



Review

Human oral microbiota and its modulation for oral health

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ABSTRACT

The oral microbiome is an important part of the human microbiome. The oral cavity contains several significantly different niches with distinct microbial communities. A wide range of microorganisms inhabit the human oral cavity, including bacteria, fungi, viruses, archaea and protozoa. These microorganisms form a complex ecological community that influences oral and systemic health. The most prevalent oral diseases, dental caries and periodontal diseases, are microbiota-associated diseases. Moreover, increasing evidences have supported that many systemic diseases are associated with disturbances in the oral ecosystem, such as diabetes, cardiovascular diseases and tumors. The current control of dental plaque-related diseases is nonspecific and is centered on the removal of plaque by mechanical means. Due to this realization about the oral microbiome, several new methods based on the modulation of the microbiome that aim at maintaining and reestablishing a healthy oral ecosystem have been developed.

1. Introduction

Human are supraorganisms composed of both their own cells and microbial cells. The number of microorganisms residing on or in the human body is tenfold over that of the body's own cells [1]. These commensal microorganisms contribute to host health by resisting pathogens, maintaining homeostasis and modulating the immune system [2]. The National Institute of Health (NIH) of the United States (US) initiated the Human Microbiome Project (HMP) to characterize the human microbiome more completely and determine the association between changes of microbiome and health/disease [3]. The oral microbiome is one of the important parts of the human microbiome, and it refers specifically to the microorganisms residing in the human oral cavity [4].

The oral cavity has been considered to possess the second most complex microbiota in human body, only behind the colon [5]. The oral microbiome is highly diverse, including bacteria, fungi, viruses, archaea and protozoa. Approximately 700 species are present in the oral cavity, and most of them are indigenous [6]. Among them, approximately 54% have been cultivated and named, 14% are cultivated but unnamed, and 32% are known only as uncultivated phylotypes (from the Human Oral Microbiome Database). An increasing number of studies have demonstrated that the oral microbiota plays a vital role in the pathogenesis and development of many oral and systemic diseases.

In this review, we describe the microbial diversity of the oral cavity, expound microbial communities of different oral niches and present evidences that have confirmed the relationship between oral bacterial community shifts and oral or systemic diseases. Moreover, several prevention and treatment methods based on oral microbiota modulation are discussed.

2. Oral microbiome composition

2.1. Bacteria

Bacteria account for the main portion of oral microorganisms, and the major knowledge of the composition of oral bacteria comes from past culture-dependent methods. Culture-dependent techniques led to the identification of specific microorganisms thought to have a causative role in caries and periodontitis [5]. However, these data substantially underestimated the composition of the oral microbiome. The development of culture-independent methods, particularly targeting 16S ribosomal RNA, has expanded our awareness of the great richness and diversity of the oral microbiome. A list of oral bacteria with a description of their characteristics and genomic information are available from the Human Oral Microbiome Database website at www.homd.org. The oral bacterial community is dominated by the six major phyla, Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes

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and Fusobacteria, which account for 94% of the taxa detected. The remaining phyla, Saccharibacteria, Synergistetes, SR1, Gracilibacteria, Chlamydia, Chloroflexi, Tenericutes, and Chlorobi, contain the remaining 6% of the taxa (Human Oral Microbiome Database. Available at: <http://www.homd.org>).

Although our understanding of oral microorganisms has gradually deepened in recent years, there is still a large proportion of oral bacteria that cannot be cultivated in the laboratory. The major reason for uncultivable microbial species is that the conditions these microorganisms have been accustomed to in vivo have not been reproduced completely. Many microorganisms have unique requirements for survival, such as specific nutrients, accurate temperature and pH, and interaction with other microorganisms of their community [7].

2.2. Fungi

Fungi are present widely in the oral cavity. Not only as opportunistic pathogens of the elderly and immune-compromised, fungi are also members of healthy oral microbiota [8]. A detailed characterization of oral fungi has been reported, in which up to 101 fungal species are present in healthy subjects [9]. It was also observed that the number of fungal species in the oral cavity of each individual ranged between 9 and 23, and the *Candida* species were the most frequent, followed by *Cladosporium*, *Aureobasidium*, *Saccharomyces*, *Aspergillus*, *Fusarium*, and *Cryptococcus* [9].

2.3. Archaea

Archaea constitutes only a minor part of the oral microbiome and is restricted to limited species. The found species are *Thermoplasmatales*, *Methanobrevibacter*, *Methanobacterium*, *Methanosarcina*, and *Methanospaera*, all of which are methanogens [10–12]. They can be observed in healthy subjects, but their prevalence and numbers are elevated in individuals with periodontitis [2].

2.4. Viruses

Most viruses in the mouth are related to diseases. Herpes simplex virus causes primary herpetic gingivostomatitis, mucocutaneous orofacial disease and recurrent lesions on the face and lips [13]. Human papilloma virus causes many lesions in the oral cavity, including benign-like oral papillomas, oral condylomas and focal epithelial hyperplasia [14]. Additionally, HIV infection can also indirectly cause many oral manifestations, such as oral candidiasis, oral hairy leukoplakia, linear gingival erythema and necrotizing ulcerative periodontitis, and Kaposi's sarcoma [15].

3. Location of oral microbiota

The oral ecosystem is very intricate because it has several significantly different niches, including saliva, soft tissue surfaces of the oral mucosa and tongue, and hard tissue surfaces of teeth [16]. Different surfaces attract distinct microbial communities because each niche provides a unique ecosystem with the optimal conditions and nutrients for its populating microbes [17,18]. Therefore, microbiomes from the same site of different individuals were more similar than those from different sites of the same individual [19]. It has been reported that the profiles of 40 cultivable bacterial species have clear differences in saliva, surfaces of oral soft tissue, and supragingival and subgingival plaques from healthy subjects [20].

3.1. Saliva

The tissue surfaces and biofilms of the oral cavity are continuously infiltrated with saliva. The salivary microorganisms mainly come from the shedding of the biofilm on the surface of the oral tissue [21].

Therefore, the microbial profile of saliva is similar to that of the soft tissues, but saliva and soft tissue colonization differ obviously from that of dental plaque [22]. Approximately 3621 bacterial taxa in the saliva of 98 healthy subjects were identified, and Firmicutes (genus *Streptococcus* and *Veillonella*) and Bacteroidetes (genus *Prevotella*) were the predominant phyla [23]. Some proteins in saliva could coat the surface of the teeth and mucous membrane to promote microbial adhesion. However, some salivary proteins also promote the desorption, agglutination and removal of microorganisms by swallowing saliva [21]. Hyposalivation is generally thought to contribute to the development of oral diseases. It was found that the number of acidogenic and aciduric microorganisms increased in subjects with hyposalivation through analyzing the microflora in rinsing samples from healthy and hyposalivation subjects [24]. In addition, the salivary microbiota could be used as potential diagnostic and prognostic markers for several specific diseases, such as dental caries and oral cancer [22,25].

3.2. The surfaces of soft tissues

Despite unceasing shedding of superficial epithelial layers, the oral mucosa is persistently colonized by microorganisms [21]. Compared with other oral niches, the colonization of microorganisms on oral soft tissue is limited [2]. The surfaces of the cheek and palate have only monolayers of bacteria originating and desquamating regularly. In contrast, the surface of the tongue has multilayers of biofilm-like bacteria. Therefore, it is thought that higher density and more diverse microorganisms inhabit the tongue compared with other mucosal surfaces. The predominant microbiota on the tongue dorsa of healthy subjects were *Streptococcus salivarius*, *Rothia mucilaginosa*, and an uncharacterized species of *Eubacterium* (strain FTB41) [26]. The microorganisms on the tongue dorsa are closely related to halitosis. The crypts of the tongue allow anaerobic microbiota to flourish, which is an established source of halitosis [27].

3.3. The surfaces of hard tissues

One distinctive feature of the mouth is the presence of the tooth surface. The non-shedding surface of the tooth could provide a stable location for the development of biofilm [21]. Dental plaque is a structurally and functionally organized biofilm built on tooth surfaces. Plaque with a variety of microbes forms in an ordered manner and remains relatively stable over time [28]. According to the location, dental plaque is divided into supragingival plaque (above the gum line) and subgingival plaque (below the gum line).

The microbial community of supragingival plaque differs from that of subgingival plaque. A study that collected supragingival plaque from 98 healthy subjects found that Firmicutes and Actinobacteria (genus *Corynebacterium* and *Actinomyces*) dominated supragingival plaque [23]. Supragingival plaque is associated with dental decay on occlusal and approximal surfaces of the tooth, and these locations are the most susceptible locations for caries [21]. Microorganisms residing in these niches tend to produce acid and/or are resistant to an acid environment [21].

Along with the supragingival plaque that extends down to the subgingival area along the root, the film contains more serum and less saliva. The environment turns more anaerobic, and the pH and temperature become extreme. Based on the 16S rRNA sequence data, the predominant subgingival microbiome consists of 347 species or phylotypes that fall into 9 bacterial phyla, including Obsidian Pool OP11, TM7, Deferribacteres, Spirochaetes, Fusobacteria, Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes [29].

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