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Mini Review

Frontiers in Human Mycobiome in Health and Disease

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Introduction

The humans are colonized by abundant and diverse fungi, collectively referred to as mycobiome which has garnered much less attention to date than the colonizing bacterial microbiome. The advancement of next-generation high throughput sequencing technologies have expanded our knowledge substantially in human microbiome and gradually in human mycobiome in association with health and disease [1,2]. Different fungal taxa were identified in the intestines, oral cavity, skin, vagina and lungs, varying across body sites [3], and also over time and with diet, environment and diseases [4,5]. In human gut, *Aspergillus, Candida, Debaryomyces, Malassezia, Penicillium, Pichia, Saccharomyces, Cladosporium, Clavispora, Cyberlindnera*, and *Galactomyces* are the most prevalent fungal genera [6-8]. Particularly, the species *Candida albicans* colonizes the oropharynx, genital, and gastrointestinal mucosa of 30-70% of healthy individuals [9]. Moreover, fungi of the genus *Malassezia* predominated the skin mycobiome [10], while *Aspergillus* species and *Scedosporium* species are regularly inhaled by lungs in humans [3]. In addition, fungal genera including *Candida* and *Saccharomyces* were identified in breastmilk [11,12]. Edible mushrooms, plant pathogen and xerophiles (all fungi) were found in vegetarian gastrointestinal tract [13,14].

Fungi have been existing at low levels in human, as commensals without causing disease in steady state, which however, under conditions of host immunosuppression, bloom to cause a life-threatening illness. For instance, in diease settings, *Cryptococcus neoformans* leads to lung pathologies [15], *Mallassezia* leads to skin disorders [16], *Candida* leads to airway inflammation [17] and *Porphyromonas gingivalis* leads to periodontitis [18]. Apart from the pathogenic role of fungi, certain fungi (*Candia albicans or Saccharomyces cerevisiae*) were revealed to be able to safeguard local and systemic immunity against injury to mucosal tissues, positively calibrating the responsiveness of circulating immune cells [19]. The dual role of human commensal fungi remains to be further defined in humans, given the large variability in human health and disease state.

A number of studies have shown mycobiome dysbiosis in diseases, including inflammatory bowel disease [20,21], obesity [22], antibiotic-associated diarrhea [23], hepatitis [24] and graft versus host disease [25]. It is often assumed that fungal diversity should be greater in more severe cases of a disease [15]. Prior studies indicate that patients with diseases such as ulcerative colitis, Crohn's disease, and gastric ulcers were more heavily colonized with the species *Candida albicans* [26,27]. In obese gut mycobiomes, the phylum *Ascomycota, classes Sacharomycetes, Tremellomycetes* and *Cystobasidiomycetes, families Erythrobasidiaceae* and *Dipodascaceae* and *genera Aspergillus, Eurotium* and *Rhodotorula* were found increased, compared to non-obese gut mycobiomes [22]. In addition, *Cladosporium herbarum* and *Candida albicans* were detected as the most abundant species in 80% of patients with diabetic foot ulcers, a common result of diabetes-induced chronic skin infections [28]. These two highly abundant fungi may form polymicrobial biofilms when co-cultured *in vitro* with bacteria, although their relatedness with wound healing versus exacerbation has yet to be dissected. Albeit, most of the current mycobiome studies in human diseases were associative without definitive causal or consequential role established, which necessitates more efforts to be devoted to unveiling the function of fungi, as well as the underlying mechanisms of actions, in humans.

Of note, causal versus consequencial relationship is elusive in disease, synergistic or competitive interactions between the mycobiome and the bacterial microbiome also play critical roles in health and disease. Antibiotic treatment is often associated with the results of fungal expansion in the gastrointestinal tract [29,30]. Similarly, gut environment may favor fungi at the cost of bacteria at the condition of Crohn's diseases [21], uncovering a balance between bacterial and fungal communities in healthy and steady

state. However, the alterations in the mycobiome is primary or secondary to the disruption of bacterial microbiome in diseases remains unknown.

As our knowledge of human-associated fungi is largely lacking compared to a wealthy knowledge of human commensal bacteria, both in terms of the mycobiome composition and function, it is imperative to develop complete and accurately curated database for mycobiome analysis, and to functionally elucidate the symbiotic versus pathogenic roles of human fungi under various conditions for host physiology. Due to the multi-dimensional inter- and intra-kingdom interactions, the intricate fungal-fungal, fungal-bacterial and fungal-viral relationships also warrant in-depth investigation for improving our perception of the inner-working of the complex human microbiome in health and disease.

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