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LETTER TO THE EDITOR

Role of *Candida* species in pathogenesis, immune regulation, and prognostic tools for managing ulcerative colitis and Crohn's disease

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Abstract

The gut microbiome plays a key role in the pathogenesis and disease activity of inflammatory bowel disease (IBD). While research has focused on the bacterial microbiome, recent studies have shifted towards host genetics and host-fungal interactions. The mycobiota is a vital component of the gastrointestinal microbial community and plays a significant role in immune regulation. Among fungi,

Candida species, particularly *Candida albicans* (*C. albicans*), have been extensively studied due to their dual role as gut commensals and invasive pathogens. Recent findings indicate that various strains of *C. albicans* exhibit considerable differences in virulence factors, impacting IBD's pathophysiology. Intestinal fungal dysbiosis and antifungal mucosal immunity may be associated to IBD, especially Crohn's disease (CD). This article discusses intestinal fungal dysbiosis and antifungal immunity in healthy individuals and CD patients. It discusses factors influencing the mycobiome's role in IBD pathogenesis and highlights significant contributions from the scientific community aimed at enhancing understanding of the mycobiome and encouraging further research and targeted intervention studies on specific fungal populations. Our article also provided insights into a recent study by Wu *et al* in the *World Journal of Gastroenterology* regarding the role of the gut microbiota in the pathogenesis of CD.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Gut mycobiome dysbiosis; *Candida* species; Immune regulation; Gut inflammation; Fecal mycobiota transplantation

Core Tip: This article investigated the relationship between *Candida* species and inflammatory bowel disease (IBD), focusing on ulcerative colitis and Crohn's disease. It examined how *Candida* affects IBD development, gut barrier function, immune response, and microbiota balance. The role of *Candida*-derived β-glucans in proinflammatory reactions and the potential use of *Candida albicans* as a disease marker were discussed. New treatment approaches, including antifungal and immunomodulatory strategies, were also covered. This review suggested that an altered number of *Candida* species can serve as biomarker for disease severity and treatment outcomes, leading to new diagnostic tools and personalized therapy for IBD.

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TO THE EDITOR

Inflammatory bowel disease (IBD) is a chronic intestinal condition characterized by immune-mediated mucosal disruption and inflammation[1]. The two primary types of IBD, including ulcerative colitis (UC) and Crohn's disease (CD), are distinguished by the location and depth of inflammation[1]. CD presents as patchy inflammation throughout the gastrointestinal (GI) tract[2], whereas UC shows continuous inflammation confined to the large intestine, typically extending from the rectum[3]. IBD greatly burdens and challenges the global healthcare system[4]. Although the etiology of IBD remains unclear, factors such as genetics, stress, diet, and gut microbiota dysbiosis, particularly in immunocompromised individuals, have been implicated.

Dysbiosis, or alterations in microbiota composition, occurs in both UC and CD patients[5]. While most microbiome studies have focused on bacteria, several studies have found that viral and fungal dysbiosis contributes to the pathogenesis of IBD[6-9]. Fungi constitute a small fraction (0.1%) of the human gut microbiome, with many species being unculturable[10,11]. However, deep-sequencing surveys have indicated that fungal dysbiosis is a hallmark of IBD[11-15]. Although many fungal genera are present in the gut, only a few dominate the mycobiome. Even though fungi are not very abundant in number, they are crucial for maintaining gut bacterial homeostasis and supporting immune responses. When fungal dysbiosis happens, it is associated with GI diseases, such as irritable bowel syndrome, colorectal cancer, and cirrhosis[16-18].

In this review, we also provided insights into our understanding of the intestinal fungal mycobiome, focusing on the abundance and role of different *Candida spp.* that help maintain homeostasis and antifungal immunity in healthy humans and patients with IBD. Additionally, this article addressed antifungal immune responses occurring in the intestinal mucosae of patients with CD while determining ways to use fungi for diagnosis and prognosis. We highlighted the role of fungi as prognostic markers in the pathogenesis of IBD. The consequences of IBD include inflammation and immunosuppression, which result in alterations in the fungal microbiome, ultimately contributing to an increase in pathogenesis. An improvement in the detection of fungi can lead to more customized treatment options, improving patient outcomes. Our assessment of the available data on the mycobiome associated with IBD revealed that specific fungal profiles are correlated with disease activity and response to therapy. Our findings indicated that understanding these markers can improve diagnostic accuracy and provide better therapeutic options.

INTESTINAL FUNGAL ALTERATIONS IN IBD

Several studies have assessed the mycobiota in the stool and colon biopsies of patients with CD; however, very few studies have investigated UC[7]. Some studies have reported that an increase in the number of Basidiomycota fungi, members of a phylum that includes mushrooms[19], coincided with a decrease in the number of Ascomycota, which showed that compared to healthy controls, CD patients had relatively high Basidiomycota-Ascomycota ratios according to Limon *et al*[11] and other researchers[11,13,20], whereas others found that CD patients had a lower ratio than healthy controls[12,21,22]. How these altered fungal communities affect the susceptibility to and severity of IBD remains unknown. Fungi that are more abundant in inflamed mucosa may exacerbate the disease to a greater extent than those in non-inflamed mucosa[23]. Hsia *et al*[24] reported 500 unique fungal amplicon sequence variants across a cohort of 82 patients dominated by the phylum Ascomycota[24]. Endoscopic inflammation in UC is associated with a higher abundance of *Saccharomyces* and *Candida* strains compared to periods of remission, suggesting that these fungal taxa may represent biomarkers and therapeutic targets for UC.

In several studies, *Candida* was found to be the most dominant genus in fecal or mucosal biopsy samples from patients with IBD. *Candida albicans* (*C. albicans*) is considered to be the most critical commensal yeast in the human intestine, although other subspecies can cause mucocutaneous or systemic candidiasis under conditions that compromise the host immune system[25]. The levels of *C. albicans* and *Candida parapsilosis* are consistently elevated in fecal samples from patients with CD, while the abundance of *Candida tropicalis* (*C. tropicalis*) varies across different studies[7,26]. Additionally, an increase in *Candida* species levels has been observed in CD and UC patients who do not respond to infliximab treatment[26].

Research into the fecal mycobiome has also included pediatric populations. Chehoud *et al*[27] reported a higher prevalence of *Candida spp.* in children with IBD pediatric IBD (PIBD), whereas *Cladosporium* was more frequently found in healthy controls. A prospective study by Lewis *et al*[28] identified positive correlations between *Saccharomyces cerevisiae* (*S. cerevisiae*), *Clavispora lusitaniae* (*C. lusitaniae*), *Cyberlindnera jadinii*, *C. albicans* and *Kluyveromyces marxianus* with CD, particularly in cases exhibiting significant bacterial dysbiosis. Fitzgerald *et al*[29] reported that *Candida and Malassezia* species were more abundant in PIBD. Additionally, in PIBD, non-responders to the tumor necrosis factor-α (TNF-α) antagonist infliximab had higher loads of *Candida spp.* than those who responded to treatment[30]. Krawczyk *et al*[31] studied the gut mycobiome of pediatric patients suffering from CD. They reported that *Candida spp.* were present in greater quantities than healthy children, with *Saccharomyces* being the most polymorphic genus. Patients with active CD presented a greater abundance of *Debaryomyces hansenii* (*D. hansenii*, formerly *Candida famata*) than patients with inactive disease and healthy controls. Additionally, the positive correlation of *Candida dubliniensis* (*C. dubliniensis*) and *Candida sake* (*C. sake*) with calprotectin levels and the pediatric CD activity index strongly indicates the critical role of fungi in the development of CD. Since mycobiome composition is largely unexplored in pediatric patients, more longitudinal studies are needed to confirm the pathogenesis of PIBD.

Qiu *et al*[32] investigated the associations between the mycobiota and CD phenotypes. They found no significant differences in alpha and beta diversity or at the phylum level between inflammatory and non-B1 CD types. In contrast, *Candida* was more abundant in the non-B1 type of CD than in the B1 type of CD, although no differences were reported at the species level[22]. Sokol *et al*[13] reported lower fungal diversity in CD patients without ileal involvement, suggesting that essential ileal functions such as the production of antimicrobial peptides and bile acid resorption may influence fungal diversity. Catalán-Serra *et al*[33] conducted a study with 89 prospectively enrolled patients with IBD (52 patients with UC and 37 patients with CD) and 22 healthy controls. Their study revealed a lower Ascomycota/Basidiomycota ratio in patients with IBD. Notably, the abundance of *C. dubliniensis* and *C. albicans* increased significantly. The latter is more prevalent in inflammation than in fibrostenosing CD. *C. dubliniensis* was more abundant in active cases and was directly related to fecal calprotectin and neutrophil gelatinase-associated lipocalin, whereas *Saccharomyces pastorianus* (*S. pastorianus*) was inversely related to disease activity. Moreover, *C. sake* was found to be associated with more complex disease manifestations, while the high abundance of *Cryptococcus carnescens* (*C. carnescens*) increases the need for surgical intervention in CD. Finally, the study also reported that *Zygomycota* abundance was markedly decreased in IBD patients regardless of disease status, which was not reported previously. Additionally, *C. albicans* is more abundant in inflammatory phenotypes than in structural phenotypes, which is consistent with its proinflammatory properties[13,21].

Zeng *et al*[22] investigated perianal disease associated with impaired quality of life and poor outcomes in patients with CD. They compared the mycobiota in CD patients with and without perianal lesions. No significant differences were noted at the phylum level between the two groups, with similar abundances of the genus *Candida*. However, they reported that *Candida* was significantly enriched in non-B1-type CD, indicating a relationship between the genus and both stenosis and penetrating lesions in CD. Various studies have associated the abundance of *Candida spp.* with active disease. Qiu *et al*[32] reported that *Candida spp.* were more abundant in active CD patients than in controls. However, no significant differences were detected between active CD patients and healthy controls or between non-active CD patients and healthy controls. Three *Candida* spp., including *C. dubliniensis, C. lusitaniae,* and *C. sake*, along with *Galactomyces candidus*, were identified. On the other hand, the abundance of *S. pastorianus* and *Saccharomyces bayanus* was lower[33]. Specifically, active CD patients showed a higher abundance of *C. sake* and significant depletion of *S. pastorianus* compared to those in remission stages[33]. Further studies are needed regarding the differential composition of the mycobiota depending on the extent of the disease in UC patients or behavior in patients with CD.

IMMUNE REGULATION BY GUT FUNGI IN IBD

Antibodies to fungal mannans, such as anti-*S. cerevisiae* antibodies (ASCA), have been used to define IBD subgroups, linking the presence of fungi to intestinal inflammation. Specifically, *C. albicans* in the GI tract acts as an immunogen for ASCA, inducing antifungal antibodies[34,35]. *Candida* colonizing mucosal surfaces in the intestine are recognized by resident macrophages, with the outcome of the induction of protective immunity or inflammation, depending on the context[36,37]. The pathogenic potential of hyphae of *C. albicans* mainly relies on their ability to invade the epithelial cell layer and release cytolytic enzymes[38,39]. Additionally, hyphal growth aids immune evasion by facilitating escape from phagocytes after engulfment[40].

In *C. albicans,* the *ECE1* gene encodes candidalysin, a novel cytolytic peptide that destroys epithelial cells[39]. Candidalysin is induced to release alarmins that activate epithelial signaling responses such as the EGFR and MAPK pathways [39,41]. Candidalysin also promotes antifungal inflammatory cascades, leading to the induction of IL-1 and IL-36 and the amplification of IL-17 expression[42]. These actions of adhesion to the epithelium, hyphal formation, and candidalysin release play significant roles in the induction of mucosal inflammation and epithelial damage *via* oxidative and necrotic mechanisms[43]. Candidalysin also has other effects related to immune evasion, including NLRP3 inflammasome activation, after phagocytosis of the fungus[44]. This phenomenon is important for virulence factors because intrastrain variation in *Candida spp*., such as *C. dubliniensis* and *C. tropicalis,* results in the production of candidalysin with differing potencies related to the induction of cellular damage and cytokine responses[45].

Antifungal immunity depends on signaling pathways initiated through pattern recognition receptors (PRPs) that recognize fungal pathogen-associated molecular patterns, such as β-glucans. C-type lectin receptors are among the key patterns of PRPs that activate antifungal signaling *via* CARD9-dependent mechanisms[46]. The genes encoding CARD9 and C-lectin receptors have been associated with IBD and fungal diseases in genome-wide association studies[47]. The CLRs include Dectin-1, Dectin-2, Dectin-3, and Mincle, whose roles include recognition of β-glucan and α-mannose, which are found in fungal cell walls[48,49]. They also contribute to adaptive immunity by modulating the differentiation of CD4+ T cells into Th1 and Th17 cells[50]. For example, Dectin-1 mediates antifungal responses by activating a CARD9-dependent inflammatory cascade, signaling *via* MAPK and NF-κB, and upregulating IL-17A, IL-22, and IL-1[50,51]. The importance of this pathway in IBD is highlighted by the fact that Dectin-1-deficient mice have greater susceptibility to DSS-induced colitis characterized by increased levels of IFN, TNF-α, and IL-17 and worsened histological severity[48]. Hence, these mice tend toward more invasive *C. tropicalis* and fewer nonpathogenic *Saccharomyces spp*., making them susceptible to yeast infections.

Various CARD9 variations can either protect or harm IBD patients, with autosomal recessive loss-of-function mutations resulting in life-threatening fungal infections[52,53]. Patients with UC have a greater presence of fungi such as *C. albicans* than controls[54]. Additionally, UC patients with active disease were reported to have high tissue levels of Dectin-1, a fungal pathogen receptor[55], which confirms this finding. This effect was also weakly to moderately associated with the levels of serum inflammatory cytokines such as IL-17 and IL-22. The absence of tissue measurements for proinflammatory cytokines is a limitation, but it strongly supports the finding that fungal components play an essential role in causing such adverse effects in UC. Furthermore, a study indicated that *D. hansenii* is enriched in inflamed ileal biopsies from CD patients, potentially impairing mucosal healing through the myeloid cell-specific type 1 interferon-CCL5 axis[15].

Secretory IgA (sIgA) is crucial for intestinal immunity and homeostasis and coats microbes to modulate host immune responses to commensal and pathogenic microbes[56]. Antifungal IgA is induced mainly by filamentous *C. albicans* in the large intestine, targeting hyphal formation, adhesins, and candidalysin[36,57]. Intervention with sIgA reduces *C. albicans* hyphae and promotes yeast growth[36]. Additionally, research has demonstrated a decrease in anti-*C. albicans* sIgA responses against hyphal virulence factors, along with an increase in hyphal morphology within the gut mucosa of CD patients[36,57]. CD patients exhibit lower antifungal IgA responses to hyphal virulence factors, contributing to the pathogenicity of *C. albicans* in IBD[36].

Unlike systemic antifungal IgG production, which depends solely on CX3CR1+ mononuclear phagocytes (MNPs), anti-*C. albicans* sIgA responses are mediated by either CX3CR1+ MNPs or $CD11c^{+}CD11b^{+}CD103^{+}$ conventional dendritic cells (cDC2) *via* distinct pathways, affects IgA+ plasmablasts in the lamina propria and IgA+ B cells in Peyer's patches[36,37]. Additionally, in CD, polymorphisms in the coding region of the CX3CR1 gene lead to an antifungal immune response. These findings suggest that antifungal sIgA helps prevent epithelial adhesion and invasion of *Candida*, thereby reducing inflammation in patients with CD.

Antifungal immunity in humans relies on Th17 cells, which defend mucosal barriers, and Th1 cells, which prevent fungal dissemination; it is strongly associated with IBD pathology[58]. Patients with IL-17 primary immunodeficiencies, specifically IL-17A and IL-17F, develop characteristic *C. albicans* mucocutaneous infections, highlighting the key role of this cytokine family in antifungal immunity[58,59]. Bacher *et al*[60] revealed that *C. albicans* is the primary inducer of the antifungal Th17 pathway in CD patients compared to healthy controls; their findings were similar to those of previous studies, which reported that excessive mucosal Th17 cells in IBD patients are correlated with disease activity. These findings indicated that the Th17 axis plays a key role in IBD and *C. albicans* immunity while also highlighting gaps in our understanding.

T-cells specific to commensals play a crucial role in regulating gut inflammation and maintaining homeostasis by promoting tolerance and supporting epithelial barrier function[61]. These cells are essential in the intestine since gut-resident $CD4^{+}$ T cells are enriched to reactivate *C. albicans*[61]. The blood of patients with CD, but not UC, contains a large number of yeast-reactive $CD4^{+}$ Th1 cells exhibiting cytotoxic features that produce IFN-γ[61]. This finding indicates that significant differences are present in the fungal species recognized and the host immune responses induced between those two subtypes of diseases, which also helps correlate fungi with intestinal inflammation and immune regulation in

IBD[17,18,61].

DIAGNOSIS AND PROGNOSIS OF FUNGAL MARKERS IN IBD

Serologic markers play important roles in the diagnosis and classification of IBD. Perinuclear anti-neutrophil cytoplasmic antibodies are primarily associated with UC, although ASCA may be associated with CD[62,63]. ASCA can detect the mannan component of *S. cerevisiae* cell walls, a carbohydrate common to many fungi, raising questions about its specificity. *Candida spp.* in the gut may also induce antifungal antibodies, which act as an immunogen for ASCA. Higher ASCA IgG and IgA are frequently observed in CD patients, with rates of over 50% in CD patients and less than 5% in non-IBD colitis patients and healthy controls[64,65].

A study from Norway showed relationships between specific fungal species and complex disease trajectories or surgical risks in patients with IBD. The results showed that the levels of *Clavispora* were high, whereas the levels of *Phaeococcomyces* and *Penicillium* were low in those with complicated disease courses[33]. Additionally, a complicated disease course was associated with high counts of *C. sake* and *Galactomyces pseudocandidus*, whereas *Penicillium* species were less abundant. CD patients who required surgery had a large number of *C. carnescens*, whereas patients with CD had a lower abundance of *C. tropicalis, Debaryomyces nepalensis*, and *D. hansenii*. Similar studies in other cohorts are currently being conducted by various researchers to repeat these results. Furthermore, extensive research performed in Finland has indicated that if many *Candida* strains are present, a good response to infliximab treatment is unlikely[30]. The use of fungal microbiota signatures as predictive tools in clinical settings remains alarming because there are no well-structured longitudinal studies. Most studies have focused on the bacterial microbiome, highlighting the need to emphasize the fungal microbiome.

THERAPY FOR CANDIDA-MEDIATED IBD

The growing interest in *C. albicans* as a therapeutic target has led researchers to study oral antifungal treatments in CD and UC patients. A pilot study assessed the effect of six months of oral fluconazole on postoperative recurrence in patients with CD and reported a decrease in recurrence-linked biomarkers[66]. Although fluconazole has shown biochemical and histological improvements in UC, more extensive randomized controlled trials are needed[67,68]. However, the risks of drug toxicity and fungal resistance make fluconazole an unlikely cure for IBD. *Saccharomyces boulardii*, a probiotic yeast related to baker's yeast, has been used to treat infectious diarrhea and preterm infants[69]. However, its efficacy in treating IBD remains inconclusive, although it has shown beneficial effects in animal models with colitis[68]. Probiotics and prebiotics are popular among patients, but data supporting their effectiveness in treating IBD are insufficient.

Fecal microbiota transplantation (FMT) has been examined as a treatment for IBD, with some studies indicating benefits for mild and moderate UC[70-72]. Variability in FMT delivery methods makes the assessment of trials challenging. Leonardi *et al*[37] reported enhanced outcomes in patients who had a higher abundance of *C. albicans* just before they underwent FMT; this indicated that *C. albicans* cannot serve as a marker for the effectiveness of FMT. Another study established that the abundance of *Candida spp.* was greater in patients with IBD. Moreover, transplantation of *Candida metapsilosis* M2006B decreased the severity of colitis in mice[73].

CONCLUSION

Dysbiosis of the fungal microbiome is generally associated with IBD, and several studies have indicated that the mycobiome plays a role in the pathogenesis of this disease. Our review suggests that specific fungi can interact with the host immune system and influence inflammatory pathways, exacerbating the symptoms of IBD. However, these interactions are multifaceted and can be influenced by various factors, including individual microbiota composition and environmental triggers. This comprehensive interaction provides insights into the associative roles of fungal components in the pathogenesis of IBD.

Fecal sequencing has greatly contributed to understanding the fungal composition in the context of IBD phenotypes, activity, and prognosis, making the mycobiome a promising candidate for precision medicine. *C. albicans* plays a key role in IBD-related dysbiosis, and its strain-specific virulence factors are necessary for mucosal immunity. Further information on immune mechanisms may help target pathogenic strains of *C. albicans* more effectively for IBD therapy and predictive markers for treatments such as FMT. Studies linking fungal makeup with response rates should encourage further research on fungi[30,37]. Improved characterization of fungal populations in IBD can help define their roles in pathogenesis, thus leading to better diagnosis and more efficient treatment options that can enhance the quality of life of patients[17,18,74].

FOOTNOTES

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