EBioMedicine 72 (2021) 103621

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Fungal microbiome and multiple sclerosis: The not-so-new kid on the block

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ARTICLE INFO

Article History:
Received 24 September 2021
Accepted 24 September 2021

Human hosts and commensal gut microbes have a symbiotic relationship, with hosts providing space and nutrients to microbes, and microbes supporting numerous physiological processes of the host, including digestion food, preventing pathogen colonization, and immune system modulation [1]. Thus, it is not surprising that perturbations in this homeostasis are linked with a number of diseases [1]. In last two decades non-culture-based sequencing techniques have afforded a better understanding of the human microbiome in health and disease, including multiple sclerosis (MS). Several groups, including ours, have shown that patients with MS have gut dysbiosis (specific bacteria either enriched or depleted) [2]. However, most studies have only analyzed bacteria even though the microbiome also consists of fungi and viruses. In this article, Shah et al. [3] profile the fungal microbiome (mycobiome) in patients with MS (pwMS) and show that these patients have a distinct mycobiome compared to healthy control (HC) participants. Study by Shah et. al and another in preprint by Yadav et. al. showing fungal dysbiosis in pwMS [4] begin to highlight the importance of the mycobiome in MS.

Shat et al. compared the mycobiomes of 25 pwMS and 22 HCs and showed that the mycobiome of pwMS had higher fungal richness than that of HCs, with mycobiome composition remaining mostly stable over six-months [3]. The mycobiome of pwMS was enriched for certain fungi such as *Saccharomyces* and *Aspergillus.* Interestingly, disease-modifying therapies, including dimethyl fumarate, which possesses anti-fungal properties, did not alter the mycobiome composition. The authors also associated mycobiome profiles with different microbiome compositions by classifying mycobiome profiles into two fungal clusters (i.e., mycotypes). Mycotype 1 was dominated by *Saccharomyces,* whereas Mycotype 2 had greater diversity with presence of *Penicillium, Malassezia* and *Mucor* besides *Saccharomyces*. There was a positive correlation between *Saccharomyces* and circulating basophil levels, and increased levels of effector memory CD4+ T cells in participants with the Mycotype 2 cluster. Collectively, these results demonstrate that the mycobiota is altered in the context of MS, which likely has implications on disease progression and severity, particularly considering a previous report showing a distinct mycobiome signature in patients with other diseases, such as inflammatory bowel disease, cancers, atherosclerosis, diabetes, obesity, and alcoholic liver disease [5,6].

Like bacteria, fungi are also proposed to play an important (symbiotic) role in maintaining immune homeostasis at mucosal surfaces by regulating both innate and adaptive immunity. Recognition of fungi through innate immune receptors such as Dectin-1, Dectin-2, c-type lectin receptors, and macrophage-inducible Ca2+-dependent lectin receptor help fine-tune immune responses in the gut [6]. Additionally, fungi specifically *Candida* and *Malassezia,* are potent inducers of a systemic Th17 response and promote expansion of the neutrophil population [5–7]. The importance of the mycobiome for T cell activation and granulocytes expansion is highlighted by two recent studies that show the mycobiome was enriched in the offspring of wild mice that received embryos from laboratory mice or in laboratory mice that were reintroduced to the wild [8,9]. Laboratory mice differ from human immune system as they have reduced numbers of activated T cells and polymorphonuclear lymphocytes in their blood and these studies suggest that lack of complex commensal fungi in mice might be responsible for these differences in immune parameters.

The study discussed here is limited by its small sample size, classification of fungi at low resolution, and the absence of a validation cohort of patients. As *Candida* and *Saccharomyces* are two of the most abundant fungi in the human mycobiome, the significantly reduced abundance of *Candida* observed here [3] is surprising. Several human studies have shown relatively higher abundance of *Candida* both in healthy participants [10] and in patients with disease, such as inflammatory bowel disease, atherosclerosis and type 2 diabetes mellitus [5,6]. We have also observed higher *Candida* levels in pwMS compared to HC using marker-based fungal classification [4]. Lower *Candida* levels in the current study may be due to the geographic location, lifestyles, or dietary habits of the participants, or the bioinformatics pipeline used. Further, *Saccharomyces* has been associated with both a healthy mycobiome and certain diseases, suggesting either a strain-specific role of *Saccharomyces* in promoting disease, or that the overall composition of the mycobiome, and the bacterial microbiome, affects its disease-protective or promoting properties. Correlating the abundance of *Saccharomyces* and *Candida* with other components of the microbiome in the context of MS will be an

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103557.
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https://doi.org/10.1016/j.ebiom.2021.103621

important next step in beginning to uncover how fungi might protect or promotes disease.

In conclusion, this study provides first evidence that the fungal component of the microbiome is disrupted in pwMS. This paves the way for future work characterizing the mycobiome in the context of disease using shotgun metagenomic sequencing and larger sample sizes, which, combined with mechanistic studies, will help in understanding the precise role of fungi in the pathobiology of MS.

Contributors

This commentary was written solely by AKM.

Declaration of Competing Interest

The author declares no conflicts of interest.

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