is expelled from the body by treatment such as human defense and medication, the flow will be clear [6]. However, in diseases caused by dysbiosis, it is difficult to understand that even if there are pathogens [6], if the amount is small, it does not necessarily cause the disease. In this respect, it can be said that a different way of dealing with normal infectious diseases is necessary [7].

II. MECHANISMS IN GUM DISEASE

The oral microbiota in the mouth of normal people is mostly bacteria and is generally in symbiotic relationship. Counting the numbers, there are 500 to 1 billion bacteria per ml in saliva and plaque covering the teeth [8]. As many as 100 billion bacteria per ml live [8]. It is known that there are 700 to 1,000 kinds of bacteria in the oral cavity [8]. The plaque, which itself can be seen as a mass of bacteria, does not cause problems to the human body unless special environmental changes occur, but When the number of certain bacterial species in plaque increases or the virulence of infections occur, which cause tooth and periodontal tissue damage, resulting in dental caries and periodontal disease [9]. To prevent the development of dental caries and periodontal disease, it is necessary to take care of plaque, a microbial mass in the oral cavity [10]. First, let's look at the process that causes dental caries and periodontal disease. When a man eats sugar, which is hexose, the smallest molecules of sugar remain in the oral cavity, and the microorganism, called mutans, breaks down the sugar [11]. In this process, acidic components are secreted on the tooth surface [11]. Mutans streptococci are the primary etiological agents, and within this group, S. mutans and *S. sobrinus* are the two most prevalent isolates from the human oral cavity[12]. *S. mutans* has been implicated as the major causative agent of dental caries [13]. and hence an appreciation of the ways in which it metabolizes sucrose is essential to our understanding of the disease process [13].

S. mutans has numerous enzymes which utilize sucrose as a substrate, and there has been particular interest in the extracellular GTFs (glucosyltransferase) [14]. GTF is the key enzyme that catalyzes sucrose to adhesive glucans and contributes significantly to the formation of dental plaque in which the accumulation of metabolic acids produced by bacterial colonies leads to local demineralization of the enamel surface [15]. GTFs of mutans streptococci are enzymes responsible for the synthesis of water-soluble and insoluble glucose polymers from sucrose [15]. Therefore, GTF activity is a potential up-stream target in the pathological cascade [16]. In periodontal disease, when the plaque, which is a bacterial mass, is grown in the oral cavity and grows repeatedly, the base of the plaque is changed to anaerobic bacteria [17]. The representative bacterium is *P gingivalis*, this bacteria develop mobility and are affected by plasma proteins,

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white blood cells, etc., which penetrate between the teeth and gums, or come out of the blood vessels of the gums, forming more tartar [17]. At this time, the gap between the teeth and the alveolar bone to form a periodontal pocket, and may develop into chronic periodontal disease and acute necrotic ulcerative gingivitis [18]. It is true that oral microorganisms that may be related only to dental diseases are living with terrifying bacteria such as Mycobacterium tuberculosis, influenza, leprosy and herpes virus [18].

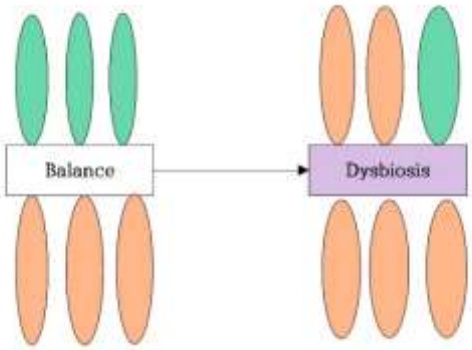

Fig. 1. From Symbiosis to Dysbiosis in Oral Microbiome.

Recent studies show that several chronic diseases of the mouth and gastro-intestinal tract are associated with alterations in the composition of the microbiome termed as "dysbiosis" [19]. Dysbiosis is a significant harmful shift in the relative abundances and individual components of the microbiome which varies with their composition and relative abundances during health status[19].This shift causes major dysbiosis related diseases in humans, namely, periodontitis, irritable bowel syndrome, chronic vaginosis, etc. Among them, periodontal disease depicts a major dysbiotic condition due to the diversity of genera involved in normal and periodontal microbiome [20]. Oral microbiota consists of two major types of bacteria: Gram-positive and Gram-negative bacteria with more than 700 species of microorganisms found in the oral cavity [21].

Periodontitis is a chronic inflammatory disease affecting tissues that surround and support the teeth [22]. Its occurrence is associated with important systemic diseases such as cardiovascular disease [22]. One of the most important etiologies of periodontitis is Porphyromonas gingivalis, a keystone Gram negative bacterial pathogen [23]. Keystone pathogens can orchestrate inflammatory disease by remodeling a normally benign microbiota, causing an imbalance between normal and pathogenic microbiota (dysbiosis) [21,22,23]. Dysbiosis of oral microbiome in periodontal disease is a hallmark of this condition [24]. Understanding the mechanism of dysbiosis, its functional relevance to disease and strategies to achieve the reversal of dysbiosis to restore health has been the prime focus of research (Fig. 1) [24]. In Figure 1 above, red means pathogenic microbiome. Recent investigations using the mouse model of this disease have demonstrated that the human periodontal bacterium Porphyromonas gingivalis acts as a keystone pathogen in manipulating the normal commensal microbiome into a dysbiotic condition even when present at low abundance; furthermore, this dysbiotic microbiome is causative of disease rather than a consequence of the altered environment in this inflammatory condition [25]. The complex equilibrium between resident species in the oral cavity is responsible for the maintenance of a healthy state (in symbiosis) or a state associated with disease (in dysbiosis) [23,26]. A dysbiotic microbiome is one in which the diversity and relative proportions of species or taxa within the microbiota is disturbed [21]. The relationship between the oral microbiome and its host is dynamic and, while in the healthy mouth the composition of microbial communities is remarkably stable (after the microbiome has matured in childhood), biological changes in a person's life can affect the balance of the species within these communities [27]. These include physiological changes, for example, age, or hormonal changes in puberty and pregnancy, to which healthy individuals can often adapt without detriment to their oral health. [27] At other times, the finely-tuned ecosystem in the mouth can become disturbed, causing a dysbiotic shift and a loss of community balance or diversity in the biofilm, with a single or few species predominating, and an associated increased risk of disease [28]. Modifiable factors driving oral dysbiosis include salivary gland dysfunction (that is, changes in saliva flow and/or composition), poor oral hygiene, gingival inflammation and lifestyle choices [25]. Recently, culture-independent techniques have revolutionized the knowledge of the gut and oral microbiota [29]. These techniques are based on sequence divergences of the small subunit ribosomal ribonucleic acid (16S rRNA) and can demonstrate the microbial diversity of the gut and oral microbiota, providing qualitative as well as quantitative information on bacterial species and changes in the gut and oral microbiota in health and disease [29]. Periodontal disease is one of the most common inflammatory diseases of humans leading to tooth loss in approximately 20% of the population [30]. It is also thought to be a risk factor for the development of other diseases including cardiovascular disease and type II diabetes [31]. Dysbiosis of the oral microbiome is induced by either the genetic status of the host or by the introduction of periodontal pathogens leads to the development of inflammatory periodontal disease and bone loss mediated through the normally benign oral microbiome [29,30].

III. Good Microbiome vs. Pathogenic Microbiome

The oral cavity is a complex environment that encompasses distinct, small microbial habitats, such as teeth, buccal mucosa, soft and hard palate, and tongue, which form a species-rich heterogeneous ecological system [32]. Numerous microorganisms exist in the mouth, among which are bacteria, fungi, and viruses. Bacteria are the main inhabitants of the mouth [33]. they primarily comprise bacteria of the Firmicutes, Bacillus, Proteobacteria, and Actinomycetes [34]. Unlike gut microbiota, these types of bacteria do not change significantly [34]. Diet and the environment have a great impact on gut microbiota, but exert minimal effect on the composition of oral bacteria [34].

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Healthy people from different countries have similar compositions of oral microbiota. In the human mouth, 85 species of fungi can be found [35]. Among these fungi, the most important one is *Candida* [35]. *Candida* is neutral when the oral microbiota is normal; however, when the oral microbiota balance is broken, *Candida* will seek the opportunity to attack oral tissue [36]. *Candida* forms a biofilm with *Streptococcus* to play a pathogenic role [37]. Viruses, mainly phages, are also part of the oral microbiota [37]. The type of phage in the mouth is constant during all stages of life [35]. Other non-original viruses may also appear in the mouth when certain diseases exist in the human body [37]. Oral bacteria are the main components of the oral microbiota [37]. Common oral bacteria include Streptococcus *mutans*, *Porphyromonas gingivalis*, *Staphylococcus*, and *Lactobacillus* [38]. *S. mutans* is the main component of the oral microbiota, and it is one of the main components of dental plaque [39]. It is also the main pathogen of caries, which is a bacterial infectious disease that occurs in hard tissues of the teeth and has the highest incidence among oral diseases [39]. *P. gingivalis* is a non-glycolytic Gram-negative anaerobic bacterium that is a periodontal pathogen [40]. Untreated *P. gingivalis* can cause gums to fall off the teeth [40]. *Lactobacillus* refers to a bacterium that can ferment sugar to produce lactic acid [41]. It is a group of microorganisms that live in the body and benefit the health of the host. Yogurt contains lactobacilli [41]. *Lactobacillus* ferments sugar and produces a large amount of lactic acid, which can easily cause caries [41]. Researchers have shown that the human body resembles an ecosystem that consists of trillions of bacteria and other microorganisms [42]. It is likely that the human ecosystem is the result of the evolutionary co-existence between the microbial community and the human body [42]. The composition of the human microbiome (microbiota) is highly personal and, therefore, it is challenging to clearly define "a healthy microbiome" [40,42,43]. It was shown that the diversity in the composition of the microbiome among the body sites is greater than it is between individuals [43]. This indicates that the human microbiome is highly variable ecosystem that possesses diverse microbiological parts [45]. However, it is possible to define "the core" of a healthy microbiome that occurs frequently within different body sites [41]. The human digestive system is a very complicated system that is composed of functionally distinct regions: the oral cavity, stomach, small intestine and colon [40]. The human oral cavity is the perfect habitat for microorganisms due to the abundance of nutrients [44]. The mouth is home to at least six billion microorganisms that belong to the Firmicutes

(Grampositive; e.g., Bacilli, Clostridia), Proteobacteria (Gramnegative, e.g., Salmonella, Escherichia, Helicobacter and Yersinia), Bacteroidetes (e.g., Prevotella, Bacteroides), Actinobacteria (Gram positive, e.g., Actinomyces, Streptomyces) and Fusobacteria (Gram negative, e.g., Fusobacterium [Table 1] [41,45]. Oral cavity is a very suitable habitat for a wide range of bacteria of which a significant proportion is facultative or strict anaerobes [46]. In healthy individuals, specific sites of the oral cavity are colonized by specific microbial communities, and a balance of the species within the community, known as "microbial homeostasis", is maintained [46].

When this balance is disrupted by ecological perturbations, the biofilm composition changes leading to the initiation of local infections that may ultimately lead to tooth loss (Table 1) [47]. At the onset of the infections, Gram-positive bacteria dominate the biofilm composition, but if left undisturbed, a more complex biofilm builds up where Gram-negative anaerobic and proteolytic rods become dominant [47]. Aerobic and anaerobic bacteria together form oral biofilms that prevent changes in their environment [47]. Pathogenic bacteria in oral biofilms contribute to the development of dental caries, periodontitis, and oral cancer [46,48]. Oral biofilms are mainly dominated by gram-negative obligate anaerobes [48]. Gram-positive aerobic bacteria, such as *Actinomyces* subspecies and oral *Streptococci* (*S intermedius* and *S oralis*) are responsible for the initial colonization in teeth surfaces [48]. Gram-negative anaerobic bacterium *F nucleatum* acts as a connecting link between early and late colonizers in the oral biofilms [48].

TABLE 1. Alterations in Predominant Bacteria in Oral Microbiome[6,7].

Alterations in Predominant Bacteria	Healthy individuals.	Dental patients
Firmicutes	Control	Elevated
Proteobacteria	Control	Elevated
Bacteroidetes	Control	Elevated
Actinobacteria	Control	Reduced
Fusobacteria	Control	Elevated

IV. NANO-ROBOT, A NOVEL ORAL HEALTHCARE.

Biology has entered a new era with the recent advances in nanotechnology, which have recently led the development of nano-sensor devices having nanoscale dimensions that are capable of probing the inner-space of single living cells [49]. Nanorobots with sizes comparable to bacteria could provide many novel capabilities through their ability to sense and act in microscopic environments [50]. Nanorobots would constitute any smart structure capable of actuation, sensing, signaling, information processing, intelligence, and swarm behavior at nanoscale [51]. A nanometer is a billionth of a meter, that is, about 1/80,000 of the diameter of a human hair, or 10 times the diameter of hydrogen atom. The nano robots will move inside the channels of the network and would have 'limited' window of interaction, through special valves with the outside environment [50]. They will interact with the outside terrain and chemically sense the presence of water or other targeted resources inside cell [50]. Nano-scientists have developed tiny nano-robots that are a mere quarter of a millimeter, powered by tiny piezoelectric motors, capable of swimming through the blood vessels to the cytoplasm [51]. The next step is to develop more efficient assembly methods, and to devise ways to control the nanorobots more accurately [51]. In the near future, it is possible that completely synthetic chemically propelled nanorobot will be developed [52]. The biomedical sectors will eventually benefit from nanorobot to perform useful tasks [52]. Nano-technology is being applied in dentistry to extend and expand treatment options [50]. Though

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no functional nanorobots have yet been developed but their design has already been suggested and is under research [53]. Nanorobots work at molecular level to perform major tasks in the field of medical fields. They have the potential to induce oral analgesia, desensitize tooth, manipulate the tissue to re-align and straighten irregular set of teeth and to improve durability of teeth [50]. Further nanorobots are used to do preventive, restorative, curative procedures [51]. Nanorobots will help dentists in managing complicated cases of microscopic level with ease and precision. Nanodentistry will make possible the maintenance of comprehensive oral health by employing nanomaterials, including tissue engineering, and ultimately, dental nanorobots [50]. Dental nanorobots might use specific motility mechanisms to crawl or swim through human tissue with navigational precision, acquire energy, sense, and manipulate their surroundings, achieve safe. cyto-penetration and use any of the multitude techniques to monitor, interrupt, or alter nerve impulse traffic in individual nerve cells in real time [52]. These nanorobot functions may be controlled by an onboard nanocomputer that executes preprogrammed instructions in response to nano- sensor in oral cavty [50]. The dentist may issue strategic instructions by transmitting orders directly to *in vivo* nanorobots via acoustic signals or other means [51].

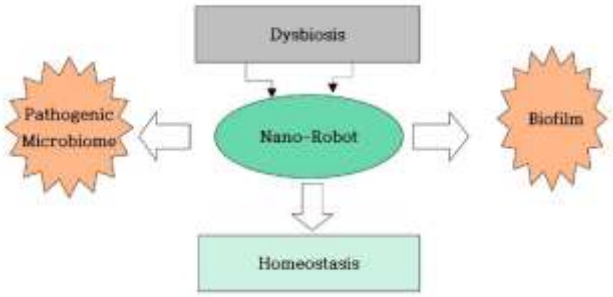

Fig. 2. Nanorobotic Wonders in Oral Healthcare.

Nano robots work in the oral cavity. Therefore, unlike nano robots that enter blood vessels or cells, immune problems rarely occur. Periodontitis occurs when pathogenic bacteria dominate the oral cavity. At this time, the balance between beneficial bacteria and harmful bacteria is broken. Nano robots that roam the mouth can easily be replaced on a regular basis. First, the nano sensor can monitor the number of pathogenic microbiome in real time. Nano-sensors could warn the patient or dentist the earliest time that pathogenic microbiome dominate the majority in oral cavity. Pathogenic oral bacteria form biofilms, and resist antibiotics. The drug-loaded nanorobot penetrates into the biofilm and removes it (Fig 2). Next, a nanorobot with powerful antibiotics approaches and removes pathogenic microbiome (Fig 2). Reducing the number of pathogenic microbiome induces the oral cavity to return to symbiosis from dysbiosis of microbes, restoring dental health. If nanotechnology is applied in the dental field, it can prevent dental diseases in advance.

V. CONCLUSION

Just as the dysbiosis of gut microbiome is the warning sign of colon health, so is the dysbiosis of oral microbiome. Properly controlling the number of pathogenic microbiome in the oral cavity is a key factor in dental health [50]. However, it is impossible to monitor the activity of oral microbiome in real time without the nanotechnology. If a nanorobot detects dysbiosis in oral cavity and reduces the number of pathogenic microbiome by dropping drugs in a timely manner, it could be maintain ed a healthy tooth by the age of 100, ensuring a high quality of life.

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