MICROBIOME

Managing the mycobiota with IgA

The mammalian immune system has evolved to tolerate commensal microbes that inhabit our mucosal surfaces. Two recent studies explore how intestinal immunity achieves this state of tolerance and show that IgA enforces commensalism of pathobiont *Candida* species.

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Fungi are common components of the mammalian intestinal microbiota, known as the mycobiota¹. In healthy people, these fungal communities interact largely with the intestinal mucosa as non-pathogenic commensal microbes². However, several studies have indicated that some members, including *Candida* species (spp.), can aggravate serious chronic inflammatory bowel diseases (IBD), like Crohn's disease (CD) and ulcerative colitis (UC)³. Commensal intestinal *Candida* spp. can also be detected in the bloodstream and can cause lethal systemic infections, especially in individuals with a compromised immune system, such as patients who have received an organ transplant³. Until now, it has not been clear how fungal species with the potential to cause disease can safely inhabit the intestinal mucosa without causing harm. Two articles, by Doron et al.⁴ in this issue of *Nature Microbiology* and by Ost et al.⁵ in *Nature*, provide new insights by showing that the intestinal mucosa induces an immunoglobulin A (IgA) response that specifically targets pathogenic fungal morphologies of *Candida* spp. (Fig. 1). These findings reveal that there is a homeostatic anti-fungal response in the healthy gut mucosa that enforces commensalism and helps to reduce the impact of *Candida*-associated tissue pathology in a mouse model of colitis.

IgA is produced by B lymphocytes and is the most abundant immunoglobulin at the mucosae, providing protection against toxins and pathogen invasion of mucosal tissues. Several research groups have shown that IgA coats a substantial fraction of gut bacteria and plays a role in both preventing infection and maintaining homeostasis with bacterial microbiota⁶. Notably, disruption of gut IgA–microbiota interactions is now appreciated to be a major player influencing health and has been linked to an increased risk of severe IBD, allergies and asthma⁶. Doron et al.⁴ and Ost et al.⁵ show that a fraction of the commensal gut mycobiota is also coated with IgA. In both mouse and human faecal samples, the *Candida* spp.

Fig. 1 | IgA targets *Candida* hyphae-associated virulence factors. *Candida* species are commonly found within the mammalian mycobiota in the gut lumen and usually interact with healthy gut mucosa as non-pathogenic yeasts. The intestinal mucosa can induce an IgA response that specifically targets *Candida* hyphae, resulting in commensalism of *Candida* yeast cells. The tissue-damaging virulence factors expressed by hyphae are targets of anti-*Candida* IgA, and this response is dependent on the presence of B and T cells within the lamina propria. How hyphae induce T- and B-cell responses is currently unclear. In addition, IgA can limit intestinal tissue damage caused by hyphal forms of *Candida* species; however, this is dysregulated in IBD, such as CD.

were among the dominant IgA-bound fungal species, with *C. albicans* showing the highest IgA reactivity. Neither IgM nor IgG bound the intestinal fungi, suggesting that IgA is the primary immunoglobulin contributing to intestinal homeostasis for fungi and

bacteria. To test whether *C. albicans* induced this IgA response, the authors performed colonization experiments in mice without microbiota (commonly referred to as germ-free mice) using known commensal fungal species. While *C. albicans* and another

pathogenic species, *Candida glabrata*, were found to be the dominant IgA inducers, non-pathogenic species, like *Saccharomyces cerevisiae*, did not induce a robust response. This specific *Candida* IgA response depended on the presence of both B and T cells since mice lacking these cells failed to generate fungus-specific IgA. Interestingly, the IgA induced by each *Candida* spp. was unique and did not cross-react with other *Candida* spp., and the response was unaltered even in the presence of bacteria.

C. albicans is a dimorphic fungus, meaning it can exist as yeasts or as filaments called hyphae⁷. The yeast-to-hyphae transition is key to the pathogenic potential of *C. albicans*. Previous studies have suggested that *C. albicans* yeasts, but not hyphae, have a survival advantage in the gut microenvironment^{8,9}, although the underlying reasons are unclear. Hyphae express several virulence factors, including degradative enzymes, a pore-forming toxin (candidalysin) and cell surface adhesins (for example, Als3) associated with tissue invasion⁷. Both studies found that binding of IgA to *C. albicans* was specific to the hyphal morphology, whilst yeast-locked *Candida* induced and bound little IgA^{4,5}. Interestingly, Ost et al.⁵ found that in the absence of a mature adaptive immune response, hypha-specific virulence factors were significantly upregulated in *C. albicans* following gut colonization, suggesting that the adaptive immune response actively suppresses fungal virulence. Indeed, both studies found that the proportion of *C. albicans* hyphae was significantly higher in the guts of mice lacking an adaptive immune system.

Identifying regions of proteins that are recognized by the immune system, commonly referred to as epitopes, is a holy grail for vaccine development. Here,

to determine the epitopes associated with the observed IgA response, Ost et al.⁵ screened a collection of *C. albicans* mutants and found that those lacking factors that promote host–cell adhesion and biofilm and hyphae formation had reduced IgA binding. This suggested that IgA specifically targets hyphae-associated virulence factors. Indeed, when Ost et al.⁵ assessed gut colonization using a mutant with defects in adhesion (*ahr1Δ/Δ*, which lacks adhesion and hyphae regulator1), they observed that significantly less IgA was produced, even though *ahr1Δ/Δ* fungal cells were able to form hyphae. This indicates that the factors produced by the hyphal cells, rather than the hyphal morphology, are the main targets of the IgA response. In fact, the adhesins Als3 and Als1 were found to be the dominant epitopes targeted by anti-fungal IgAs, and when they were expressed by non-pathogenic *S. cerevisiae*, these adhesins were targeted by IgA (ref. ⁵).

To determine the relevance of these observations in health and disease, Doron et al.⁴ analysed mucosal washings from patients with CD and observed dysregulated anti-*Candida* IgA levels and high numbers of hyphae. These data suggest that mechanisms that induce anti-*Candida* IgA may be altered during CD. Additionally, Ost et al.⁵ demonstrated that a vaccine¹⁰ using an epitope of Als3 could alleviate *C. albicans*–associated gut tissue damage in a mouse model of colitis. This therefore shows tremendous promise for the use of such vaccines in the management of IBD.

In sum, the studies by Doron et al.⁴ and Ost et al.⁵ represent a major advance in our understanding of how *Candida* gut commensalism is regulated by the mammalian immune system through the mucosal IgA response. They also shed light on how potentially pathogenic

microbes are controlled and sequestered safely in the gut lumen. However, a more comprehensive picture of the underlying immunological mechanisms is needed. For example, it is unclear whether the gut epithelial layer senses commensal fungi at steady state and what role it plays in these responses. Our understanding of how B- and T-cell anti-fungal responses are induced and maintained during homeostasis and disease is also limited. Lastly, it is not well understood whether inflammation, as seen in IBD, is the main driver of non-protective antibody induction against other commensal fungal species, known as ASCA (anti-*S. cerevisiae* antibodies), nor whether these responses impact the protective IgA response towards *Candida* hyphal epitopes. No doubt the answers to these important questions are forthcoming. □

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Published online: 22 November 2021
<https://doi.org/10.1038/s41564-021-01006-7>

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Competing interests

The authors declare no competing interests.