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MINIREVIEWS

Fungi in Gastrointestinal Tracts of Human and Mice: from Community to Functions

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Abstract Fungi are often ignored in studies on gut microbes because of their low level of presence (making up only 0.1% of the total microorganisms) in the gastrointestinal tract (GIT) of monogastric animals. Recent studies using novel technologies such as next generation sequencing have expanded our understanding on the importance of intestinal fungi in humans and animals. Here, we provide a comprehensive review on the fungal community, the so-called mycobiome, and their functions from recent studies in humans and mice. In the GIT of humans, fungi belonging to the phyla *Ascomycota*, *Basidiomycota* and *Chytridiomycota* are predominant. The murine intestines harbor a more diverse assemblage of fungi. Diet is one of the major factors influencing colonization of fungi in the GIT. Presence of the genus *Candida* is positively associated with dietary carbohydrates, but are negatively correlated with dietary amino acids, proteins, and fatty acids. However, the relationship between diet and the fungal community (and functions), as well as the underlying mechanisms remains unclear. Dysbiosis of intestinal fungi can cause invasive infections and inflammatory bowel diseases (IBD). However, it is not clear whether dysbiosis of the mycobiome is a cause, or a result of IBD. Compared to non-inflamed intestinal mucosa, the abundance and diversity of fungi is significantly increased in the inflamed mucosa. The commonly observed commensal fungal species *Candida albicans* might contribute to occurrence and development of IBD. Limited studies show that *Candida albicans* might interact with immune cells of the host intestines through the pathways associated with Dectin-1, Toll-like receptor 2 (TLR2), and TLR4. This review is expected to provide new thoughts for future studies on intestinal fungi and for new therapies to fungal infections in the GIT of human and animals.

Keywords Commensal fungi · Community · Diet · Intestinal immune · *Candida albicans* · IBD

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Introduction

The gastrointestinal tracts (GIT) of human and animals harbor large numbers of microorganisms (10^{12}–10^{14}), including bacteria, archaea, virus, and fungi [1]. Such gut microbiota mediates different pathways involved in energy metabolism [2], intestinal barrier function, and the immune system of the host [3]. GIT microorganisms are also associated with regulation of blood glucose and other physiological processes [4]. Most studies so far on GIT microorganisms have focused on pathogenic commensal bacteria, but recent studies indicate that fungi may be another vital microbial group associated with nutrient metabolism and the intestinal health of human and animals [5]. Fungi make up approximately 0.1% of the GIT microorganisms and there is a stable relationship of antagonism, synergy, or symbiosis between, or among fungi, bacteria, and viruses in the animal gut under normal circumstances [6]. The total number of fungi increases from the ileum to the colon and reaches the highest density in the distal intestine of most monogastric animals [7]. Although there have been extensive studies on the bacterial community in the gut of human and animals, research efforts aiming to explore fungal diversity in the GIT of monogastric animals are very limited.

With traditional culture-dependent methods, only a small number of intestinal fungal species can be identified and classified [8]. DNA-based culture-independent methods, such as

restriction fragment length polymorphism (RFLP) analysis, temperature gradient gel electrophoresis (TGGE), denaturing gradient gel electrophoresis (DGGE), and oligonucleotide fingerprinting of rRNA genes (OFRG) have been used in the past decade and have contributed to our understanding of the fungal community in the GIT [9]. These methods are superior over culture-dependent methods for revealing fungal complexity, but are not suitable for identifying specific fungal species. Thus, other molecular methods, such as PCR amplification of the small subunit ribosomal RNA (i.e., 18S rRNA gene) were developed to explore fungal diversity [10]. In recent years, high-throughput sequencing has been used by targeting the fungal 18S rRNA and the internal transcribed spacer (ITS) regions to study fungal communities in GIT and other environments [11].

There exists a large number of studies on the relationship between the bacterial community in the GIT and metabolic diseases or inflammatory bowel disease (IBD) [12–15], but similar studies on fungi are quite limited. Dysbiosis of the gut fungal community is thought to contribute to some intestinal diseases, such as IBD [16], colitis [17], peptic ulcers [18], and antibiotic associated diarrhea (AAD) [19]. *Candida albicans* is a predominant gut fungus that colonizes the GIT. It can invade tissues or disseminate in the body when the host is immune-suppressed [20], thereby indicating disruption of the gut microbiome and increased intestinal mucosal permeability. The out-growth of *Candida* in the GIT has been associated with certain diseases such as diabetes [21] and IBD [22]. In addition to *Candida* species, an overall increase of gut fungal diversity and/or abundance has also been associated with disease [23]. Compared to a large body of literature on the benefits of bacteria in the animal GIT, the beneficial role of fungi, if any, remains largely unexplored. It is also unknown if there is mutual benefit, or a reciprocal relationship between the gut mycobiome and the host [23].

Here, we summarize the recent advances on our understanding of the fungal community in the GIT of monogastric animals and discuss the interaction between the gut fungi (with major emphasis on *C. albicans*), diet, and the immune function of the GIT. With novel molecular technologies, diverse fungal groups have been found in the intestines of rats, rabbits, pigs, dogs, and humans [7]. Of these, fungi in the intestines of mice and human have been widely researched and were the major subjects of this review.

Fungal Communities in the Intestines of Human and Mice

Fungi are detectable in all gastrointestinal segments in approximately 70% of healthy adults [24]. There are more than 400 fungal species associated with humans, mainly affiliated to three major phyla: *Ascomycota*, *Basidiomycota*, and *Chytridiomycota* [25]. A study on a young healthy man from Senegal, using both culture-dependent and DNA sequences of the 18S rRNA gene and ITS regions revealed that fungi were the dominant eukaryotes in his fecal samples [26], which is consistent with the results of previous studies showing that fungi are widely distributed in the human gut [6, 27, 28]. The predominant fungal genera in human feces belong to the genus *Candida*, while other fungal genera, such as *Aspergillus*, *Cryptococcus*, *Rhodotorula*, *Mucor*, and *Trichosporon* are occasionally detected in the enteric cavity [26]. Since the latter are the most common residents of the skin or respiratory tract, they are thought to be only transients in the gut [29]. Another study by deep sequencing of marker genes in DNA samples purified from stool specimens from 98 healthy individuals showed that the most prevalent fungal genus in the feces was *Saccharomyces* (in 89% of the samples), followed by *Candida* (57%) and *Cladosporium* (42%), accounting for more than 50 common species [30]. So far, a total of 133 genera have been reported. Of these genera, *Penicillium*, *Candida*, *Aspergillus*, *Saccharomyces*, *Cryptococcus*, and *Malassezia* are predominant, with each genus represented by 3 to 13 different species. *Penicillium*, with 13 species, is the most diverse, followed by *Candida* with 12 species, and *Aspergillus* and *Saccharomyces* with 5 species each [31]. It is hard to explain the existence of *Penicillium* and *Aspergillus* in the GIT, but they both belong to the *Basidiomycetes*, whose members form large quantities of microscopic spores that can easily be inhaled or ingested. Additionally, some genera such as *Saccharomyces* and *Penicillium* can be found in food products, such as bread and meat [31]. A study on the fecal samples from 111 healthy subjects, using pyrosequencing, showed that *Penicillium*, *Aspergillus*, and *Candida* were the most abundant genera (22.3, 22.2, and 16.9%, respectively) [32] and that there was no significant difference in the fungal composition between males and females. Furthermore, infants and children had higher richness of fungi compared to adults as indicated by the number of the observed operational taxonomic units (OTUs). *Candida albicans* colonizes the GIT of humans and is probably the most abundant fungal species [32]. However, in a study of 151 stool samples, collected in 2006 and 2010, from indigenous people living in a remote region of French Guiana, the prevalence of *C. albicans* was very low (3 and 7% of all fungi, respectively). This is not consistent with previous studies [33]. Overall, fungi have much lower diversity and abundance than bacteria in the GIT and the composition of fungi in human gut appears to be diverse and instable [34].

Compare to human fungal microbiota, less data are available from mice. The OFRG analysis provided evidence that the murine intestine harbors a diverse array of fungi. The largest assemblages of fungal rRNA gene sequences were related to the fungi belonging to the genera *Acremonium*, *Monilinia*, *Fusarium*, *Cryptococcus*/*Filobasidium*,

Scleroderma, *Catenomyces*, *Spizellomyces*, *Neocallimastix*, *Powellomyces*, *Entophlyctis*, *Mortierella*, and *Smittium*, as well as, the order *Mucorales* [7]. Recently, over 100 different well-annotated fungal species, representing at least 50 genera, were identified in Dectin-1 knockout and wild-type mice, illustrating the diverse fungal community in the murine GIT [17]. Of those fungi, 7 of the 20 most common genera were also found in the mice feed. However, these food-sourced fungi only made up 1.5% of total fungi in the GIT, suggesting that wild-type mice harbor a higher level of indigenous fungi. Within all the fungal sequences, 97.3% were identified from 10 species with most (65.2%) of the sequences belonging to a single species, *Candida tropicalis* [35]. So far, there are only a few publications on the fungal diversity and community in the murine GIT [7, 17, 35]. Compared with those fungal taxa identified in the human gut, fungi identified from mice showed a relatively smaller overlap. Common genera such as *Aspergillus*, *Candida*, or *Cryptococcus* were identified in the intestinal of most mice, while *Penicillium*, an extremely common taxon found in human intestine, was observed in only one study in mice. The most commonly identified fungal species from the GIT of humans and mice are summarized in Table 1.

Association Between Diet and Intestinal Fungal Taxa

The gut is colonized by microbial organisms soon after birth. In addition to maternal transmission, the main way of microorganisms entering the GIT is via food ingestion [47]. Diet is also the main factor influencing microbial composition. Fungi can be found in many animal and plant-based foods and these foodborne microorganisms enter the GIT and become transient colonizers [45, 48]. Certain food components might shape the fungal community in the human gut. In a study reported by Hoffmann et al. [30], the abundance of *Candida* was shown to have positive correlation with recent consumption of carbohydrates, but negative association with increased ingestion of amino acids, proteins, and fatty acids. *Aspergillus* was found negatively correlated with recent ingestion of short chain fatty acids. However, diet did not show significant effect on abundance of *Saccharomyces* [30]. Both *Candida* and *Penicillium* in human feces were found to have a negative correlation with the consumption of almonds and pistachios [39]. Two interesting studies revealed different profiles of fungi in the human gut with different types of diet. In the first study, a total of 16 fecal samples were collected from 15 vegetarians and analyzed [49], while in another study, the fungal community of 69 fecal samples from 45 healthy human volunteers fed a conventional Western diet were also investigated [34]. Plant pathogenic fungi, *Fusarium* (88%) and *Malassezia* (81%), and foodborne fungi, *Penicillium* (75%) and *Aspergillus* (68%), were present in more than 60% of vegetarian stool samples (n = 16) [49], but were rarely found in the samples from those individuals with Western diet (n = 69) (3, 12, 1, and 6%, respectively) [34]. Moreover, a high proportion of *Candida* was observed in the samples from both populations (63% in vegetarian samples and 84% in the samples consuming Western diet). Intestinal microbiota is proposed to be related to obesity through diet. The role of gut fungi in

Table 1 Most commonly identified fungal species from the GIT of human and mice

Genus	Species	Subject	Sample type	References
Aspergillus	*Aspergillus versicolor*	Human	Feces	[27, 34, 36]
	Aspergillus clavatus	Human	Ileal mucosal specimens, feces	[34, 37]
Candida	*Candida albicans*	Human	Feces	[27, 34, 36, 38]
	Candida tropicalis	Mice, human	Small intestine or colon, feces	[7, 39, 40]
	Candida parapsilosis	Human	Feces	[27, 40, 41]
	Candida glabrata	Human	Feces	[16, 41, 42]
Cryptococcus	*Cryptococcus neoformans*	Human	Ileal mucosal specimens, feces	[16, 37]
Cladosporium	*Cladosporium herbarum*	Human	Feces	[43, 44]
Saccharomyces	*Saccharomyces cerevisiae*	Human	Feces	[26, 34, 45]
Penicillium	*Penicillium chrysogenum*	Human	Feces	[40, 41]
	Penicillium roqueforti	Human	Feces	[39, 46]
Malassezia	*Malassezia globosa*	Human	Feces	[36, 44, 45]
	Malassezia pachidermatis	Human	Feces	[26, 36]
	Malassezia restricta	Human	Feces	[34, 46]
Mucor	*Mucor racemosus*	Human	Feces	[16, 27]
Galactomyces	*Galactomyces geotrichum*	Human	Feces	[36, 46]
Trichosporon	Unknown	Mice, human	Colon, feces	[17, 44]

obese and non-obese subjects was characterized using Internal Transcribed Spacer (ITS)-based sequencing. Compared to non-obese individuals, family biodiversity was significantly lower in obese subjects. *Candida*, *Nakaseomyces*, and *Penicillium* (present in 6.57, 4.33, and 3.12%, respectively) were the most prevalent genera detected in obese patients. *Mucor* (8.07%) was the most abundant genus in non-obese patients, followed by *Candida* and *Penicillium* (5.79 and 2.49%, respectively) [50]. A study on digesta samples from the cecum, proximal colon and distal colon of pigs using chromatin immunoprecipitation (ChIP) also showed an effect of diet on the composition of intestinal fungi of suckling piglets [51]. Relative abundance of *Eubacterium pyruvativorans* was remarkably decreased by diet containing pure cellulose (94.24% neutral detergent fiber, the pure cellulose containing diet was composed of basal diet and 1% pure cellulose) compared with the basal diet. All these results indicate strong association between diet and abundance and community of intestinal fungi.

Relationship Between Enteric Fungi and Intestinal Immunity

As described above, many factors could impact the community of intestinal fungi which, in turn, influences physiological functions of the host directly or indirectly. Pathogenic fungi have been widely researched in the past few decades, but the influence of commensal fungi on gut health of the host still remains unclear. Several recent studies examined the relationship between specific intestinal fungi and the host gut immune system [16, 31, 52]. Intestinal fungi may induce innate immune responses of intestinal epithelial cells (IECs), respiratory and urinary systems, and skin tissues. They also contribute to the maturation of mesenteric or intestinal lymphatic immune system. The host immune response to fungi is a complex process involving many signaling molecules and multiple cells. Pathways mediated by pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and NOD-like receptors (NLRs) [52], are possible mechanisms. Fungal cell wall components [53] (such as β-glucan, zymosan, mannan, and chitosan) and the genetic materials of fungi (DNA and RNA) could be recognized by PPRs (such as TLR2, TLR4, dectin-1, and dectin-2) on antigen presenting cells located in intestinal mucosa [54] with subsequent activation of the downstream signaling pathways [55]. CLRs recognize the fungal cell wall components to activate tyrosine kinase and the adaptor molecule caspase-associated recruitment domain 9 (CARD9) associated signaling pathways, leading to activation of the NLRP3 and NF-κB inflammasome and production of cytokines, which finally activate innate immune responses [56]. In addition, the development of adaptive immunity, particularly the helper T cell (such as Th1 and Th17) responses induced by dendritic cells, can also be modulated by PRRs. Th17 cells primarily produce IL-17A and IL-22, whereas Th1 cells mainly produce IFN-γ, leading to neutrophil recruitment, defensin production, phagocyte activation, and finally elimination of pathogenic fungi [38]. It was reported that enriched fungal species in mammalian gut could influence the host immune system through the innate immune receptor Dectin-1, a C-type lectin receptor recognizing β-1,3-glucansin in the fungal cell wall [17]. Dectin-1 could also activate intracellular signals through CARD9 that promotes production of inflammatory cytokines and induces Th17 responses [57] (Fig. 1). In human or mice, deficiency of either CARD9 or Dectin-1 would result in the failure of recognition of pathogenic fungi and increased susceptibility to potential intestinal diseases [61, 62].

Candida albicans and Inflammatory Bowel Disease

Besides bacterial perturbation, there was distinct dysbiosis of fungal microbiota in IBD characterized by alterations in biodiversity and composition [41]. Compared to the non-inflamed mucosa, the richness and diversity of fungi were significantly increased in the inflamed mucosa [37]. Sequencing analysis based on the 18S rRNA of colonic biopsy mucosa tissues and stool samples of ulcerative colitis patients and healthy individuals showed that the fungal communities between the two groups were remarkably different, and the ulcerative colitis patients were heavily colonized with *C. albicans* [16], causing aggravated mucosal injury and generation of anti-*Saccharomyces cerevisiae* antibodies (ASCA), the most commonly used serological biomarker for Crohn's disease [63, 64]. Severe colitis in mice was generally accompanied with fungal invasion to colonic mucosa, general expansion of opportunistic fungi such as *Candida* and *Trichosporon*, and decrease of non-pathogenic species such as *Saccharomyces*, suggesting that fungal dysbiosis might be closely associated with IBD [65]. High abundance of *Candida* colonization is frequently observed in ulcer and IBD patients [37, 41, 66, 67]. To elucidate the interplay between the mycobiome and IBD, animal models with GIT diseases are generally employed. Cysteamine is a chemical used to induce duodenal ulcers. In rats receiving cysteamine treatment and *C. albicans* inoculation, most of the animals (94.1%) developed perforated duodenal ulcers. Those rats receiving cysteamine treatment, but without *C. albicans* inoculation, displayed much lower incidence (26.7%, $p < 0.01$). The depth and area of the ulcers was also greater with in *C. albicans* positive animals, indicating that *C. albicans* aggravated cysteamine-induced duodenal ulcer perforation in these rats [68]. A study on the stool samples from 235 patients with IBD and 38 healthy subjects using ITS2 sequencing showed that the fungal community was markedly changed in IBD

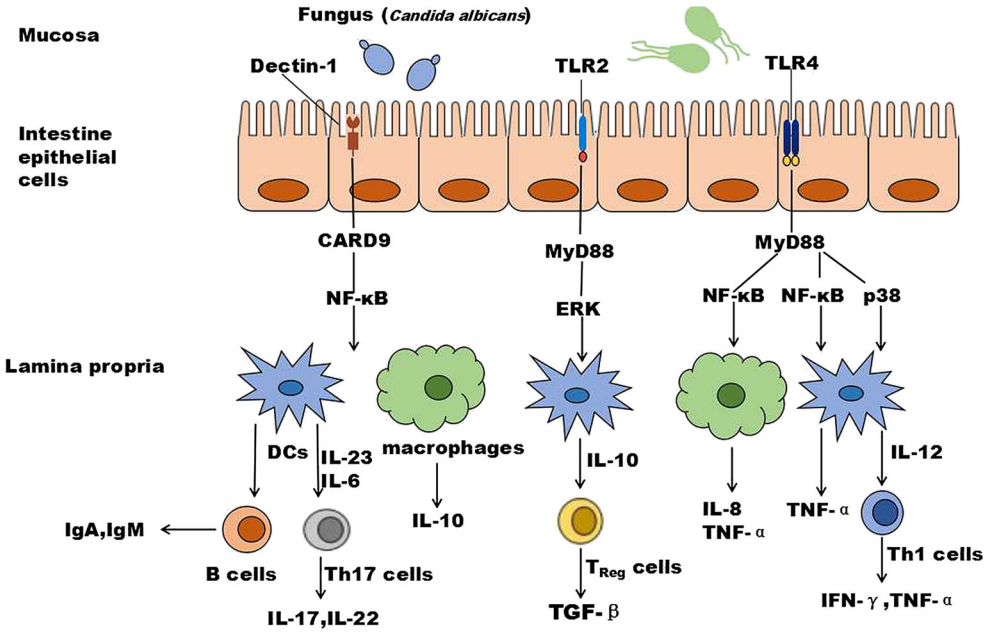

Fig. 1 Interactions between fungi, such as *Candida albicans,* and intestinal immune cells (summarized according to cited references). Recognition of fungi by the cell membrane of host is mediated by TLRs- and CLRs-associated pathways. Dectin-1 activates intracellular signals through CARD9 that promotes the production of inflammatory cytokine and induces the immune responses of Th17 [58]. TLR2 stimulates IL-10 and TGF-β responses and subsequent proliferation of T_{Reg} cells and immunosuppression through MyD88-mediated ERK pathways [59]. TLR4 induces proinflammatory signals through the MyD88-mediated NF-κB pathways, stimulating TNF-α production in macrophages and DCs. TLR4 induces the secretion of IL-12 and IFN-γ stimulating TH1 responses in DCs through the MyD88-mediated MAPK pathways [60]. TGF-β, transforming growth factor-β; TNF-α, tumor-necrosis factor-α

patients. Sequence data showed that there was an increase in the *Basidiomycota/Ascomycota* ratio, an elevated proportion of *C. albicans,* and a decrease of *S. cerevisiae* [41]. It was reported that Dectin-1 encoded by C-type lectin domain family 7 member A (*CLEC7A*) gene was associated with severity of ulcerative colitis in mice [17]. Dectin-1-deficient ($Clec7a^{-/-}$) mice exhibited greater severity than wild type mice of IBD symptoms with increased histological alterations (crypt destruction, mucosal erosion, and inflammatory cell infiltration) and production of proinflammatory cytokines than wild-type mice [17]. Moreover, the number of opportunistic pathogenic fungi such as *Candida* increased, whereas non-pathogenic *Saccharomyces* decreased in $Clec7a^{-/-}$ mice during colitis, indicating that deficiency of Dectin-1 might lead to altered composition of indigenous fungi [17]. These results indicate that over-colonization of *C. albicans* in the intestine may increase the severity of ulcers and inhibits healing. Microbial dysbiosis involved in gut inflammation creates an environment favoring *Candida* species and their possible overgrowth, which subsequently exacerbates inflammatory diseases such as IBD. Moreover, colonization of *Candida* delays healing of the lesions. There appears to be a vicious cycle between intestinal inflammation and dysbiosis of the mycobiome.

In addition to *Candida*, a recent study also showed a relationship between *S. cerevisiae* and colitis in germ-free mice. Inoculation of *S. cerevisiae* in germ-free mice increased permeability of the intestine and exacerbated colitis. Metabolomics analysis further revealed that colonization of *S. cerevisiae* enhanced purine metabolism of the host, causing increased uric acid production. Thus, over-colonization of *S. cerevisiae* in the GIT may also have negative effects on IBD development [69]. The interaction between certain fungi in the intestine and the immune system of the host suffering IBD is summarized in Table 2.

Possible Interaction Between *Candida albicans* and Host Intestinal Immunity

As an opportunistic pathogenic fungi, *C. albicans* is normally adapted for commensalism and can thrive in different host niches (gut, vagina, oral mucosa, and skin) without causing disease [70]. Under normal conditions when the intestinal mucosal barrier is intact and host innate immune system is functional, *C. albicans* presents as one of the commensal members. When homeostasis between *C. albicans* and the host is disrupted, adverse relationship may probably arise. In this case, *C. albicans* can break through the intestinal mucosal barrier and cause several diseases of the GIT, such as Crohn's disease and ulcerative colitis [60, 71]. The intestinal immune system is essentially comprised of IECs, intra epithelial lymphocyte, lamina propria lymphocyte, Peyer' patches, and mesenteric lymph nodes [72]. IECs are in unique position of being

Table 2 The interaction between certain intestinal fungi and the immune system of host suffered IBD

IBD	Sample	Intestinal fungi	Histopathologic characteristics	Potential association with immune cells and/or cytokines
Crohn's disease (CD) [37]	Feces	*Candida albicans* (14.2%), *Saccharomyces cerevisiae* (14.0%), *Cryptococcus neoformans* (8.6%), *saccharomyces castellii* (6.6%), *Gibberella moniliformis* (6.1%), *Aspergillus clavatus* (5.0%), *others* (40.5%)	Crypt dilation, goblet cell depletion, mixed cell infiltration, involving mainly mononuclear cells and lymphocytes, and injury with ulceration	Fungi→ PRRs(CLRs/TLRs)→ NF-κB→T helper cells activated→production of IL-17/TNF-α/ IFN-γ
Ulcerative colitis(UC) [65]	Sample from pouch endoscopic biopsies	*Candida* (6%), *Penicillium* (61.5%), *Saccharomyces* (24.1%) uncultured *Ascomycetes*, *Basidiomycetes* (7.7%).	Crypt destruction, mucosal erosion and inflammatory cell infiltration	CARD9,IL-17,IL-22, NF-κB, nuclear factor of activated T cells(NFAT)
Dextran sulfate sodium (DSS)-induced colitis [16]	Colonic samples	*Aspergillus*, *Penicillium*, *Cladosporium*, *Wickerhamomyces*, *Alternaria*, *Wallemia*, *Emericella*, *Cryptococcus*, *Phialemonium*, *Fusarium*, *Candida*, unidentifed *Saccharomycetales*	Mucosal and submucosal inflammation, bowel wall thickening, a moderate level of lymphocyte infltration and regeneration with crypt depletion	Two key tight-junction proteins (occludin and ZO-1) were decreased, IL-17A, IL-23, and TNF-α were strikingly increased in colonic mucosa samples

in constant contact with *C. albicans* and thereby constitute the first line of defense [73]. In response to invasion of *C. albicans*, IECs can secrete cytokines and chemokines, leading to recruitment, differentiation, and activation of various immune cells including neutrophils, dendritic cells, and T cells [74]. Neutrophils protect host IECs against infection of *C. albicans* through up-regulation of TLR4 or direct killing of the fungal cells by ingestion and degranulation [75]. Recognition of fungi by dendritic cells through PRRs (Dectin-1 or Dectin-2) associated pathway has been shown to play an important role in promoting development of Th17 cells, indicating close relationship between fungal invasion and Th17 cells [76, 77]. The proinflammatory cytokines IL-17 and IL-22 produced by Th17 cells play a significant role in anti-fungal immune responses [78]. These cytokines in turn induce production of β-defensins by IECs which have anti-fungi activity and limit outgrowth of colonizing *C. albicans* [46, 47]. Although IL-17 acts on IECs and neutrophils and continuously induces production of antimicrobial peptides, matrix metalloproteases (MMPs) and other inflammatory mediators, and functions as a bridge between adaptive and innate immune responses [48], the exact role of IL-17 in anti-*Candida* response remains controversial. Evidence suggests that the influence of IL-17 on *C. albicans* growth may be either positive or negative [79, 80]. A study found that IL-17 increased *C. albicans* burdens after infection through inhibition of protective Th1 immunity [79]. Similarly, IL-22 acts on IECs and has been reported to directly control yeast growth and integrity of the epithelial layer during infection [81]. IL-22 knockout mice showed epithelial damage of the GIT and increased systemic bacterial burden and infection-related mortality [82]. Thus, IL-22 may be anti-fungal.

Inoculation of *C. albicans* into pathogen-free mice induced proliferation and differentiation of B lymphocytes accompanied with increased number of IgA-secreting plasma cells [83]. The complement receptor 3-related protein (CR3-RP) of *C. albicans* is an antigen to induce secretion of IgA [84]. With increased secretion of *C. albicans*-specific IgA, the number of *C. albicans* and its adhesion to cecal IECs was decreased [83]. The specific IgA combines with the fungal antigens to form antigen-antibody complexes that prevent adhesion of pathogenic fungi to epithelial cell surfaces through agglutination in the intestinal lumen, entrapment of immune complexes in mucus and final clearance by peristalsis. Furthermore, Fc-peptide, a possible product of IgA proteolysis, was also found as anti-fungal on experimental mucosal and systemic candidiasis in a mouse model [85] (Fig. 1). Therefore, mounting specific IgA antibody barrier may be an effective alternative method to prevent intestinal *C. albicans* infection [84].

Summary

The long-term stability of fungi in the GIT, although present in a small number, is essential to maintain homeostasis of the entire intestinal microbiota. The interactions between commensal fungi and intestinal immunity have received

increasing attention. Colonization and dissemination of intestinal fungi is a dynamic and complex process involving the host immune effectors. Although dysbiosis of symbiotic fungi can be found in IBD patients and some fungi can promote or inhibit intestinal inflammatory responses, it is not clear whether alteration of the mycobiome in GIT results from dysbiosis of other gut microbes such as bacteria or is directly induced by intestinal dysfunction in IBD patients. It is also not known whether dysbiosis of the mycobiome is a cause or result of IBD. The role of fungi in maintaining health of the host might be beyond our imagination.

Most of the existing data on intestinal fungi are based upon human subjects or murine models. However, the functions of fungi in the GIT of other monogastric animals are rarely examined. Nevertheless, possible interactions between intestinal fungi and other microbes, such as bacteria, archaea, or even viruses in the GIT under health, or diseased conditions, remain unknown. Because of importance of gut microbes in digestion of nutrients, it is also necessary to explore the relationship between diets and the community and function of commensal fungi, as well as the underlying mechanisms. When symbiotic fungi become opportunistic pathogens in the GIT, further research is needed to see if nutritional regulation could alleviate the pathogenic conditions of the gut. Findings of such studies may provide new insights and therapies to fungal infections in the GI tract of human and animals.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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