International Journal of Medical Microbiology 311 (2021) 151490

Contents lists available at ScienceDirect

International Journal of Medical Microbiology

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

Fungi of the human gut microbiota: Roles and significance

J. Christian Pérez [a,b,*]

[a] Interdisciplinary Center for Clinical Research, University Hospital Würzburg, Germany
[b] Institute for Molecular Infection Biology, University Würzburg, Würzburg, Germany

ARTICLE INFO

Keywords:
Fungi
Gut microbiota
Candida albicans
Inflammatory bowel disease

ABSTRACT

It is becoming increasingly clear that fungi are important components of the gut microbiota. Fungi residing in the human intestine, for example, elicit the induction of T helper 17 cells, which are central orchestrators of protective immune responses. Likewise, fungal members of the intestinal microbiota have been shown to influence the immunological responses of the mammalian host by dampening or promoting local inflammatory responses. Here I review some of the latest developments regarding symbiotic fungi of the gastrointestinal tract and the consequences that fungal dysbiosis may have on human health. A major focus of the review is on the relationship between *Candida albicans*, the most prominent fungus inhabiting the human gut, and the mammalian host. Advances in the field underscore the need to further investigate the fungi that inhabit the human body to understand how the mixed array of microbes that constitute our microbiota contribute to health and disease.

1. Fungi inhabiting the human gastrointestinal tract

The intestinal microbiota is an intricate assembly of bacteria, archaea, viruses, protists and fungi. Commonly used approaches to inventory and study the microbiota, such as sequencing the stretch of DNA that encodes 16S ribosomal RNA, are nonetheless designed to target exclusively the bacterial component, inadvertently neglecting the other constituents. For a long time, fungi remained particularly underrepresented in the studies of the microbiota (Perez and Johnson, 2013). However, the realization that fungi residing in the human gut can elicit important physiological processes – for example the induction of T helper 17 cells, which are central orchestrators of protective immune responses – is generating renewed interest in commensal fungal research (Fiers et al., 2019; Kong and Segre, 2020; Perez, 2019).

In contrast to the vast resources dedicated to inventory the bacterial portion of the microbiome, relatively fewer projects have attempted to identify the entire set of fungal species residing in humans. The endeavour is still hampered by multiple technical difficulties (Limon et al., 2017; Richard and Sokol, 2019). For example, the fact that fungi are surrounded by thick cell walls means that DNA preparation methodologies developed for recovering bacterial DNA are less than optimal. Moreover, the fungal rDNA 'internal transcribed spacer regions' (ITS) – which are used to identify specific fungal species in the same manner that 16S rDNA is used for bacteria – vary in length between fungi, adding a potential source of bias when employing common next-generation sequencing platforms. ITS variation is also often insufficient to discriminate among species. Finally, there is a lack of quality-controlled reference databases to comprehensively identify the organisms represented in a pool of generated sequences.

Despite the aforementioned caveats, a diverse group of fungi has been found associated with the human digestive tract. For example, 101 species belonging to 85 fungal genera were found in the oral cavity of healthy people (Ghannoum et al., 2010). In fecal samples taken from 45 healthy human volunteers, 72 operational taxonomic units (OTUs), representing two phyla and ten classes of fungi, were recovered (Hallen-Adams et al., 2015). In another cohort consisting of 96 stool samples (Hoffmann et al., 2013), the authors detected 66 fungal genera and 13 additional lineages that could not be classified to the genus level. In a larger study that looked at stool samples from 147 healthy volunteers (Nash et al., 2017), 701 fungal OTUs encompassing 247 genera were identified (17 % of the fungal OTUs could not be assigned to any known species). The number of OTUs within samples, however, ranged from 2 to 92 in the study of Nash et al. (2017). These numbers translate into a reduced Shannon diversity index – which is a popular measure of evenness and richness of communities within a sample – implying low alpha diversity for the majority of samples. Compared to the composition typically found in human gut bacterial communities, both the number of observed OTUs and the Shannon diversity index values are

* Corresponding author. Current address at: Department of Microbiology and Molecular Genetics, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, USA.
E-mail address: jose.c.perez@uth.tmc.edu.

https://doi.org/10.1016/j.ijmm.2021.151490
Received 9 September 2020; Received in revised form 4 February 2021; Accepted 23 February 2021
Available online 25 February 2021

lower for fungi (Nash et al., 2017). Yeasts from the genera *Saccharomyces, Malassezia* and *Candida* have been the dominant fungi found in stool samples in most studies. *Saccharomyces* spp. and *Malassezia* spp. are either associated with certain foods or known residents of the skin, respectively, raising questions on whether members of these two genera should really be considered natural residents of the gastrointestinal tract (Table 1) (Fiers et al., 2019). Evidently, there is no consensus yet on which fungi constitute a 'core gut mycobiome,' or even if such a concept can be applied to these microorganisms. The field would clearly benefit from additional large-scale studies aimed at identifying the entire set of fungal species residing in humans.

2. *C. albicans* is the major fungal species in the human gut

While several species of the genus *Candida* are generally accepted as true gut symbiotic fungi (Fiers et al., 2019), *C. albicans* is the most frequently detected fungus in faeces of healthy humans. The fungus, therefore, is considered a normal component of the human gut microbiota (Odds, 1987; Spellberg et al., 2012). *C. albicans* appears to have no major environmental reservoir, suggesting that it has extensively coevolved with its host and cohabiting microbes. The fungus can colonize multiple body sites in addition to the intestine (*e.g.* mouth, skin, vagina) and is a common cause of fastidious mucosal disease in otherwise healthy people (Revankar and Sobel, 2012). *C. albicans* can also disseminate from the human gut into the bloodstream and invade almost every internal organ producing invasive, life-threatening infections (Koh et al., 2008; Zhai et al., 2020). Disseminated *Candida* infections typically occur in individuals with debilitated immune systems, such as organ transplant recipients or cancer patients receiving chemotherapy (Clancy and Nguyen, 2012). In European countries, the incidence of invasive candidiasis hovers around 10 cases per 100.000 inhabitants and 1.09 cases per 1.000 hospital admissions (Yapar, 2014).

Historically, it is the association of *C. albicans* with disseminated infections what has received the most attention from fungal researchers. As a consequence, progress in understanding the biology of *C. albicans* in the gastrointestinal tract has been slow compared to other members of the gut microbiota (Perez, 2019). Another issue has been that the organism is diploid yet lacks a complete sexual cycle, which makes conventional yeast genetic analysis unfeasible. Fortunately, the development of genomic and genetic tools for this fungus has flourished in the last two decades (Anderson and Bennett, 2016) and it is now possible to carry out systematic and unbiased searches for genes involved in traits of interest. For instance, forward genetic screens have been conducted in *C. albicans* to explore processes such as yeast to filament transition (Noble et al., 2010), biofilm formation (Nobile et al., 2012), adherence to substrates (Finkel et al., 2012), sensitivity to a variety of stresses (Blankenship et al., 2010) and overall fitness in various murine models of infection or commensal colonization (Bohm et al., 2017; Meir et al., 2018; Noble et al., 2010; Perez et al., 2013; Witchley et al., 2019). These technical developments pave the way for a comprehensive understanding of how this fungus interacts with its host and with other microbes in health and disease.

Table 1
Significant fungal species often found in the human intestine.

Name	Observations/Comments
Candida albicans	Most prevalent fungus in the gastrointestinal tract of human adults. Major inducers of Th17 cells.
Candida glabrata	Opportunistic pathogen. Unknown role(s) in the gut.
Candida parapsilosis	Opportunistic pathogen. Unknown role(s) in the gut.
Rhodotorula mucilaginosa	Higher abundance in neonates associated with childhood atopy (Fujimura et al., 2016).
Issatchenkia orientalis (*Candida krusei* or *Pichia* kudriavzevii)	Increased abundance in infants associated with atopic wheeze (Arrieta et al., 2018).
Malassezia restricta	While often found in stool samples, this skin fungus may not be a true symbiont of the human gut (Fiers et al., 2019).
Saccharomyces spp.	While they are often found in stool samples (likely because they are components of many beverages and foods), these yeasts are not considered natural residents of the human gut.

3. Fungi, gut immunity and inflammatory bowel disease

Fungal members of the intestinal microbiota have been shown to influence the immunological responses of the host by dampening or promoting local inflammatory responses (Iliev et al., 2012; Wheeler et al., 2016). Comprehensive reviews of the immune response to fungi have been published elsewhere (Gow et al., 2012; Hatinguais et al., 2020; Netea et al., 2015), although it should be noted that there is still limited data on the interactions between intestinal immunity and gut fungi, at least compared to the larger volume of literature addressing immune responses in other mucosal surfaces or during systemic infections. A crucial finding in the gut, nonetheless, has been that *C. albicans* is a central modulator of human T helper 17 (Th17) responses in health and during intestinal inflammation (Acosta-Rodriguez et al., 2007; Bacher et al., 2019). Indeed, among 30 members of the human mycobiome, *C. albicans* was found to be the major inducer of Th17 cells in humans. Th17 cells orchestrate protective immunity at barrier sites and, consequently, are largely confined to intestinal tissues and the skin under homeostatic conditions (Honda and Littman, 2016). Disregulated Th17 responses contribute to local inflammatory disorders, such as inflammatory bowel diseases (Schirmer et al., 2019), although clinical trials with antibodies that block IL-17 activity have thus far failed to induce improvement in these patients (Fauny et al., 2020). As outlined below, a growing body of literature connects alterations in the gut fungal community to these inflammatory diseases.

There are at least three lines of evidence linking gut commensal fungi to inflammatory bowel diseases (Crohn's disease and ulcerative colitis). First, for a long time it was observed that patients with Crohn's disease harbor high levels of antibodies against fungal cell wall sugars (Quinton et al., 1998). While these antibodies were originally associated with the yeast *Saccharomyces cerevisiae*, it is now clear that they are not specific to this species but rather recognize many other fungi as well (Muller et al., 2010; Standaert-Vitse et al., 2006). Second, single nucleotide polymorphisms (SNPs) in several genes that encode receptors or signaling molecules mediating fungal recognition in humans have been associated with inflammatory bowel diseases (Kong and Segre, 2020). For example, SNPs in *CLEC7A* (C-type lectin domain–containing 7A), which encodes Dectin-1, and in *CARD9*. Dectin-1 is a C-type lectin receptor (CLR) that recognizes β-glucan in fungal cell walls and signals through *CARD9* to induce inflammatory mediators and Th1 and Th17 cell differentiation. Mice deficient in Dectin-1 display more severe experimentally-induced colitis whereas a SNP in human *CLEC7A* is associated with more severe ulcerative colitis (Iliev, et al., 2012). Genetic ablation of *CX3CR1* mononuclear phagocytes – which are essential cells for the initiation of immune responses elicited by *C. albicans* and other intestinal fungi – also exacerbate experimental colitis in mice (Leonardi et al., 2018). A *CX3CR1* missense mutation in Crohn's disease patients has been associated with reduced immunoglobulin G (IgG) responses to fungi. And, third, in mouse models of dextran sodium sulfate (DSS)-induced colitis, fungal co-colonization has been shown to modulate the severity and immunophenotype of the immune response (van Tilburg Bernardes et al., 2020) whereas administration of *C. albicans* has been found to increase the severity of colitis (Jawhara et al., 2008; Sovran et al., 2018). Taken together, these studies indicate that inflammatory bowel diseases may result from host-fungal imbalances.

While commensal fungi such as *C. albicans* have immune modulatory roles and can protect against disease locally in the intestine, they also appear to do so systemically in extra-intestinal tissues (Perez, 2019). In gnotobiotic mice, for example, gut colonization by a small community of

five fungal species promoted broad systemic immunological changes to immune cell populations and their secreted cytokines in the spleen (van Tilburg Bernardes et al., 2020). Even more strikingly, Jiang et al. (Jiang et al., 2017) found that *C. albicans* monocolonization efficiently overturned the fatal susceptibility to influenza A virus infection in commensal-bacteria-depleted mice. In the same study, the authors established that similar protective effects were obtained by simply administering mannans, a major carbohydrate in the cell wall of the fungus, and that TLR4 was necessary for the animals to receive protection. Tso et al. (Tso et al., 2018) also reported that priming mice with *C. albicans* strains — although in this case the strains employed had been passaged multiple times through the murine intestinal tract to improve the fungus' fitness — led to cross protection against multiple fungal and bacterial pathogens. The phenomenon was considered a case of "trained immunity" (Cheng et al., 2014; Netea et al., 2016) because it was rapidly established, independent of adaptive immunity, relatively short lived and required cytokine production (d'Enfert, 2018). The findings of Jiang et al. (Jiang et al., 2017), on the other hand, disagree with the concept of "trained immunity". These authors found that the systemic immune modulation effects depended on the tonic presence of commensal fungi whereas "trained immunity" is primed by invasive fungi and triggered by the sensing of pathogens in sterile tissues after parental injection (Cheng et al., 2014). Without detailed follow-up studies to address the mechanisms operating in these two reports, it remains unclear whether the described phenomena represent variations of a common theme or intrinsically disparate molecular processes.

More recently, investigations in mice and humans point to Th17 cells as pivotal players in connecting intestinal fungi to responses elicited in other body sites. Shao et al. (Shao et al., 2019) demonstrated that, in mice, intestinal colonization with *C. albicans* drives the systemic expansion of fungal-specific Th17 cells and IL-17 responsiveness by circulating neutrophils, which synergistically protect against *C. albicans* invasive infection. The authors found that the protection conferred by commensal *Candida* required persistent fungal colonization and extended to other extracellular invasive pathogens such as *Staphylococcus aureus*. Human anti-fungal Th17 cells also appear to result mostly from the induction by *C. albicans* (Bacher et al., 2019). Intriguingly, these authors reported that Th17 cells directed against other fungi are induced by cross-reactivity to *C. albicans*. Based on these observations, Bacher et al. (2019) postulated that *C. albicans*-specific T cell responses broadly modulate human anti-fungal Th17 immunity *via* propagation of Th17 cells that cross-react with other fungal species. A striking example of this phenomenon appears to be at play in the case of airborne fungi, such as *Aspergillus fumigatus* and especially during acute allergic bronchopulmonary aspergillosis.

The described studies underscore the notion that *C. albicans*, and commensal fungi in general, elicit consequential and diverse responses from the gastrointestinal tract.

4. Interactions between gut bacteria and fungi

C. albicans inhabits the gastrointestinal tract along with hundreds (or even thousands) of other microbial taxa. It seems highly likely, then, that the intestinal microbiota can significantly affect the proliferation of the fungus. Indeed, as early as in the 1960s it was observed that antibiotic treatment in humans resulted in *Candida*'s overgrowth (Seelig, 1966a, b), presumably due to the dampening of competing bacteria. More recent studies equipped with the tools to monitor the entire intestinal fungal community have revealed that antibiotic treatment broadly alters fungal composition (Sovran et al., 2018). Thus, targeting bacteria can inadvertently result in fungal dysbiosis. Evidence is also accumulating to suggest that targeting fungi can lead to changes in bacterial communities. For instance, in one of these studies mice treated with antifungal drugs exhibited pronounced alterations in the composition of their bacterial community (Wheeler et al., 2016). In another study in gnotobiotic mice, a small community of fungi (5 species) was found to induce strong ecological changes in the assembly of gut bacteria (van Tilburg Bernardes et al., 2020). In the same study, interkingdom interactions (bacteria-fungi) were found to have a particularly strong effect on the early-life assembly of the bacterial and fungal communities. *C. albicans* itself has been shown to impact the reassembly of gut bacterial communities after antibiotic treatment (Erb Downward et al., 2013; Mason et al., 2012). And, more generally, gut fungal dysbiosis has been associated with reduced efficacy in faecal transplants currently in use to treat recurrent *Clostridium difficile* infections (Zuo et al., 2018). Taken together, these reports point to the existence of physiologically-relevant interdependencies between fungi and bacteria in the mammalian gut.

In spite of the growing evidence of significant interplay between fungi and bacteria in the mammalian gastrointestinal tract, only limited progress has been made on the actual molecular mechanisms underlying such *in vivo* interactions. This is not to say that there is a shortage of reports looking at how particular bacteria affect fungal traits (*e.g.* in *C. albicans*) or vice-versa. However, the vast majority of the data on fungi-bacteria interactions have been collected using either *in vitro* systems (*e.g.* biofilm formation) or non-intestinal mucosal settings (*e.g.* oral or vaginal). Many of these reports are neatly summarized in a recent review (Richard and Sokol, 2019) and will not be covered here. The enormous complexity of the mammalian gut microbiota as well as the lack of a convenient and tractable animal model of gut fungal colonization may account for the paucity of studies looking at interactions in the actual intestinal tract.

Two studies that have looked at the basis of antagonistic relationships between bacteria and *C. albicans* — in murine models of intestinal colonization — point to the involvement of the host's immune response. In one of the studies (Markey et al., 2018), *C. albicans* was found to protect against lethal murine *Clostridium difficile* infections. The effect appeared to be mediated, at least in part, by the fungus promoting the production of IL-17, a pro-inflammatory cytokine. In the other study (Fan et al., 2015) several Bacteroidetes and clostridial Firmicutes were found to antagonize *C. albicans* in the murine intestine. These bacteria limited proliferation of the fungus by stimulating the production of gut mucosal immune defences against *C. albicans*. Priming responses by the host's immune system is a common mechanism by which commensal bacteria protect the mammalian host from invading pathogens (Khosravi and Mazmanian, 2013). While such mechanism is typically invoked in the context of bacteria-bacteria antagonistic relationships, the two examples described here indicate that the concept can be extended to fungi-bacteria relations as well. It is noteworthy that, according to the two studies mentioned here, *C. albicans* has dual roles: As a commensal that can elicit a response to protect the host from a bacterial pathogen; and as a fungal pathogen from which the host is protected *via* immune responses elicited by commensal bacteria.

5. Exploring the biology of *C. albicans* in the mammalian gut

While mice are not the natural hosts of *C. albicans*, they have been by large the most often used animal model to explore the biology of the fungus in the mammalian gut. Adult mice with mature intact microbiota, however, are resistant to *C. albicans* intestinal colonization (Fan et al., 2015; Koh et al., 2008; Nucci and Anaissie, 2001). Accordingly, murine gut colonization by *C. albicans* is routinely achieved by the non-selective reduction of the mouse indigenous bacterial community through antibiotic treatment (Koh et al., 2008; Pande et al., 2013; White et al., 2007). We, as well as other laboratories, have used antibiotic-treated animals to identify *C. albicans* genes needed for the fungus to colonize the murine gut (Perez et al., 2013; Pierce et al., 2013; Pierce and Kumamoto, 2012; Rosenbach et al., 2010; White et al., 2007). These studies point to the important roles of genetic circuits that regulate nutrient acquisition, that manage iron toxicity and that detoxify reactive oxygen species, among others. All these processes and the implicated genes, in the context of gut colonization, have been reviewed elsewhere (Perez, 2019; Perez and

Johnson, 2013; Romo and Kumamoto, 2020).

Oral administration of the antibiotics commonly used to achieve *C. albicans* intestinal colonization in mice leads to a reduction of bacteria in the intestine. However, a significant amount of indigenous bacteria — particularly anaerobes — still persists during treatment (Fan et al., 2015). Untangling microbiota- from host-derived effects on the biology of *C. albicans* is thus rather challenging in this experimental setup. To circumvent this limitation, my laboratory started to experiment with gnotobiotic mice. In this setting, *C. albicans* is administered orally to animals that have been raised in a microbe-free environment (germ-free mice). Our experiments with gnotobiotic NMRI mice indicate that *C. albicans* can successfully colonize the gastrointestinal tract of these rodents for at least three weeks after a single gavage of 10^6 - 10^7 cells with no overt effects on the health of the animals (Bohm et al., 2017). These observations are in agreement with reports from the 1960s and 1970s on the feasibility of establishing long-term *C. albicans* colonization in the gut of various strains of germ-free mice (Clark, 1971; Phillips and Balish, 1966).

C. albicans cells can adopt multiple morphologies, ranging from the oval-shaped 'yeast' form to elongated 'opaque' cells and long filaments, although additional, specialized morphologies have also been postulated (Gow and Yadav, 2017; Noble et al., 2017). The metabolic preferences as well as the cell surface differ significantly across morphologies. Consistent with this notion, host immune cells have been shown to interact differently with each *C. albicans* morphology (Lohse and Johnson, 2008; Moyes et al., 2010). Filaments, which are favoured at 37 °C and in the presence of serum, constitute the most common morphology associated with mucosal (oral and vaginal) and disseminated infections (*e.g.* in kidneys or liver). In the murine intestine of mice monocolonized with *C. albicans*, on the other hand, the oval-shaped 'yeast' form was the most common cell morphology observed (Bohm et al., 2017). The imaging studies of Böhm et al. are supported by a wide variety of genetic evidence collected in multiple laboratories (Del Olmo Toledo et al., 2018; Pierce and Kumamoto, 2012; Tso et al., 2018; Vautier et al., 2015; Witchley et al., 2019): Mutations that favour the yeast form (for example the deletion of positive regulators of filamentation) increase the fitness of the fungus in the standard antibiotic-treated mouse model of gut colonization. Mutations that favour filamentation (for example the ectopic expression of positive regulators of filamentation), as expected, have the opposite effect. Thus, while filamentation is deemed essential for invasive growth and colonization of mucosal surfaces such as oral tissue (Meir et al., 2018), maintaining the oval-shaped 'yeast' form appears critical for *C. albicans* to remain as a symbiont in the gastrointestinal tract.

Imaging studies have detected *C. albicans* throughout the digestive tract (from stomach to small and large intestine) in both gnotobiotic and antibiotic-treated conventiona l mice (Bohm et al., 2017; Witchley et al., 2019). In the colon cross-sections, which have been evaluated in more detail, the fungus appears to be mainly localized in the intestinal lumen. This would be at odds with the observation that, at least in the colon, the microbiota typically occupies the outer mucus layer, a gel-like structure which represents a niche vastly different from the adjacent lumen (Li et al., 2015). High-resolution microscopy analyses conducted with colon sections derived from gnotobiotic mice co-colonized with *C. albicans* and single bacterial species indicate that a significant amount of fungal cells (roughly 50 %) indeed localize to the outer mucus layer (Eckstein et al., 2020). These observations suggest that the spatial distribution of *C. albicans*, at least in the colon, is shaped by the presence of gut bacteria. It is tempting to speculate that *C. albicans* up- or down-regulates some of its genes (to turn on or turn off associated biological functions) depending on the particular microhabitat (*e.g.* lumen *vs*. outer mucus layer) that occupies in the colon. In fact, it has recently been shown that the gut bacteria *B. fragilis* expresses different sets of genes depending on the particular intestinal niche where it localizes to (Donaldson et al., 2020). Future experiments, based either on single-cell RNA-sequencing or HCR-FISH (Choi et al., 2018), will address whether the fungus follows a similar paradigm.

6. Outstanding questions and Outlook on future developments

Some of the most urgent questions concerning the mycobiome can be summarized in a simple phrase: Who is there and what do they do there? The first part of the question is far from resolved as no consensus has emerged yet on which fungi constitute a more-or-less defined 'gut mycobiome'. Large-scale cataloguing studies aimed at finding the entire set of fungal species residing in diverse human populations are still needed to settle this. The undoubtedly more interesting part of the question, '*what do they do there?*' has just started to be investigated, mostly from the host immunology perspective. There is ample room for further research that incorporates high-resolution microscopy and cell biology studies of the intestine of animals carrying (or missing) fungal species. Future work to develop and establish well-defined gut microbial communities that combine bacterial and fungal species – and dissect their mutual roles – is also needed to take us a step closer to the goal of understanding how the mixed array of microbes that constitute our microbiota contribute to health and disease.

7. Concluding remarks

While the fugal component of the gut microbiota remains understudied – at least compared to its bacterial counterpart – there is growing evidence that intestinal commensal fungi elicit multiple, consequential responses from the mammalian gut. The relatively recent incorporation of gnotobiotic mice to dissect the biology of *C. albicans*, a ubiquitous yeast of the human gastrointestinal tract, promises to untangle the particular role(s) of fungi in the gut ecosystem. Furthermore, as the field moves forward, it is evident that such experimental system will be critical to investigate the synergistic, symbiotic or antagonistic interactions between fungal and bacterial members of the microbiota.

Fungi of the genus *Candida* (for instance *C. albicans* and *C. parapsilosis*) are typically referred to as opportunistic pathogens. Because they reside in the gut, it has been hypothesized that the intestinal microbiota may play a major role in *Candida*'s pathogenesis. Recent clinical evidence adds support to this notion. In patients with disseminated *Candida* infections, *C. albicans* and *C. parapsilosis* translocation into the bloodstream was found to be preceded by an expansion of both species in the gastrointestinal tract (Zhai et al., 2020). Furthermore, fungal dysbiosis was found to be tightly associated with bacterial dysbiosis, particularly the loss of anaerobic bacteria (Zhai et al., 2020). While cause and effect are difficult to pinpoint, one may in the long term envision potential interventions that target the gut microbiome to inhibit *Candida* dissemination from the gastrointestinal tract in people at risk of infections, something that has yet to be achieved for fungal infections.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

Funding: The work from the Pérez laboratory discussed in this manuscript was supported by funding from the Deutsche Forschungsgemeinschaft (DFG) Priority Program - SPP 1656 (project PE 2371/3-1).

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