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INSIGHTS

One in, one out: Commensal fungus protects against infection

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Gut-resident fungi have a broad influence over health and disease. In this issue of *JEM*, Sekeresova Kralova et al. (https://doi.org/10.1084/jem.20231686) identify a commensal yeast that displaced fungal pathogen *Candida albicans* and protected against subsequent invasive infections that originate from the gut.

A new study has found that a commensal yeast has the potential to protect against life-threatening invasive fungal infection by helping to displace the fungal pathogen from the microbiota (Sekeresova Kralova et al., 2024). Fungal members of our microbiomes, collectively referred to as the mycobiota, have a wide influence over human health and disease. Although still poorly understood relative to the more commonly studied bacterial constituents, the mycobiota has been demonstrated to exert significant influence over cancer progression (Dohlman et al., 2022), immune system development (van Tilburg Bernardes et al., 2020), and responses to chronic viral infection (Kusakabe et al., 2023). In the current issue, a new study by Steffen Jung and colleagues has characterized a new fungal commensal with exciting potential as a therapeutic that might boost our mycobiome to protect against invasive infections (Sekeresova Kralova et al., 2024).

One of the most commonly isolated fungal commensal organisms from human microbiomes are *Candida* species. *Candida* is a large genus of fungi that contains many potential pathogens, the most common of which is *Candida albicans*. *C. albicans* causes a range of human disease, from mucosal infections such as oral thrush and vulvovaginal candidiasis to the systemic infection invasive candidiasis, which is a leading cause of hospital-related mortality (Lionakis et al., 2023).

Many *Candida* infections originate from commensal populations, particularly in the gastrointestinal (GI) tract (Zhai et al., 2020). There is therefore strong interest in studying the factors controlling *Candida* colonization of the gut and how that might be manipulated for therapeutic gain. However, this field of research has suffered from a lack of good animal models to study *Candida* gut colonization. This is because lab-bred mice are typically resistant to *Candida* gut colonization, and exhibit very low or undetectable amounts of *Candida* under baseline conditions. This colonization resistance can be broken with the use of antibiotics or immune suppression (Fan et al., 2015); however, these interventions introduce confounding factors that complicate data interpretation and translation to humans, particularly since antibiotics also impair systemic antifungal immune responses and promote susceptibility to invasive infection (Drummond et al., 2022).

In the current study (Sekeresova Kralova et al., 2024), the authors describe their serendipitous discovery of a fungal commensal in their animal colony that colonized mice without prior antibiotic treatment or other interventions, and could colonize mice of many genetic backgrounds. The authors identified this fungus as belonging to the *Kazachstania* genus, a group of yeasts that are closely related to *Candida* species but lack many of the pathogenic qualities *Candida* possesses, such as formation of the invasive hyphal morphology. The authors named their strain *Kazachstania weizmannii* after the institute it was discovered in.

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The authors performed co-colonization models, exposing mice to both *K. weizmannii* and *C. albicans*. They found that *K. weizmannii* was able to out-compete *C. albicans*, and this was completely independent of the bacterial component of the gut microbiota since displacement also occurred in germ-free animals. Interestingly, the ability of

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K. weizmannii to out-compete *Candida* was specific to some species but not others. *Candida parapsilosis* was out-competed by *K. weizmannii* similar to *C. albicans*; however, *Candida glabrata* was largely resistant to this and maintained its colonization levels even in the presence of *K. weizmannii*. This may reflect differences between these *Candida* species in how they colonize the GI tract and the location of this colonization. For example, *C. albicans* closely adheres to the squamous epithelium of the murine stomach (Vautier et al., 2012), while the specific locations of *K. weizmannii* and other fungal commensals are less well characterized. A closer analysis of which parts of the gut are resident to different types of fungal commensals will be an important future direction going forward, since this could reveal additional mechanisms by which *K. weizmannii* drives displacement of potential fungal pathogens from the gut.

The ability of *K. weizmannii* to displace *C. albicans* was independent of the adaptive immune system, as the same effect was observed in mice lacking lymphocytes (*Rag2*$^{-/-}$). Unlike *C. albicans*, which has a notable effect on both local and systemic immunity during GI colonization (Proctor et al., 2023), *K. weizmannii* did not induce Th17 responses in draining lymph nodes or affect production of myeloid cells from the bone marrow. However, both fungal species did induce an IgA antibody response. The antibodies generated in response to *K. weizmannii* colonization were cross-reactive to *C. albicans*, but not to the dietary yeast *Saccharomyces cerevisiae*. This is important as IgA selects against the invasive hyphal form of *C. albicans* in the gut, thereby promoting *C. albicans* commensalism (Ost et al., 2021). Furthermore, IgA-producing plasma cells that originate from the gut and develop in a microbiota-dependent manner populate distant border tissues in the central nervous system, where the IgA they produce limits the spread of *C. albicans* into the brain (Fitzpatrick et al., 2020). The induction of cross-reactive IgA by *K. weizmannii* colonization may therefore have broad consequences for protecting against *C. albicans* infections in multiple tissues, and these will be exciting questions to explore in future studies.

Since *K. weizmannii* could displace *C. albicans* from the mouse gut, the authors analyzed whether this could limit the pool of potential fungal pathogens within the gut that may cause an invasive infection. For that, the authors orally delivered *K. weizmannii* to *C. albicans* colonized mice prior to initiating immune suppression, which typically allows *C. albicans* to cross the intestinal barrier and establish bloodstream infection, eventually invading organs such as the kidney and liver. Importantly, *K. weizmannii* prevented *C. albicans* dissemination from the gut and limited the development of systemic infection. This work indicates that *K. weizmannii* may have therapeutic potential by preventing overgrowth of *C. albicans* in vulnerable patients. This is highly relevant in populations of patients who develop "fungal blooms" in the microbiota prior to the development of invasive infection (Zhai et al., 2020). Deploying antifungal drugs in these at-risk patient groups to control these commensal fungal populations is currently used to prophylactically limit *Candida* growth and subsequent infection (Lionakis et al., 2023). However, increasing rates of antifungal drug resistance, particularly in *Candida* species, have raised concerns about whether this approach can be relied upon going forward. This is because there are fewer antifungal drugs available for clinical use than there are antibiotics, and the rise of fungal species that are inherently resistant to many of the available antifungal drugs (such as *Candida auris*) have demonstrated the urgent clinical need for more antifungal drugs and adjunctive alternative therapies (Lionakis et al., 2023).

The therapeutic potential of *K. weizmannii* will depend on the ability of the fungus to colonize the human gut. To address this, the authors searched published human gut and vaginal microbiota datasets to determine whether *K. weizmannii* is found in the healthy human mycobiota. Although rare, the authors found the presence of *K. weizmannii* or closely related *Kazachstania* species in several datasets across a wide geographical range. This work suggests that this fungus may be a naturally occurring fungal commensal in some populations and could be safe to use as a prophylactic strategy to protect vulnerable patients from developing invasive *C. albicans* infections. Future work will need to determine the genetic variability of *Kazachstania* species and determine its prevalence in the population and the factors that influence this. For example, while *C. albicans* is commonly reported in human microbiome data, there is evidence that this is driven by high-sugar/high-fat diets and levels of antibiotic exposure in the population (Proctor et al., 2023). It will also be important to determine whether *Kazachstania* species could exacerbate infections in immune-suppressed patients. While this has not been reported so far, this may reflect low levels of the fungus in the human population.

In addition to exploring the potential therapeutic uses of *Kazachstania* species, an important future direction will be to examine the influence of this fungus on other human diseases and gut health. *C. albicans* and other fungal commensals can promote inflammation in inflammatory bowel disease (IBD) and alcoholic liver disease, in part through release of β-glucan that activates inflammatory cells via Dectin-1 signaling (Yang et al., 2017), or by damage to the epithelial layers via toxins and adhesins that these fungi produce (Li et al., 2022). Interestingly, despite being able to displace *C. albicans* from the mouse gut, *K. weizmannii* was not able to mitigate damage to epithelial cells caused by *C. albicans* in coculture in vitro experiments. These data suggest that *K. weizmannii* may have limited effects in different disease conditions, particularly in the inflammatory environment of the damaged intestine found in IBD patients.

Our understanding of the mycobiota is still in its infancy. Yet, this field holds much promise for novel discovery and therapeutic potential. The last decade has yielded multiple exciting findings that have demonstrated the importance of fungal commensals and how they instruct the immune system. This latest study is a further example of commensal yeast exerting significant influence over health outcomes, and is an exciting new advance for the mycobiota and fungal immunology fields.

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