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Bacterial-fungal interactions and their impact on Human Mucosal Mycobiome

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Abstract

With the advent of high-throughput sequencing techniques, the astonishing extent and complexity of the microbial communities that reside within and upon us has begun to become clear. Moreover, with advances in computing and modeling methods, we are now beginning to grasp just how dynamic our interactions with these communities are. The diversity of both these communities and their interactions-both within the community and with us-are dependent on a multitude of factors, both microbial- and host-mediated. Importantly, it is becoming clear that shifts in the makeup of these communities, or their responses, are linked to different disease states. Although much of the work to define these interactions and links has been investigating bacterial communities, recently there has been significant growth in the body of knowledge, indicating that shifts in the host fungal communities (mycobiome) are also intimately linked to disease status. In this review, we will explore these associations, along with the interactions between fungal communities and their human and microbial habitat, and discuss the future applications of systems biology in determining their role in disease status.

Keywords: Mycobiome, Microbiome, bacterial-fungal interactions, fungal-fungal interactions, host-fungal interactions, systems biology

Introduction

With the global burden of fungal diseases rising, researchers have begun to turn to next-generation sequencing (NGS) technology to investigate the role fungi play in the spectrum of human health and disease. At the forefront of this advancement is the "Super organism" hypothesis, where humans are considered to be complex organisms made up of numerous mutually independent smaller organisms (i.e., bacteria, fungi, virus, and archaea) and their genomes. This group of microbial cells and their genomes are collectively referred to as the human microbiota and microbiome, respectively. Over the past decade, the bacterial portion of the microbiome has been well characterized in a number of health and disease states of man, including: Type 2 diabetes [1]; liver cirrhosis; colon cancer; rheumatoid arthritis, and; inflammatory bowel disease. In contrast, however, research into the mycobiome (the fungal proportion of the microbiome) has received less attention, such that the field of mycobiome research is still in its infancy.

There are currently several common challenges facing microbiome and mycobiome researchers. First, irrespective of their biomass, fungi account for a relatively small percentage of the human microbiome compared to their bacterial counterparts [2]. Second, similar to what we have seen with bacteria, the isolation of nucleic acids from fungal cells can be problematic, and often requires a combination of enzymatic, chemical and mechanical lysis steps. Third, the ability to discriminate between fungal taxa is influenced by sequencing primer choice and, finally, curated databases for taxonomic assignment and/or the annotation of fungal genomes are lacking or are incomplete. It is against this backdrop that a number of authors have begun to unravel the mystery of the human mycobiome.

Akin to the microbiome, the human mycobiome has been shown to play an integral role in the pathology of health and disease in man. In fact, changes to the mycobiome have been shown to play vital roles in the modulation of the host immune response, disease progression [3], the maintenance of microbial population structures, as well as metabolic functioning of the host. This review aims to explore the current status of human mucosal mycobiome research, focusing on the gastrointestinal tract.

The Mycobiome

The advancements we have seen in high-throughput NGS technology over the past decade, has dramatically changed the landscape against which we study the mycobiome. From traditional, culture-based methodologies, we have moved towards the use of amplicon based technologies that target fungal specific house-keeping genes, which allow researchers to identify both cultivatable and non-cultivatable fungal species in a wealth of environmental samples. Theses fungal house-keeping genes are situated within the fungal ribosomal RNA gene cluster (rRNA), and include the 18S rRNA, 5.8S rRNA and 28S rRNA genes, as well as the internal transcribed spacer regions (ITS1 and ITS2). Similar to what has been seen with the 16S rRNA gene in amplicon-based bacterial microbiome studies, there is currently a lack of consensus between authors regarding which genetic target offers the best level of taxonomical and phylogenetic resolution, and as such several alternative primer sets exists that target different regions of these fungal genes (Cui et al. gives a good overview of the different fungal rDNA primers used in mycobiome studies to date). Confounding this issue in mycobiome studies is the lack of completely sequenced and annotated fungal genomes that can be used for taxonomic identification. Current fungal rRNA databases routinely used to assign fungal taxonomy in microbiome studies include UNITE for ITS, SILVA for fungal 18S and 28S rRNA genes, as well as RDP [4] for fungal 28S rRNA genes.

Unlike the field of microbiome research, mycobiome studies

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tend not to use shotgun metagenomic sequencing approaches. As metagenomic approaches simultaneous sequence all of the genetic material within a sample (host, bacterial, fungal, archael, etc.), they have the potential to generate both taxaonomic and functional information. However, this technique relies on a lot of computational power and is limited by the inclusion of both bacterial, fungal and archael genes in reference catalogs [5]. In fact, in a current metagenomic reference catalog used for studying gut microbial populations, only 0.1% of the 3.3 million reference genes were reported to be of eukaryotic origin. Until we overcome the limitation posed by a lack of fungal reference genes in these catalogs, the true potential of mycobiome research using metagenomic approaches cannot be fully realized.

Mucosal Mycobiomes in Health and Disease

There is mounting evidence linking the host's mucosal microbiomes to the modulation of host immunity. One's ability to untangle the complex interactions between the microbiota, mycobiota and immune response at a given body site begins with developing an understanding of which microbes frequently call these mucosal niches home. A summary of our current knowledge of the mycobiota and microbiota that colonize the oral cavity and the lower gastrointestinal tract (GIT) in states of health [6].

The Oral Mycobiome

The concept of a "core healthy oral mycobiome" was introduced in 2010 by Ghannoum and colleagues when they characterized the oral mycobiome of 20 healthy adults. In this study interrogation of ITS1F/ITS2 sequences identified a total of 85 fungal genera within the oral cavity, 11 of which related to non-culturable fungal genera. Although the exact number of fungal genera in the oral cavity varied between participants (range 5–39), a core set of genera were identified in the oral cavities of more than 20 percent of study participants: Candida (75%); Cladiosporium (60%); Aureobasidium (50%); Aspergillus (35%); Fusarim (30%), and; Cryptococcus (20%). The high prevalence of Candida in the oral cavity is consistent with previous culture-based studies, and subsequent molecular studies confirmed the high prevalence of Candida spp. within the oral cavity, reporting Candida albicans, Candida parapsilosis and Candida dubliniensis as the most abundant oral Candida species.

The constituents of the "core healthy oral mycobiome" were refined in 2014, when Dupuy and colleagues identified only eight of the key oral mycobiome genera originally classified by Ghannoum et al. in their healthy saliva samples. This highlights that although a healthy core oral mycobiome may exist, the overall abundance and diversity of fungal taxa may be somewhat individualized [7]. One of the most interesting aspects of this study was the report of a relative high abundance (13–96%) of Malassezia within the oral cavity of their entire study cohort, which is in contrast to previous studies which failed to identify Malassezia spp. at all. Although, subsequent molecular studies are yet to confirm the reports of Malassezia within the oral cavity of man, its presence can be logically explained. First, Malassezia is a common skin commensal that has been isolated from the nares and respiratory tract of man, thus its presence in the oral cavity is not unexpected. Secondly, as Malassezia has a relatively robust cell wall structure, the choice of cell lysis methodology may significantly affect the ability to isolate Malassezia DNA, resulting in a subsequent underestimation of fungal abundance. In light of this, it is important to consider here the differences in the DNA extraction processes used in the two studies. In fact, both studies used the same FAST DNA Spin Kit for DNA isolation; however, Dupuy et al. modified the protocol to include a robust mix of ceramic and zirconia beads to facilitate mechanical digestion, and also tripled the timing at the homogenization step.

The importance of bacterial-fungal, and fungal-fungal interactions in the homeostatsis of oral health, was recently highlighted in individuals with and without HIV. In this study, the authors concurrently profiled the microbiome and mycobiome in the oral cavity of 24 subjects and identify a number of significant fungal-fungal correlations in individuals with and without HIV. Although both Candida and Penicillium were isolated from the oral cavity of all individuals, significant differences in the overall mycobiome profiles were identified between the health and disease states. For example, Alternia, Epicoccum and Trichosporon were only found in HIV positive patients, whilst Pichia, Cladosporium and Fusarium were associated with health. In contrast, assessments of the microbial populations, identified a stable oral microbiome between the two groups, predominated by Streptococcus and Prevotella. When the authors evaluated the bacterial-fungal relationships in this dataset, they identified a number of significant correlations, including a significant negative correlation between the abundance of Rothia and Cladosporium in the oral cavity of healthy individuals [8], although no mechanistic justification for this correlation has been given. Interestingly, the authors go on to identify an antagonistic effect between the oral fungal genera Candidia and Pichia, such that a relative increase in Pichia colonisation was associated with a reduction in the abundance of Candida. Highlighting the importance for elucidating the role of bacterial-fungal and fungal-fungal interactions on microbiome and mycobiome community structures as well as health and disease.

The Gut Mycobiome

Perhaps the most widely studied fungal niche in humans is the gastrointestinal tract. The higher burden of fungal cells in the gut compared to other body niches, along with the wealth of data linking the gut microbiome to systemic inflammation makes the gut mycobiome an important area of study. Numerous authors have begun to unravel the role of the mycobiome in gut health, and disease, including; inflammatory bowel disease (IBD), obesity, and inflammation.

Molecular studies of the gut mycobiome have identified that healthy stools contain fungal genera belonging predominately to either the Ascomycota or Basidiomycota fungal taxa [9]. Furthermore, these studies report a rich and diverse fungal community within the GIT of healthy individuals which is predominated by Candida, Saccharomyces, Trichosporon and Cladosporium.

Modeling of the Mycobiome, Microbiome and Host Interactions

Metagenomic analysis can provide information for the genes and species of the bacteria and potentially fungi, and through using different functional databases such as KEGG, the metabolic functions of these communities can be determined. However, due to the extreme complexity of human microbial ecosystems, multi-omics analyses are incapable of dissecting the overall metabolism of these ecosystems from community-level to individual level and thus elucidating the interactions between microbial species/strains, microbe and host, and other environmental factors. In the study of these complex biological ecosystems, mathematical modeling can provide critical insights that will assist in understanding the underlying mechanisms of these complex systems through the evaluation and testing of different hypothesis [10]. Among these mathematical models, genome-scale metabolic models (GEMs) are perhaps the most important, and have been used to understand the molecular mechanisms of individual organisms in a biological system through the analysis of genotype-phenotype relationships. Tissue/cell specific GEMs have been

successfully applied to both human health and disease, to identify novel biomarkers for early diagnosis and efficient treatment of a variety of conditions, such as non-alcoholic fatty liver disease and certain cancer cell-types. GEMs have shown their worth and utility in the study of fungi, through prediction of their phenotype in taking up different substrates, the effects of gene knockouts and as a platform for network independent analyses to identify key metabolites and sub-networks.

Recently, these powerful tools have been applied to the study of microbial communities, such as human gut microbiome. Using GEMs in community metabolic modeling can successfully predict the contribution of individual species and interactions between them to the overall simplified community metabolism and elucidate the interactions between the bacteria [11].Through the generation of comprehensive toolboxes for community modeling, such as CASINO (Community And Systems-level Interactive Optimization), and the use of GEMs for predominant bacteria in human gut, the alteration in the amino acid profile of both feces and serum in response to diet interventions can be simulated and validated. These successful examples of metabolic modeling of human tissue/cell-lines, fungi, and microbiome communities pave the way for the application of these methods on mycobiome research, enabling us to better understand the interactions between fungi and bacteria, other fungi and their host habitat; this allows us to elucidate their role in different diseases [12], alongside their overall contributions in human host-microbial metabolism.

Conclusions

As we develop an improved understanding of the pivotal role played by microbial communities in health and disease, we also increase our appreciation for the key role played by fungal communities in these situations. These fungal communities unsurprisingly show significant variation between different body habitats and with changes in disease status. We are beginning to grasp the significant role that these variations play in host homeostatic responses and pathologies, although our understanding here is still very much in its infancy. As we develop an increasing understanding of how factors such as host and microbial responses impact on the mycobiome and, likewise, how the mycobiome affects other microbial communities and the host, so we will improve our ability to predict the significance of changes in the mycobiome on host status. As we move forward, the importance and significance of advanced in silico modeling techniques (such as GEMs) associated with systems biology will be of ever-increasing importance, enabling us to create even more complex predictions of the role of different species, cell types and metabolites, with the ultimate goal of being able to determine specific, personalized interventions that improve the health of an individual.

Conflicts of Interest

The authors declare no conflict of interest

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