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Shaping the oral mycobiota: interactions of opportunistic fungi with oral bacteria and the host

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Abstract

The oral mycobiota is an important component of the oral microbiota that has only recently received increased attention. The diversity and complexity of the oral mycobiota in healthy humans is greater than any other body site. Dysbiotic imbalance of indigenous fungal communities in immunosuppressed hosts has been proposed to lead to oropharyngeal fungal infections. As in other body sites, to survive and thrive in the oral cavity fungi have to maintain mutually beneficial relationships with the resident bacterial microbiota and the host. Here we review our current understanding of the composition of the oral mycobiota and how it may be influenced by oral commensal bacteria and the host environment.

Graphical Abstract

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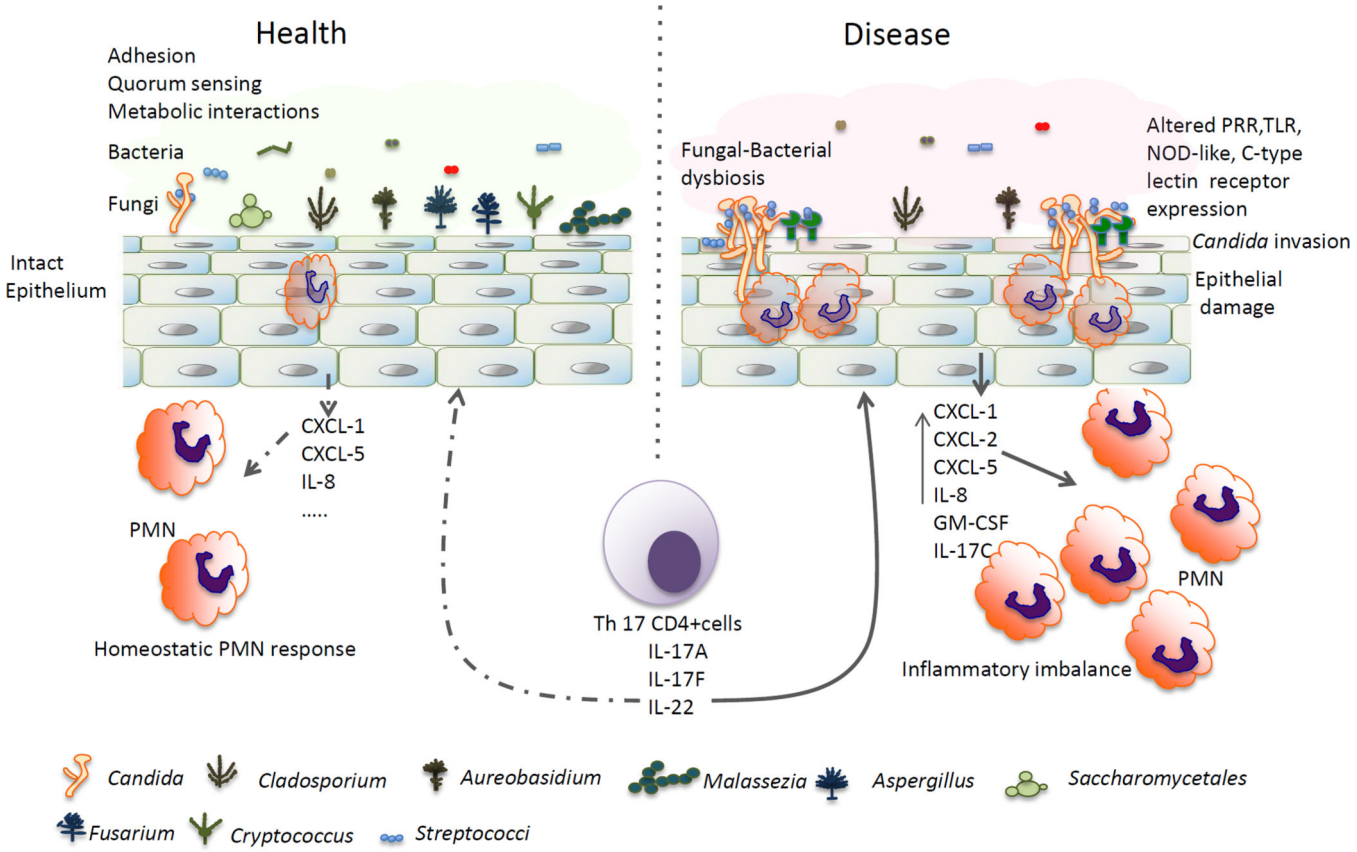

The oral mycobiota in heath and disease: Functional deficiency in the Th17 cell subset mediates a dysbiotic state characterized by *Candida* overgrowth. Commensal bacteria may interact with *Candida* species to augment the mucosal inflammatory response resulting in epithelial damage. PRR: Pattern Recognition Receptors, TLR: Toll-like receptors, NOD: Nucleotide-oligomerization domain

Keywords

oral mycobiota; bacterial interactions; host immunity

Introduction

The oral microbiota is a complex ecosystem primarily represented by the bacterial and fungal Kingdoms. Although not yet fully established, it has long been assumed that fungi are a minor component of the oral microbiota, compared to prokaryotes. Shotgun sequencing studies are needed to confirm this assumption. With the advent of new high-throughput sequencing methodologies, global analyses of the oral bacterial Kingdom received much more attention over the past few years compared to fungi. This is because sophisticated 16S rRNA gene sequencing pipelines and a comprehensive, curated sequence database that facilitates accurate oral bacterial taxonomic assignment have been available to investigators [1]. As a result, the complexity and biodiversity of the bacterial component of the oral microbiota in health, and community shifts in common oral diseases such as periodontitis and caries have been well characterized [2–6]. However, despite the possibility that bacterial

community shifts in these diseases may be influenced by fungal shifts, only one study included simultaneous analysis of fungi [6].

The mycobiota is a medically important component of the oral microbiota since opportunistic fungal infections commonly afflict the oral mucosa of immunocompromised hosts. Most infections are triggered by the genus *Candida* and are assumed to result from an overgrowth of indigenous species in a permissive host environment [7]. However, because only recently a universal DNA barcode was described for fungal identification [8], no studies have explored the role of global fungal population shifts during oral fungal infection and the ecological determinants of these shifts. As fungal genomic technologies are developing, explorations of the human mycobiome in different body sites have started to shed some light on the complexity and heterogeneity of fungal communities at these sites [9–12]. Recently, two studies describing the oral mycobiota have also emerged [13,14]. These studies are important because they gave new insights on the complexity of the core oral mycobiota in health. However, they did not contribute significantly to a deeper understanding of the relationships between the mycobiota and the resident bacteria or the host in the healthy state.

As in other mucosal sites, to survive and thrive in the oral cavity fungi have to develop mutualistic relationships both with the indigenous bacterial microbiota and the host. Mutualistic interactions of fungi with commensal bacteria involve physical binding, communication via signaling molecules, and metabolic exchange during co-adaptation in the multiple oral micro-environmental niches [15]. In addition, alterations in the host environment are essential in shaping the fungal microbiota composition and in the development of fungal diseases [15–17]. Thus, fungi, bacteria and host form complex and dynamic ecological relationships in the oral cavity. In this review, we summarized the current state in our understanding of the influence of commensal bacteria and host environment on colonization patterns and virulence of oral opportunistic fungi.

Core oral fungal microbiota in health

Assembling accurate information on the diversity and composition of the healthy state or core mycobiota is important for subsequent studies of fungal community shifts in oral diseases. The first insight into the diversity and composition of the oral mycobiome in health came from Ghannoum and colleagues [14]. This group utilized a novel multitag pyrosequencing approach to investigate the fungal taxa in the oral cavity of 20 healthy individuals. The diversity of the oral mycobiota was exemplified by the discovery of 85 fungal genera, including 74 culturable and 11 non-culturable [14]. Compared to the fungal diversity in skin and other mucosal sites this represents significantly greater diversity [17]. Increased diversity may be due to the constant exposure to environmental fungi via food intake and mouth breathing, and the diverse micro-environments present in the oral cavity which allow different taxa with unique nutritional requirements to thrive. This study used oral rinse samples, thus the diversity reflects the diversity in oral ecological niches such as the tongue, buccal mucosa and supragingival plaque. However, it is possible that the oral diversity was still underestimated since fungi forming tenacious biofilms with bacteria in anaerobic environments within gingival sulci or in periodontal pockets [18] are not well

represented in rinse samples. As expected, *Candida* species were most frequently identified (sequences detected in 75% of participants) and included one or more of the following species: *C. albicans, C. parapsilosis, C. tropicalis, C. khmerensis* and *C. metapsilosis*. Other oral fungal genera included *Cladosporium, Aureobasidium, Saccharomycetales, Aspergillus, Fusarium*, and *Cryptococcus*. Thirteen taxa were overall identified as core components of the "basal" oral mycobiome found in >20% of individuals sampled [14]. Interestingly, the true pathogenic fungi *Aspergillus, Fusarium*, and *Cryptococcus*, were identified as healthy oral colonizers for the first time. It is reasonable to hypothesize that these fungi may be under continuous surveillance and control by healthy immune systems. In this study low abundance (<1%) fungal sequences were not analyzed, potentially omitting low abundance organisms that may overgrow in disease states. Finally, the type of taxonomic analysis used may have led to the identification of a large percentage of sequences (36.1%) as non-culturable fungi [14].

More recently, the core oral mycobiota was revisited in a pyrosequencing analysis of internal transcribed spacer 1 amplicons in saliva samples of 6 healthy subjects [8]. In order to capture low abundance genera that might be present in a relatively large percentage of healthy individuals, this study did not apply a 1% abundance threshold for further taxonomic analysis. Also, although the sampling method was similar to the earlier study of the oral mycobiome [14], taxonomic assignments were generated using a different database that excludes "uncultured" reference sequences. Despite the differences in methodology between the two studies there was substantial overlap in defining the core oral mycobiota. Seven consensus members of the core oral mycobiome, *Candida*/*Pichia*, *Cladosporium*/*Davidiella*, *Alternaria*/*Lewia*, *Aspergillus*/*Emericella*/*Eurotium*, *Fusarium*/*Gibberella*, *Cryptococcus*/*Filobasidiella*, and *Aureobasidium* were identified [13,14]. Five genera that were identified in all healthy individuals only in the second study [13], were *Malassezia*, *Irpex*, *Cytospora*/*Valsa*, *Lenzites*/*Trametes*, and *Sporobolomyces*/*Sporidiobolus*. Although *Malassezia* is a bona fide human skin commensal and pathogen [19], it was also identified in the sputum of all cystic fibrosis patients sampled by Hogan and co-workers [12], suggesting that the oral cavity may be a portal of entry for this organism into the respiratory tract under compromising host conditions. The other four genera are common soil and/or plant pathogens, raising the possibility that they are transient and not stable colonizers of the oral cavity. Longitudinal sampling of the same individuals is required to resolve this issue.

Several challenges remain in interpreting and integrating data on the composition of the core oral mycobiota using fungal genomic or metagenomic approaches from different groups. First, there is lack of uniformity in the utilization of curated databases among studies. Since fungal taxonomic nomenclature differs in each database, and in fact is continuously evolving as more sequences become available, interpretation of sequence data from different groups becomes a formidable task [17,20]. Although further curation is needed, a recently updated ITS1 sequence database for use in the Visualization and Analysis of Microbial Population Structures website, may provide a useful tool for more standardized metagenomic analyses of human samples by different groups [12]. Second, a consensus abundance level in each sample that "qualifies" sequences for further taxonomic analysis is lacking. This may affect our ability to discriminate between transient environmental passers-by and low abundance

but stable colonizers. Thirdly, because of large subject to subject variability in sequencing data [13,14], the number of healthy individuals sampled may have a great impact on which fungal genera are identified as members of the core fungal microbiota. The identification of a large proportion of sequences as unculturable fungi [14] and challenge in utilizing culture methods to verify sequence data, sometimes even for culturable species [21], raises the question whether these data should be verifiable with culture approaches before new organisms are “fully vetted” as bona fide members of the core mycobiota.

Influence of host environment on the oral mycobiota

Several core components of the oral mycobiota are stable intra-individually over time but variable between healthy individuals [22]. However, virtually nothing is known about host factors affecting the composition of the oral mycobiota in health that could explain the inter-individual variability. Ghannoum and co-workers suggested that such differences may be associated with gender or ethnicity, but evidence is weak due to limited sample size and lack of consistency across all gender groups and ethnicities [14].

Systemic host health alteration is associated with most oral fungal diseases, regardless of whether they result from overgrowth of indigenous species as in the case of candidiasis, or from exposure to environmental pathogens, as in the case of oral histoplasmosis. This underpins the universal importance of a permissive host environment in influencing colonization or overgrowth of fungal organisms in the oral cavity. Although alterations of host immunity have been hypothesized to directly impact the core oral mycobiota composition leading to a disease-promoting dysbiotic state, there are limited studies to date that have examined global oral fungal community shifts in immunosuppressed humans. A global analysis using 454 pyrosequencing showed a significant shift in the oral mycobiome, with *Epicoccum* and *Alternaria* abundantly colonizing HIV-infected patients but not healthy individuals, whereas *Candida* was abundant in both groups [16]. In pharmacologically immunosuppressed solid organ transplant recipients both culture and pyrosequencing studies showed the oral mycobiota to be dominated by *Candida* species [23–25]. *Candida* species load and diversity were positively correlated with the dose of mycophenolate mofetil in a renal transplant population, suggesting a causal link [24].

Several types of genetic disorders are also associated with *Candida* overgrowth and increased risk of infection, such as chronic mucocutaneous candidiasis and the autoimmune polyendocrine syndrome type I [17]. However, global changes in other members of the oral mycobiota have not been examined in these conditions. A common underlying link between all known host systemic conditions associated with oral *Candida* overgrowth is functional immunodeficiency in the Th17 CD4+ cell subset, confirming their central role in mucosal protection.

The innate oral epithelial fungal recognition systems and subsequent responses that drive a protective Th17 immunity in the oral mucosa are presently unclear. Toll-like receptors, NOD-like receptors, and/or C-type lectin receptors may survey fungi that come in contact with the superficial oral epithelial cell layers and trigger appropriate responses controlling the growth of certain fungal species, while sparing others, to maintain a homeostatic

balance. Along these lines an analysis of the intestinal mycobiota in Dectin-1 knout-out mice with experimentally-induced colitis showed that the proportion of opportunistic pathogenic fungi including *Candida* and *Trichosporon* increases, whereas nonpathogenic *Saccharomyces* decrease [26], which suggests that dectin-1 has role in maintaining a homeostatic fungal community balance in the gut. Whether the oral mycobiota is similarly affected by a functional deficiency in recognition receptors is unknown, although C-type lectin receptors such as CLEC6A have been proposed as suitable candidates [17]. On the other hand, a fungal-bacterial dysbiotic state associated with overexpression of certain oral epithelial pattern recognition receptors, such as TLR2, may lead to an aggravated inflammatory response to fungal opportunistic pathogens, that promotes neutrophil-mediated oral pathology [27].

Influence of oral bacteria on the mycobiota

There is a growing understanding that bacterial and fungal communities are integrally associated in the oral cavity, since they occupy the same micro-environmental niches. However, only two studies to date have examined both the bacterial and fungal component of the microbiota in the same oral samples using next generation sequencing [16, 23]. The two studies tested the hypothesis that in immunosuppressed states oral fungal community shifts are accompanied by shifts in bacterial communities. However, a study of HIV+ individuals reported that fungal community shifts occurred in the absence of significant bacterial shifts [16]. Despite this general observation, some data in this study suggested that positive associations between certain fungal and bacterial taxa identified in health, diminished and even became negative in the HIV+ host background [16]. A study conducted in lung transplant recipients showed distinct shifts in both the bacterial and fungal oropharyngeal communities associated with immunosuppression [23]. However this study did not perform statistical analyses to evaluate the strength of associations between specific bacterial and fungal genera. Interestingly, the vast majority of lung transplant recipients were co-colonized with an increased abundance of *Streptococci* and *Candida* species [23].

Because *Candida* species are the most amenable to isolation, identification and culture, culture studies have concentrated on the effects of bacteria on this genus. Changes in bacterial diversity or abundance by antibiotic treatments may increase oral *Candida* growth in humans, albeit with lower frequencies or intensities compared to other mucosal sites [28]. In immunocompromised patients on long-term prophylactic antibiotics erythematous candidiasis is common [29], but the combined effects of antibiotics and immunosuppression may be required for fungal infection. There are no high-throughput sequencing studies on the effect of antibiotics on the oral mycobiota in humans or animals.

Interestingly, a triple antibiotic combination treatment that significantly diminished gut bacterial diversity in mice, resulted in sustained, high-level GI colonization with *C. albicans*, a species not indigenous to mice. Even more interesting was the fact that high-level *C. albicans* colonization in antibiotics-treated mice was associated with high probability of increased relative abundance of *Streptococcus* [21]. These results are in agreement with the reduced bacterial diversity and high levels of oropharyngeal colonization with *Streptococci* and *Candida* in lung transplant recipients receiving antibiotic prophylaxis

[23]. Taken together, these reports suggest that *Streptococci* and *C. albicans* may interact through several molecular mechanisms to promote synergistic upper and/or lower GI tract colonization in mammalian hosts.

Because *C. albicans* and viridans *Streptococci* are dominant oral commensals in humans, the molecular mechanisms of their interaction have been extensively studied and include physical adhesion, signaling molecules and metabiotic molecules that may influence fungal growth, gene expression and pathogenicity [reviewed in 15]. Early studies showed viridans species to form biofilm communities with *C. albicans* in vitro in which the hyphal biomass was enhanced [30,31]. Co-aggregation interactions between *C. albicans* and oral *Streptococci* are mediated by adhesins that are multifunctional proteins [32–34]. Co-aggregation also requires fungal O-Mannosylation and benefits from the synthesis of bacterial and fungal exopolymers such as soluble α- and β-glucans [35–38]. Oral *Streptococci* can have a positive effect on hyphal growth via quorum sensing molecules, such as autoinducer-2, and small metabolic molecules, such as hydrogen peroxide [8,39]. Gene expression analysis of *C. albicans* forming polymicrobial biofilms with oral bacteria in vitro showed that known virulence genes encoding certain secreted aspartyl-proteinases (SAP4/SAP6) were up-regulated [40]. Altering virulence gene expression patterns as a result of cell-cell signaling in polymicrobial biofilms may play a significant role in disease development.

It is possible that positive fungal-bacterial interactions result in enhanced fungal colonization of sites favored by bacteria that may otherwise not be populated by fungi, as in the case of the mouse gut or human tooth surfaces by *C. albicans* [18,21]. Increased fungal colonization of ectopic sites combined with increased virulence gene expression may promote disease development in these sites. Although strong evidence of pathogenic synergy in humans is lacking, organotypic model and animal studies showed that certain oral streptococcal species display synergistic virulence with *C. albicans* on oral mucosal or tooth surfaces [27, 37, 40, 41].

Future directions

The roles that individual members of the core oral mycobiota may play in the community dynamics that sustain health or promote disease remain to be elucidated. Characterizing the interactions of newly recognized members of the core oral mycobiota with dominant *Candida* and *Streptococcal* species and assessing their impact on community development is an important first step in our understanding of the role of these fungi in health or disease. A reappraisal of the pathoecology of common oral fungal diseases such as oropharyngeal candidiasis using metagenomic sequencing is currently needed. Shotgun sequencing approaches may not only reveal new fungal genera associated with fungal disease but may also unveil previously unrecognized roles for oral bacteria or the host response in pathobiology. Improved statistical models to more accurately estimate the effect size of host and bacterial parameters have to be employed in such high-throughput surveys [21].

The representation of unculturable fungi in healthy and disease states needs to be accurately assessed and progress needs to be made in their culturability. Microbial loads in addition to

mere presence of certain species have to be assessed, as there is considerable overlap in species community membership in oral health and disease for both fungal and bacterial organisms [3,15]. However, even when coupled with qPCR quantification [12], next generation sequencing data cannot differentiate between live and dead organisms. Until these methods are optimized to prevent genomic amplification in non-viable cells, microscopic, culture and/or biochemical approaches will be needed for definitive species identification or quantification. In addition, coupling phenotypic heterogeneity with genomic information (reviewed by Scaduto and Bennett, this issue), as in white, opaque, or grey cell morphologies associated with ploidy in *Candida* (reviewed by Gerstein and Berman, this issue), holds great promise in identifying novel community-based traits associated with health or disease states. Finally, development of appropriate infection models to include fastidious fungal organisms in the study of microbial community-level interactions with the host, coupled with integrated systems-based approaches, are needed to improve our understanding of the transition to dysbiosis and loss of homeostasis in the oral mucosa.

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Highlights

- The membership of the core oral mycobiota in health has been defined
- Global community shifts in disease have not been identified yet
- Host influences composition and pathogenic activity of the oral mycobiota
- Commensal bacteria may contribute to a fungal dysbiosis