THE ROLE OF MICROFUNGI IN THE HUMAN GUT MICROBIOTA

Abstract

The gut mycobiome has recently gained significant attention due to its vast myriad of implied roles. The fungal commensalism residing in human guts, in low amounts, is involved in host homeostasis, digestion, mental balance and immunity. Several antifungal have been seen useful in relieving symptoms of neurological diseases. Dysbiosis of different fungal species is proved to be associated with gastric, autoimmune, and psychiatric diseases. A deeper understanding of the nature of dysbiosis involved in diseases and immunity can prove gut fungi to be instrumental in clinical treatments.

Keywords: gut mycobiome; dysbiosis; neurological diseases; microeukaryotes; gastric disorders; immunity

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I. INTRODUCTION

Microbes, both beneficial and harmful, which reside as communities all over our bodies are collectively called the human microbiome. Specifically in the gut, bacteria, archaea, protists, viruses, and fungi colonize to form an essential ecosystem [1], called the gut microbiota. The fungi here are termed as the gut mycobiome [2].A fungus-free existence is both implausible and undesirable. Gut microbial studies have primarily focused on gut bacteria until very recently, due to the larger quantity of the bacteriobiome, and to the sole and limiting prominence of culture-dependent methods of studying fungi. Techniques like polymerase chain reaction and next generation sequencing are now helping DNA-based detection of this less studied diversity of fungal communities of the human gut. This is crucial, because fungi occur as commensals as a part of our holobiomes and are crucial in maintaining the ecology in our guts along with the other gut communities. They do not live isolated, they interact extensively and benefit the host, provided they occur in low amounts.This multi-kingdom diversity and interplay of gut microbes is fundamental in maintenance of health and homeostasis of the host and their dysbiosis has been linked to several diseases[1], including the inflammatory bowel diseases[3], diabetes[4, 5] and cancer[6]. It is also clear now that fungi in the gut act as "intestinal vaccines". The potential of utilizing fungal metabolites in clinical applications is being examined.

II. GENERAL COMPOSITION AND INTER KINGDOM INTERACTIONS

By far, fungi occupy less than 0.1% of the total human gut microbiome (by genomic equivalence)[7]. The members of the phylum Ascomycota, and fewer members from phyla Zygomycota and Basidiomycota are prevalent. The most predominant genera in the intestinal niche are *Malassezia, Candida,* and *Saccharomyces* [8], although there also occur *Cryptococcus, Aspergillus, Cladosporium, Fusarium, Penicillium, Pichia, Trichosporon*among others [9]. The composition varies among humans, genders, and ages, the reason behind which is not apparent. It is hypothesized that distinct colonizationfrom mother during birthand different environmental exposures such as antibiotic use and diet early in life bring about such diversity among individuals. Infants have the most dynamic communities, where all carry *C. albicans,* although the fewer number of fungi in infants is probably because they are yet to be fully colonized[10]. Healthy females have higher fungal diversity than healthy males[10].

Yeasts, discovered in stool samples in the early 20th century, were considered to be saprotrophs in the intestines of humans. *Candida albicans,* at its colonization levels (1-2% of the total fungal count), interacts with the archaeon*Methanobrevibacter* to ingest carbohydrates in our diet [11]. On the other hand, *Saccharomyces* and *Pichia* can independently help to keep *Candida*levels under control within the commensal level, since increase in their number would lead to diseases. Fungi can also participate in forming 'mixed-species biofilms', characteristic of different diseases including Crohn's disease[12],which enable the different communities involved to remain more protected and grow better[10].

III. RELEVANCE OF GUT MYCOBIOME IN DISEASES

1. **Role in Gut-Brain Axis and Neurological Diseases:** Several clinical and experimental evidences for the role of fungi in the gut-brain axis can be seen. *Sterilized animals show increased blood-brain barrier permeability, changes in the myelin sheath and anxiety-depressive behaviours[13]*.The fungal diversity of anorexic patients showed certain species of fungi including Aspergillus ruber, Penicillium solitum, and Cladosporium bruhnei which were previously not found in healthy humans [14].

   Autism spectrum disorder (ASD) patients showed a trend involving an increased abundance of the genera*Candida*,*Saccharomyces* and *Aspergillus*. Out of 507 studied species, the levels of *Aspergillus versicolor*weredecreased while those of*Saccharomyces cerevisiae*were increased in children with ASD when compared to control [15].Patients with Rett Syndrome showed elevated *Candida* levels [16].

   Schizophrenic patients showed increased quantitiesof*C. albicans* and *S. cerevisiae*[17]. Psychiatric symptoms were improved using probiotics with *Lactobacillus rhamnosus* and *Bifidobacterium animalis*, which essentially reduced *C. albicans* levels in the blood as a remedy[18].On sequencing fungal rRNA ITS1 gene from Alzheimer's disease (AD) patients, certain families of fungi were notably higher in amount - the specific genera *Botrytis, Kazachstania, Phaeoacremonium* and *Cladosporium*were abundant compared to healthy individuals, and the patients' mycobiomes were closely linkedto their diets, individualbacteriobiomes and their corresponding AD markers [19].

2. **Role in Gastric Disorders and Cancers:** Gut fungi were seen involved closely with the inflammatory bowel diseases (IBD). There are two IBDs, Crohn's disease (CD) and ulcerative colitis (UC). IBD-affected individuals carry greater quantities of fungi in their guts.IBD patients' guts are found to have, at the phylum level, a significantly increased Basidiomycota to Ascomycota ratio; at the genus level, *Candida* increases while *Saccharomyces* decreases [20]. *Malassezia* levels are seen to rise in IBD patients, with UC patients specifically showing a negative correlation between *Malassezia* and bacteria; the association between *Malassezia* and IBD may be attributed to the aryl hydrocarbon receptor [21].*Candida tropicalis*, *E. coli* and *Serratia marcescens* increase in Crohn's disease patients, which interact and stick together to form digestive plaques (mixed-species biofilms) [12].

   Gut mycobiome may be closely related to the pathogenesis of irritable bowel syndrome (IBS)[22]. Rats with induced gut fungal dysbiosis showed visceral hypersensitivity, a symptom which is typical in rats affected by IBS [23]. An increase in*Kazachstaniaturicensis*, *Monographella nivalis*, *Alternaria alternata*, and *Davidiellatassiana* may be used as biomarkers for IBS[23]. *Saccharomycesboulardii*substitutions improved symptoms in IBS-affected rats [24].Different fungi also cause typical symptoms of UC, such as *Zygosaccharomyces* causing abdominal pain and *Candida* positively correlating with bloating [25].

   With respect to tumor formation, gut fungi were seen to displace to the pancreas - particularly, *Malassezia* spp. filled up pancreatic tumors[6]. A C3 protein is triggered by mannose binding lectin due to the binding with an unidentified carbohydrate structure on

Malassezia, resulting into a complement cascade and tumour formation in the pancreas[6]. Gut fungal dysbiosis has also been implicated in colorectal cancer[26].

IV. GUT MYCOBIOME IN INNATE IMMUNITY AND THERAPEUTICS

It was seen that healthy individuals with no history of any fungal infection carried antifungal antibodies in their bloodstreams, which prevented infections from several pathogenic fungal species[27]. Immunocompromised individuals, on the other hand, carried declined quantities of such antifungal antibodies, rendering them susceptible to fungal infections[27]. When purified antibodies were injected into these patients, they fought the common infections better[27]. This indicated the role of the commensal intestinal fungi, like *Candida*, as an "intestinal vaccine" against fungal infections. Furthermore, the CARD9 gene is seen in its wild-type form in healthy individuals with antifungal antibodies, while a mutated form is seen in patients without the antibodies[27]. At the same time, intestinal fungi like *Candida* and *Saccharomyces* can effectively replace bacteria in case of enteric bacteria eradication, and with their mannans play a protective role against viral diseases and colitis [28]. Fecal Microbiota Transplant is showing potential in treating several diseases, as also in preventing their relapses. Interestingly, while performing FMT in patients with UC,those with higher levels of *Candida* prior to the procedure showed better responses, and the transplant then acted to decrease the population of *Candida*[29]. Possible strategies targeted at the gut mycobiome for managing inflammatory bowel diseases will now have to be explored [30].

Antifungal have found interesting uses in neurological diseases, like miconazole being used for the treatment of multiple sclerosis [31], and antifungal therapy using fluconazole being now widely used for individuals with ASD. Fungal vaccine development has been proposed as one of the treatments and prevention strategies in the last decade, which is why fungal vaccines are under research, although none has yet been approved.

V. CONCLUSION

Despite constituting a minor portion of the gut microbiome, gut fungal dysbiosis introduces the risk for several diseases in the gastrointestinal tract, anxiety-depressive behaviours, diabetes, cancers etc. Maintenance of a healthy gut ecosystem is thus proven excessively crucial. Research is now being conducted to identify the exact genera and species involved in each, so that a focused treatment method for such diseases can be established.

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