Huang *et al. Gut Pathogens* (2024) 16:59
https://doi.org/10.1186/s13099-024-00651-7

Gut Pathogens

REVIEW Open Access

Unveiling the overlooked fungi: the vital of gut fungi in inflammatory bowel disease and colorectal cancer

Yilin Huang[1,2], Yang Wang[1], Xiaotian Huang[1*] and Xiaomin Yu[1*]

Abstract
The fungi of the human microbiota play important roles in the nutritional metabolism and immunological balance of the host. Recently, research has increasingly emphasised the role of fungi in modulating inflammation in intestinal diseases and maintaining health in this environment. It is therefore necessary to understand more clearly the interactions and mechanisms of the microbiota/pathogen/host relationship and the resulting inflammatory processes, as well as to offer new insights into the prevention, diagnosis and treatment of inflammatory bowel disease (IBD), colorectal cancer (CRC) and other intestinal pathologies. In this review, we comprehensively elucidate the fungal-associated pathogenic mechanisms of intestinal inflammation in IBD and related CRC, with an emphasis on three main aspects: the direct effects of fungi and their metabolites on the host, the indirect effects mediated by interactions with other intestinal microorganisms and the immune regulation of the host. Understanding these mechanisms will enable the development of innovative approaches based on the use of fungi from the resident human microbiota such as dietary interventions, fungal probiotics and faecal microbiota transplantation in the prevention, diagnosis and treatment of intestinal diseases.

Keywords Fungus, Intestinal inflammation, Inflammatory bowel disease, Colorectal cancer

Introduction

Fungi make up the human microbiome, widely colonising the skin, oral cavity, vagina and intestine, mainly as intestinal symbionts. In the gut, the fungal community is mostly made up of the genera *Aspergillus*, *Candida*, *Debaryomyces*, *Malassezia*, *Penicillium*, *Pichia* and *Saccharomyces* [1]. This community, like the bacterial one, can be altered by diet, the environment and genetic factors [2]. It is in this context that research indicates a positive correlation between the proliferation of Methanobrevibacter and Candida and a diet rich in carbohydrates, and a decrease in these microorganisms when ingesting amino acids, proteins and fatty acids [3].

The importance of fungi as components of the intestinal microbiome is indisputable, since the health of the host is closely related to the communities of these microorganisms in the intestine. In fact, in order to be successful and cause disease, exogenous pathogenic fungi need to disturb the balance of the body's symbiotic fungal microbiota. In immunocompromised individuals, for example, the uncontrolled translocation of commensal fungi can destabilise the balance of the intestinal microbiota and lead to infections [4]. In addition, individuals

*Correspondence:
Xiaotian Huang
xthuang@ncu.edu.cn
Xiaomin Yu
yuxiaomin@ncu.edu.cn
[1]School of Basic Medical Sciences, Jiangxi Medical College, Nanchang University, Nanchang 330006, China
[2]Huankui Academy, Jiangxi Medical College, Nanchang University, Nanchang 330031, China

undergoing prolonged antifungal therapy show exacerbated colitis and intensified symptoms of allergic airway diseases such as asthma [5].

Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition of uncertain origin that affects various parts of the digestive system, such as the ileum, colon and rectum. The symptoms of the disease are usually abdominal pain, diarrhoea, rectal bleeding, anaemia, weight loss and fatigue. IBD includes Ulcerative Colitis (UC) and Crohn's Disease (CD). Over the last three decades, the number of global cases of IBD has risen from 3 million in 1990 to almost 7 million in 2017. IBD usually manifests in young individuals, significantly compromising their quality of life [6]. IBD is characterised by recurrent flare-ups and periods of remission, which can persist for months or even years, resulting in tissue damage and ulceration in the intestines, and is associated with abnormalities in the body's immune response. Patients also face the risk of various complications, including intestinal cancer, intestinal obstruction, anal fistula and mesenteric ischaemia. Such signs and symptoms have made IBD a significant focus of attention and study among gastrointestinal diseases.

In IBD, persistent chronic inflammation can promote malignant transformation of the colonic mucosa through various mechanisms, which can result in Colorectal cancer (CRC) [7]. CRC is the third most common cancer worldwide and the second leading cause of cancer death [8, 9]. Even with high rates, the incidence of CRC is increasing worldwide, with the highest prevalence coming from Western countries compared to developing countries [9]. This trend observed in these societies can be attributed to rising obesity rates, dietary and lifestyle factors [10]. It is clear, however, that IBD-related RCC may represent a higher-risk subtype with a more serious prognosis that deserves more attention and care. This is because IBD patients are two to six times more at risk of developing CRC when compared to healthy individuals. Moreover, IBD-associated CRC is highly aggressive, typically presents at a younger age compared to sporadic CRC, and has a poor prognosis, with a five-year survival rate of only 50% [11]. Additionally, compared to sporadic CRC patients, those with IBD-related CRC exhibit poorer differentiation, mucinous or signet ring cell carcinoma, increased synchronous tumors, a higher incidence of right-sided colorectal cancer, a predominance of male patients, and a lower rate of R0 resection [12].

Fungi represent only 0.01–0.1% of the gut microbiome [13], an estimate that is considered to be underestimated due to the difficulties faced in cataloguing and analysing fungi in genomic databases [14]. Furthermore, the influence of these microorganisms on the intestinal ecosystem is disproportionately significant in relation to their numerical abundance [15]. Given the importance of fungi in intestinal inflammation and gastrointestinal diseases, it is essential that more attention and research is devoted to this aspect. This article provides a comprehensive overview of how intestinal fungi colonise and interact within the intestinal ecosystem, particularly their connections to intestinal inflammation and diseases such as Inflammatory Bowel Disease (IBD) and Colorectal Cancer (CRC). Our exploration focuses on the role of fungi in the initiation and progression of intestinal inflammation, aiming to deepen our understanding of disease mechanisms in conditions such as IBD and its associated CRC. This research approach may reveal new strategies for the prevention and treatment of gastrointestinal disorders, including IBD and CRC.

Characteristics of the normal gut fungal community structure

Fungal colonisation and the formation of the human intestinal microbiome begins from birth, from vertical transmission from mother to baby and/or horizontal transmission from the environment [16, 17], making a significant contribution to human growth, development, and health. However, the abundance and diversity of intestinal fungi are considerably lower than those of bacteria. In fact, the human gut contains around 1,520 bacterial species [18], while the exact number of intestinal fungal species remains unclear. Among the main components of this community are the yeasts (such as *Malassezia* and *Candida*) and other fungi (such as *Aspergillus*, etc.) [19–21].

In terms of phyla, the most abundant in the human gut are Ascomycota and Basidiomycota, distributed in inverse proportions in most samples [3]. Among the genera, Saccharomyces is the most prevalent, followed by *Candida* and *Cladosporium*, respectively. On the other hand, according to Nash et al. [19], yeasts constitute the predominant group among fungal species in the intestinal microbiota of healthy individuals. The data indicate that the genus *Saccharomyces* exhibits the highest relative abundance in the intestinal fungal community, followed by *Malassezia* and *Candida*. Among the 15 most abundant fungal genera, eight are yeasts: *Saccharomyces*, *Malassezia*, *Candida*, *Cyberlindnera*, *Pichia*, *Debaryomyces*, *Galactomyces* and *Clavispora*. However, the composition of the intestinal fungal community is remarkably specific between different individuals, with significant variations observed over time and between different individuals [19].

The intestinal fungal microbiota is significantly influenced by the host's diet [3, 22], and there is a correlation between the types of food consumed and the presence of certain species of fungi [20]. In this sense, the intake of dairy products, for example, has already been positively associated with the abundance of yeasts and *Meyerozyma*

and negatively associated with the abundance of *Candida*. Carbohydrate intake, on the other hand, has been shown to be positively associated with *Candida* abundance [19]. This relationship between intestinal fungal composition and diet suggests that modifying the dietary habits of individuals shows potential for the prevention and treatment of fungal-related diseases, specifically gastrointestinal disorders [23].

Changes in the fungal community structure under gut inflammation conditions

The rising incidence of IBD in recent years has garnered increasing attention from researchers. Gut inflammation is a critical mechanism in the onset and progression of IBD, and components of the gut microbiome, including bacteria and fungi, play roles in this context. The alteration of the gut microbiome can disrupt the gut microecological balance, leading to dysfunction of the intestinal mucosal barrier and abnormal activation of the immune system, thereby triggering inflammatory responses [24, 25]. Although the bacterial components in the guts of IBD patients are now well understood, a global imbalance in bacterial structure, characterized by reduced biodiversity, has been demonstrated. Some studies have shown a decrease in certain *Firmicutes* such as *Faecalibacterium prausnitzii*, *Lactobacillus*, *Roseburia*, and *Ruminococcaceae*, while others have reported an increase in *Firmicutes* such as *Ruminococcus gnavus*, *Flavonifractor plautii*, *Clostridium symbiosum*, and *Clostridium scindens* in IBD. Additionally, an increase in the abundance of *Proteobacteria*, including *Escherichia coli* and other *Enterobacteriaceae*, is consistently observed [26–31]. However, changes in the composition of other related microbiota in the inflammatory gut environment of IBD patients, particularly fungi, have only recently been recognized as significant, leading to a paucity of research findings [32].

The composition of gut fungi is associated with the development of IBD [6, 33]. Studies indicate that, compared to healthy individuals, the proportions of the main fungal components in the guts of individuals with IBD undergo significant changes. In IBD, an increase in *Basidiomycota* and a corresponding decrease in *Ascomycota* are particularly pronounced during active disease phases [6]. The *Basidiomycota*/*Ascomycota* ratio is highest during the active phase of IBD compared to healthy states (HS) and periods of remission [6]. At the species level, the proportions of major gut fungi such as *Candida* and yeasts are altered in individuals with IBD. The abundance of yeasts such as *C. albicans*, *Candida tropicalis*, *Clavispora lusitaniae*, *Cyberlindnera jadinii*, and *Kluyveromyces marxianus* decreases, while that of *Saccharomyces cerevisiae* increases, especially during periods of remission, both in proportion and absolute numbers [6, 34, 35]. Notably, studies have shown an overexpression of *C. albicans* within the mucosa of UC (Ulcerative Colitis) patients [34]. It is driven by several key factors. Gut inflammation creates a favorable environment that promotes *C. albicans* proliferation, particularly when antifungal immunity is impaired, a common issue in IBD. Additionally, corticosteroid treatments, often used to manage UC, further weaken colonization resistance, allowing *C. albicans* to flourish. Once established, certain strains of C. albicans can elicit robust Th17 immune responses and contribute to inflammation through IL-1β-dependent mechanisms. In contrast, less abundant fungal genera such as *Debaromyces*, *Galactomyces*, and *Malassezia spp.* do not exhibit changes during exacerbations of IBD [34]. This stability is likely due to their limited interaction with the host immune system and inability to exploit the inflamed environment for growth. Therefore, it may be the specific pathogenic properties of fungi like *C. albicans*, rather than overall fungal diversity, that play a critical role in disease progression [34].

Fungi are also closely associated with CRC. Liu et al. [36] observed significant changes in the abundance of 108 fungal species in CRC patients, with the majority exhibiting increases. Research has demonstrated that the integration of fungal and bacterial species into diagnostic models for CRC enhances diagnostic effectiveness. The study determined a combination of 16 biomarkers, including 4 fungal species (*Talaromyces islandicus*, *Aspergillus rambellii*, *Sistotremastrum suecicum*, and *Aspergillus niger*), capable of diagnosing CRC non-invasively and reliably. Furthermore, research by Coker et al. [37] revealed that the fecal microbiota of CRC patients was enriched with *Malasseziomycetes*, while *Saccharomycetes* (including *Lypomyces starkeyi* and *Saccharomyces cerevisiae*) and Pneumocystidomycetes experienced significant reductions. This study also demonstrated that the *Basidiomycota*/*Ascomycota* ratio increased with disease progression in CRC patients relative to healthy individuals, indicating changes in the intestinal fungal community structure. Notably, according to research by Sokol et al. [6], an increased Basidiomycota/Ascomycota ratio is also observed in IBD. The similarities in changes to the gut fungal community in both CRC and IBD suggest that fungi might play a key role in the development of these conditions. Since intestinal inflammation is a critical factor in the progression of CRC and IBD, it's thought that fungi could significantly contribute to this inflammation, thereby influencing both diseases. The relevant details will be explained in the next part.

The changes in fungi within the inflammatory environment may be influenced by numerous factors. Notably, the interaction between bacteria and fungi is significant. Sokol et al. [6] found that the unique intestinal inflammatory environment in IBD could inhibit bacterial growth while promoting fungal growth. Additionally, fungal

alterations can be associated with receptors such as Dectin-1 and Card9, which play crucial roles in the body's immune response to intestinal fungi. A deficiency in either can lead to a significant increase in fungi, making the host more susceptible to colitis [6].

The body's inflammatory response is also an important contributing factor. Zelante et al. [38] showed that activation of the IL-23/Th17 pathway could weaken the resistance of neutrophils and macrophages to fungi while promoting the production of inflammatory factors, which in turn promotes the growth of fungi in the body. An excessive Th17 immune response can result in extensive infiltration of inflammatory cells at the infection site, releasing numerous proteases, compromising tissue structure, and thereby creating a more favorable environment for fungal growth. However, in the absence of IFN-γ, IL-23 can exert an antifungal effect. Research by Doron et al. [39] demonstrated that in the normal intestinal immune state, macrophage subgroups such as CX3CR1+monocytes and CD103+dendritic cells can induce the production of sIgA antibodies against *C. albicans*, thus inhibiting the formation of *C. albicans* hyphae. In contrast, an inflammatory intestinal state (such as Crohn's disease) disrupts this regulatory function, leading to an increase in the formation of *C. albicans* hyphal form, thereby facilitating its colonization and infection.

Other studies have demonstrated that the IL-1 family of cytokines plays a crucial regulatory role in fungal infections, with some exhibiting inhibitory effects and others exerting promoting effects. IL-1α/β, IL-18, and IL-36 are induced by various fungi (including *Mucor* and *Candida*) and exert significant antifungal effects, inhibiting the colonization and infection of fungi within the body. IL-1α/β promotes the recruitment of neutrophils, enhances the killing ability of macrophages and neutrophils, and drives the immune responses of Th1 and Th17 [40–44]. IL-18 is known to promote Th1 immune responses and the production of IFN-γ [45]. IL-36 is capable of promoting the expression of IL-23, thereby indirectly facilitating the Th17 response [44, 46, 47]. Meanwhile, certain family members, such as IL-1Ra, IL-18BP, and IL-36Ra, exhibit inhibitory effects and are able to control the pro-inflammatory effects of the IL-1 family, thereby reducing resistance to fungi [45]. Numerous studies have demonstrated the inhibitory effects of IL-17 on fungi. IL-17 stimulates the production of antimicrobial peptides by epithelial cells and fibroblasts, thus directly killing fungi or inhibiting their growth, and can additionally recruit and activate granulocytes to clear fungi through chemotactic factors [48, 49]. However, concurrently, the IL-17 response also enhances inflammation, thereby becoming a risk factor for inflammatory diseases [50, 51].

TNF is effective in inhibiting the over-proliferation of fungi within the host. Research conducted by Roilides et al. [52] demonstrated that TNF-α significantly increases the production of superoxide in human polymorphonuclear leukocytes (PMNs) stimulated by *Aspergillus fumigatus* hyphae, thus enhancing their fungicidal activity against this fungus. Reduction of TNF-α may compromise host defenses against fungal infections, necessitating cautious application of anti-TNF-α therapies. Rocha et al. [53] further discovered that TNF can directly interact with *C. albicans* through its lectin-like domain, inhibiting the formation of *C. albicans* biofilms, yet it is ineffective against pre-formed biofilms.

Although research into the impact of fungal changes on the intestinal inflammatory state remains incomplete, the results of various studies have consistently shown a close relationship between fungi and intestinal inflammation. This indicates that fungi may play a significant role in IBD, IBD-associated CRC, and other intestinal inflammation-related diseases.

The role of fungi in modulating intestinal inflammation

The development of intestinal inflammation in humans is closely linked with the presence of fungi, particularly in conditions such as inflammatory bowel disease (IBD) [54, 55]. Besides the fact that intestinal inflammation leads to changes in the gut mycobiome, fungi actively regulate intestinal inflammation through various mechanisms. Specifically, the impact of fungi on host intestinal inflammation can be classified into several categories: Direct action on the gut barrier, interactions with other gut microbes and Immune regulation.

Direct action of fungal bodies or components and products on the gut barrier

Certain fungi, especially pathogenic ones like Candida albicans, can downregulate tight junction proteins such as ZO-1 and Occludin. This disruption weakens connections between intestinal epithelial cells and increases gut permeability, leading to inflammation and infection. Additionally, non-pathogenic fungi, like those containing β-glucans, also affect the intestinal barrier, which is further explained below.

Fungi such as *C. albicans* can directly damage the intestinal barrier, thus increasing the risk of intestinal inflammation. The study by Böhringer and colleagues [56] found that *C. albicans* downregulate the expression of Tight junction proteins. This disruption weakens the connections between epithelial cells and increases the permeability of the gut barrier. As a result, host infection occurs, ultimately leading to damage of the host's intestinal epithelial cells, a cytotoxic effect. Infection leads to the upregulation of MAPK, TNF, and NF-κB pathways, and activates the downstream target genes of NF-κB, specifically GDF15. The NF-κB pathway plays a crucial

role in protecting intestinal epithelial cells; specifically inhibiting NF-κB can increase the cytotoxic effects of infection. It is worth noting that the impairment of barrier function and the cytotoxic effects represent two independent processes. The NF-κB pathway is involved in the protection of epithelial cells yet does not govern barrier integrity. Mao and colleagues [57] also discovered that *C. albicans* SC5314 can inhibit the expression of the NLRP3 and NLRP6 inflammasomes. This inhibition leads to a notable decrease in the expression of proteins related to the inflammasome signaling pathway, such as NLRP3, NLRP6, ASC, BD-2, BD-3, occludin, and ZO-1. As a result, the intestinal barrier is impaired. Furthermore, these effects are independent of the metabolic activity of *C. albicans* SC5314; even after heat inactivation, the organism continues to exert these effects.

Additionally, certain fungi and their specific components, particularly non-pathogenic fungi found in the resident microbiota, such as yeasts, can enhance intestinal barrier function. Their active compounds, including β-glucans and mannans from fungal cell walls, upregulate the expression of tight junction proteins like Claudin-1 and ZO-1. This helps reduce the risk of inflammation. While not all of these fungi are resident microbiota, some have been shown in animal models to protect the gut barrier. Research led by Duan [58] has shown that components such as Ergosterol peroxide from *Cryptoporus volvatus* elevate the expression of Claudin-1 and ZO-1 in the small intestine, thus preserving gut barrier integrity. Zhang and his team [59] d discovered that β-glucans in fungi inhibit the TLR4-NF-κB signaling pathway, thereby enhancing the expression of ZO-1, Occludin, and Claudin-1 in the gut barrier. This strengthening of the intestinal barrier function may contribute to the prevention of Necrotizing Enterocolitis (NEC). Additional research has indicated that mannans in the fungal cell wall decrease gut barrier permeability in mice whose gut bacteria has been eradicated by antibiotics, effectively preserving the integrity of the gut barrier and diminishing the risk of intestinal inflammation [60] (See Fig. 1).

Fungal interactions with other gut microbes

In the intestinal microbiota, fungi are capable of causing or inhibiting inflammation. *C. albicans*, for example, after inducing dysbiosis of mucosal bacteria, promotes invasive infection [61]. Chemotherapy using 5-fluorouracil weakens the host's immune defenses, making mice more susceptible to *C. albicans* infection. This infection not only induces dysbiosis but also leads to significant alterations in the intestinal bacterial community, reducing bacterial diversity and increasing *Enterococcus*. *Enterococcus*, in turn, produces extracellular proteases such as

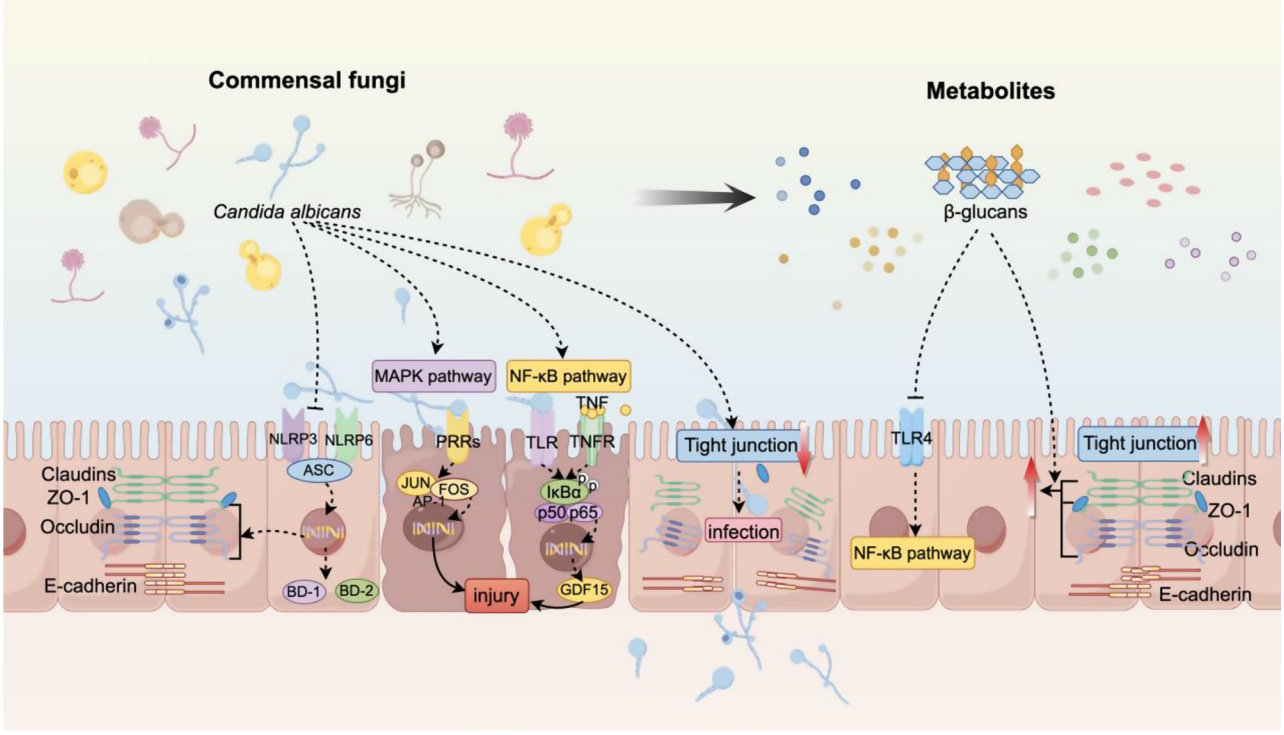

Fig.1 Direct action of fungal bodies or metabolites on the gut barrier. Fungi can directly affect the intestinal epithelial barrier through their mycelium or metabolites, exhibiting both protective and destructive effects. Their actions can involve interacting with intestinal epithelial cell receptors, which can activate or inhibit corresponding signaling pathways. This interaction may directly cause cell damage or alter the expression of tight junction proteins between cells, thereby affecting the risk of intestinal inflammation

gelatinase (GelE). These proteases degrade intestinal epithelial E-cadherin, disrupting the gut barrier. This disruption facilitates the further invasion of C. albicans, thereby exacerbating inflammation.

Certain commensal fungi in the intestinal microbiota, such as those that produce β-glucans, modulate microbial components, including Lactobacilli and Bifidobacteria. This process promotes gut health and reduces the risk of inflammation. β-glucans are derived from yeast (Saccharomyces cerevisiae) and mushrooms (e.g., shiitake, reishi). They promote the growth of probiotics such as Lactobacilli and Bifidobacteria in the gut, which helps reduce intestinal inflammation. Research has demonstrated that pretreatment with β-glucans from fungi significantly affects the gut microbiota in mice suffering from NEC. Specifically, it increases the levels of *Actinobacteria*, *Clostridium butyricum*, *Lactobacillus johnsonii*, *Lactobacillus murinus*, and *Lachnospiraceae bacterium* mt14. Concurrently, it reduces the proportion of *Klebsiella oxytoca e Klebsiella* [59]. Numerous investigations have established that β-glucans promote the growth of *Lactobacilli* and *Bifidobacteria* in the gut [62–64]. However, Wang and colleagues found that β-1,3-glucans produced by C. albicans can enhance the antibiotic resistance of Staphylococcus aureus within a complex microbial community. This interaction exacerbates the severity of Staphylococcus aureus infections in the host and impairs gut health [65]. Consequently, the specific roles and mechanisms of fungal β-glucans in the gut necessitate further investigation and exploration. While the current research is primarily based on studies conducted with mice, further research is required to determine whether these findings are directly applicable to humans (See Fig. 2).

Immune regulation

The effects of fungi on intestinal inflammation are mainly achieved by regulating the host immune system.

Some fungi manipulate the host immune system in a way that heightens the likelihood or severity of the body's inflammatory response. Jain and colleagues [66] discovered that *Debaryomyces hansenii*, a foodborne fungus, preferentially colonizes and multiplies within the inflamed mucosal tissues of patients with Crohn's Disease (CD). This colonization activates the Type I interferon signaling pathway in macrophages and enhances the expression of CCL5. This process inhibits normal tissue regeneration and repair at the site of intestinal mucosal

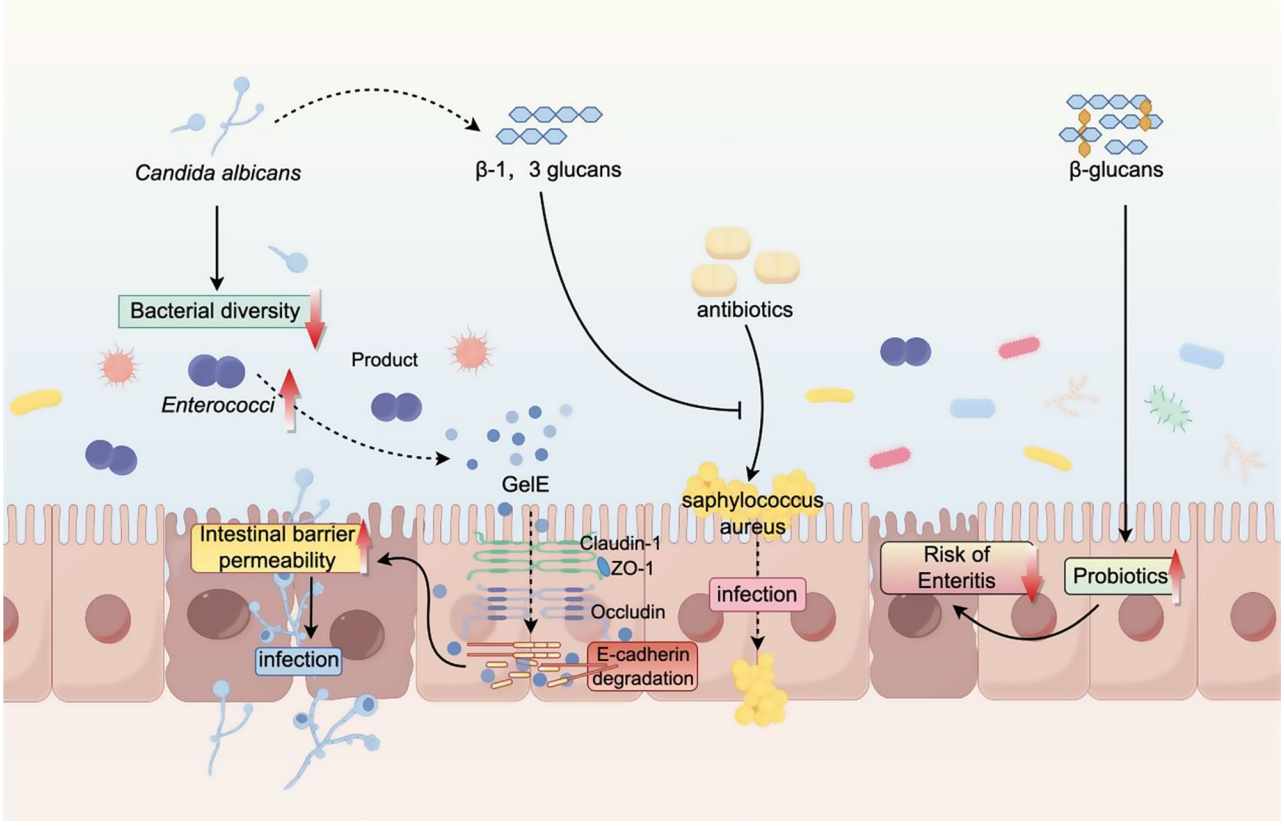

Fig.2 Fungal interaction with other gut microbiota. Fungi can also affect the structure and diversity of the gut microbiota, thereby indirectly influencing the tight junctions of intestinal epithelial cells and the integrity of the intestinal barrier. These effects are similarly dual-faceted, ultimately resulting in either a reduced risk of intestinal inflammation or various scenarios in which gut microbial infections result in inflammation

injury, thus exacerbating the symptoms of intestinal inflammation. The Type I interferon pathway, along with CCL5 and its receptor CCR5, are crucial in this process. Li et al. [34] discovered that *Candida* secretes candalysin, which induces Th-17 differentiation via the IL-1β signaling pathway This mechanism aggravates intestinal inflammation in patients with Ulcerative Colitis (UC). Bacher and associates [51] found that in patients with Crohn's Disease, there is an enhanced Th17 immune response against *Candida*. Additionally, Th17 cells originating from the gut migrate to peripheral tissues, where they are reactivated by heterologous antigens, such as respiratory fungi, contributing to the inflammatory responses in these locations. During acute exacerbations of allergic bronchopulmonary aspergillosis, Th17 cells specific to *A. fumigatus* are selectively activated and expanded due to cross-reactivity with C. albicans. This suggests that *Candida* is crucial in regulating systemic Th17 immune responses and potentially a key microbial agent in the etiology of Crohn's Disease, an intestinal inflammatory condition. Zhu and colleagues [67] observed that in Dectin-3 knockout mice (Dectin-$3^{-/-}$ mice), the *Candida* burden increased, which elevated glycolysis in macrophages and enhanced IL-7 secretion. This induction leads RORγt+innate lymphoid cells (group 3 ILC3s) to produce IL-22 via the aryl hydrocarbon receptor and STAT3, which promotes an intestinal inflammatory response and may contribute to the development of colon cancer. β-1,2-mannosides on the fungal cell wall bind to Galectin-3 in macrophages, enhancing the TLR2- and TLR4-mediated immune responses in primary splenocytes and THP-1 cells [68–70].

However, the regulation of the host immune system by specific fungi aids in the body's resistance to inflammation. Kim and colleagues [71] found that the fungal product ergosterol can inhibit the activation of NF-κB p65 in the colonic tissue of mice with DSS-induced ulcerative colitis, and significantly alleviate weight loss, colon shortening, and the disease activity index in these mice. In another study, the investigation focused on the CAE3DU3 strain of *Candida*, which lacks the crucial gene for ergosterol biosynthesis, ERG3, and revealed that the absence of the ERG3 gene reduced its colonization ability in the mouse gut and its ability to transfer from the gut to the liver and kidney. Additionally, it lowered the levels of pro-inflammatory chemokines in the infected mouse gut and serum, as well as the degree of intestinal tissue necrosis, significantly reducing the pathogenicity of *Candida* [72]. The research discussed above indicates that the fungal product ergosterol plays a critical role in intestinal inflammatory responses and could potentially serve as a preventive and therapeutic agent for intestinal inflammatory diseases. However, given its significant role in fungal pathogenicity, the efficacy and safety of ergosterol as a therapeutic agent still require extensive validation.

Furthermore, yeast β-glucan can reduce the expression of TLR4, NF-κB, IL-1β, IL-6, and TNF-α in the intestines of mice with NEC. It also increases the expression of intestinal IL-10 [59]. Additionally, yeast β-glucan supplementation may help regulate exercise-induced immune suppression and improve inflammatory responses. Supplementing yeast β-glucan has been shown to downregulate pro-inflammatory cytokines, such as IL-8, MCP-1, MIP-1β, and TNF-α, in the blood 72 h after exercise [73]. Additionally, its supplementation may help regulate exercise-induced immune suppression and improve inflammatory responses; supplementing yeast β-glucan can downregulate pro-inflammatory cytokines IL-8, MCP-1, MIP-1β, and TNF-α levels in the blood 72 h after exercise [58]. Briard et al. [74] found that galactosaminogalactan (GAG) from the cell wall of *A. fumigatus* specifically activates the NLRP3 inflammasome, enhancing the host's defense against *A. fumigatus*. The mechanism involves the positively charged galactosamine in GAG interacting electrostatically with negatively charged amino acid residues in peptide chains, inhibiting the elongation process of protein synthesis, leading to endoplasmic reticulum stress and activating the NLRP3 inflammasome. GAG can also alleviate experimental colitis symptoms through an IL-18 related mechanism; in IL-18 knockout mice, GAG treatment could not alleviate colitis symptoms.

Other studies have demonstrated that, in the absence of commensal bacteria, commensal fungi can functionally substitute for intestinal bacteria and play an immunomodulatory role through mannans. Research conducted by Jiang and colleagues [60] revealed that after eradication of intestinal bacteria by antibiotics, colonization with either *C. albicans* or *Saccharomyces cerevisiae* could protect mucosal tissues and modulate the reactivity of circulating immune cells. This modulation reduces the host's susceptibility to DSS, thereby decreasing the likelihood of colitis. This protective effect is primarily attributed to mannans. In addition to maintaining the integrity of the intestinal mechanical barrier, mannans in the fungal cell wall activate intestinal and immune cells, such as macrophages via TLR4 and Dectin-1, which stimulate the NF-κB pathway. This activation through various pattern recognition receptors, including CD206, TLR2, TLR4, and Dectin-1, promotes the production of cytokines and effector molecules, thereby regulating the intestinal immune status. Moreover, in mice deficient in Dectin-1, intestinal colonization with *C. albicans* could still ameliorate the heightened colitis sensitivity caused by antibiotic treatment, though this improvement vanished in the absence of TLR4. This observation suggests that in the mouse model with antibiotic-disrupted gut microbiota, the protective effect of mannans on the intestine does

not rely on Dectin-1, but rather, TLR4 is essential. Interestingly, this contrasts with the observations reported by Iliev and colleagues [75], who noted that the absence of Dectin-1 altered immunity against gut commensal fungi, resulting in a marked increase in the proliferation of fungal species such as *Candida* and *Trichosporon*, and heightened susceptibility of Dectin-1-deficient mice to DSS-induced colitis. Dectin-1, an immune receptor, primarily functions to recognize and bind β-glucan, a polysaccharide primarily found in fungal cell walls, thereby facilitating a response to fungal infections with negligible recognition of bacteria. Therefore, the discrepancy between the conclusions of these two studies may stem from additional stimulation by commensal bacteria in the gut or variations in the composition of such bacteria in Dectin-1-deficient mice [76]. This implies that research into the role of fungi in intestinal diseases should not overlook the interactions between other microorganisms, such as bacteria, and fungi (See Fig. 3).

Interactions between fungal and bacterial microbiota in intestinal diseases

Intestinal bacteria and fungi have complex interactions that significantly influence the stability of the intestine. Dysbiosis in the fungal community, for example, can impact the human body, possibly through direct fungal actions on the host or indirectly by altering the abundance of specific bacterial species [5]. Furthermore, the use of antifungal medications not only leads to fungal dysbiosis but also results in significant changes in the composition of bacterial microbiota [5], further underscoring the close and inseparable link between bacteria and fungi. In intestinal diseases such as IBD and CRC, this intimate connection persists and plays a critical role.

Studies indicate that fungi and bacteria are interrelated in terms of abundance in both IBD and CRC. Data suggest that in IBD patients, the abundance of *Saccharomyces* is positively correlated with certain bacteria whose levels are diminished in IBD, such as *Bifidobacterium*, *Roseburia*, and *Ruminococcus*, while the abundance of unidentified *Malasseziales* exhibits a negative correlation with these bacteria [6]. Furthermore, the correlation between fungi and bacteria varies between CD and UC. Sokol et al. [6] investigated the correlation between fungal and bacterial microbiota at the genus level based on the disease phenotype. Subsequently, they established a correlation network for both groups. Their findings revealed that this correlation was most pronounced in UC patients, followed by HS (Healthy Subjects), and was somewhat less pronounced in CD, albeit similar to that observed in HS. The distinct fungal-bacterial correlations in CD and UC indicate that the fungal microbiota may play varied roles in the pathogenesis of CD and UC, and further investigation is required to elucidate the specific mechanisms.

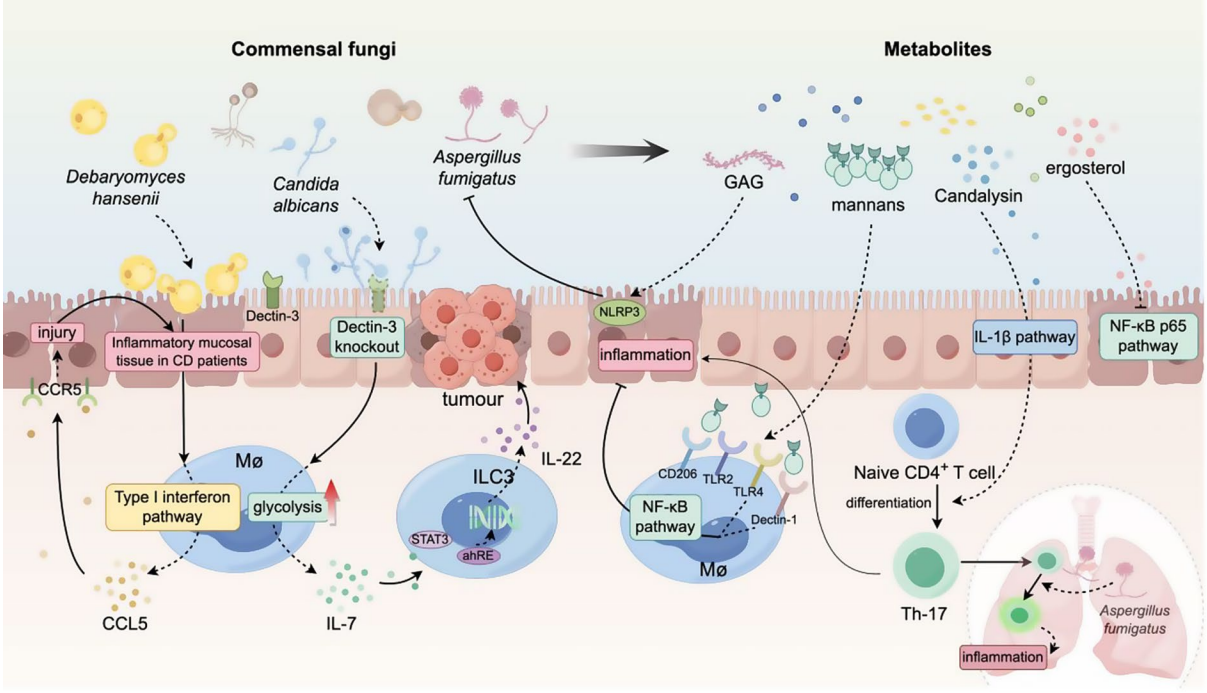

Fig.3 Immunoregulatory effects of fungi. Fungi and their metabolites can also affect local or systemic immune systems by influencing the expression of immune pathways, the metabolism of immune cells, and the production of cytokines, thereby impacting the occurrence of inflammation and the risk of related intestinal diseases

In CRC, the research team led by Liu [36] performed a co-abundance analysis to construct an ecological network of differential species. The results demonstrated that the microbial ecological network in colorectal cancer patients (272 species, 2338 associations) was more complex than that observed in the normal control group (236 species, 1804 associations). The ecological network comprised not only a large number of internal associations between bacteria and fungi but also 706 interactions involving both bacteria and fungi. For instance, the fungal biomarker *Talaromyces islandicus* showed positive correlations with various gut bacteria, including *Clostridium saccharobutylicum* (r=0.76), *Hungateiclostridium clariflavum* (r=0.64), *Clostridium baratii* (r=0.38), and *Faecalibaculum rodentium* (r=0.35). Furthermore, the study suggested that butyrate might play a role in the tumor microenvironment, and the interaction between bacteria and fungi could be involved in regulating this metabolic process. The activation of the butyrate metabolic pathway was observed in colorectal cancer patients with an upregulation of key genes bdhA and bdhB, while the abundance of butyrate-producing gut bacteria decreased. A positive correlation was observed between the butyrate-producing bacterium *Clostridium saccharobutylicum* and the fungus *Talaromyces islandicus*. Chitosan oligosaccharide (COS), a low molecular weight derivative of chitosan, exhibits multiple biological activities, including antibacterial, antioxidant, anti-inflammatory, anti-tumor, and immune-stimulating effects [77]. Research has demonstrated that COS can regulate gut bacteria and fungi, mitigate inflammatory responses, and effectively prevent the occurrence of colitis-associated rectal cancer [78]. Evidence indicated that it resulted in a decrease in the prevalence of *Escherichia-Shigella*, *Enterococcus*, and *Turicibacter*. In addition, it prompted an increase in the quantities of *Akkermansia*, butyrate-producing bacteria, and *Cladosporium* fungal genus [79]. The collective findings suggest that in exploring the regulatory roles and mechanisms of fungi in intestinal inflammation, one should consider the interaction between bacteria and fungi.

Based on extensive prior research, bacteria have been shown to significantly impact IBD and CRC [80–89]. The interplay between fungi and bacteria further indicates that fungi also play a significant regulatory role, meriting further investigation by researchers. Moreover, alterations in the composition of fungi and bacteria can serve as targets for the onset and progression of intestinal diseases, facilitating more precise diagnosis through analysis of the microbial community. Continued investigation of the interactions between fungi and bacteria could also achieve the goal of preventing and treating intestinal diseases through the regulation of the gut microbiome.

Fungal-derived therapeutics in treating intestinal diseases

IBD, CRC, and other intestinal diseases annually impact the lives of many, reducing their quality of life and posing life-threatening risks, thereby underscoring the urgency of developing effective prevention and treatment methods. Historically, antibiotics have been commonly employed in managing intestinal inflammatory diseases, yet their therapeutic efficacy has proven to be limited [90, 91]. Recently, microbiota research has emerged as a highly promising direction for treatment. Currently, numerous bacteria-based fecal microbiota transplants have been deployed in IBD treatment, demonstrating significant therapeutic benefits [92–94]. Fecal microbiota transplantation with relevance to CRC has also recently captured researchers' attention [95–98]. In recent years, the exploration of strategies such as modulating intestinal mycobiota through dietary therapy and employing fungal probiotics to alleviate intestinal inflammation has gradually caught the attention of researchers. These methods are increasingly seen as viable options for the prevention and treatment of diseases like IBD and CRC.

Dietary therapy

As the importance of fungi for gut health is increasingly acknowledged, the role of dietary interventions in modulating gut mycobiota and managing related diseases is attracting increasing attention from the scientific community.

Gunsalus et al. [23] demonstrated that dietary regulation can diminish intestinal colonization by opportunistic pathogenic fungi, which in turn alleviates intestinal inflammation. Compared with diets containing butter or soybean oil, a coconut oil-enriched diet can reduce the colonization of *C. albicans* and alter the metabolic program of the colonizing *C. albicans*. Moreover, even if the diet includes butter, the addition of coconut oil, which is high in medium-chain fatty acids (mcFA), still reduces the colonization of *C. albicans* in mice. The study results indicate that the metabolic program of *C. albicans* varies according to the supply of long-chain fatty acids in the gastrointestinal tract. Foods such as butter and soybean oil, rich in long-chain fatty acids, enhance the expression of *C. albicans* pathogenicity-related factors, including stress resistance, cell wall structure, and virulence factors, thereby promoting the colonization of *C. albicans*. Coconut oil, predominantly consisting of medium-chain fatty acids, exhibits antimicrobial properties that may help reduce the colonization of *C. albicans* in the gastrointestinal tract of the fed mice. These findings suggest that in patients with intestinal inflammatory-related diseases such as IBD, long-term or intermittent dietary interventions utilizing foods rich in medium-chain fatty acids, including coconut oil, palm oil, and goat's milk, could be

explored. These dietary interventions could adjust the composition of the intestinal mycobiota and other microorganisms, thereby slowing down intestinal inflammation and achieving therapeutic effects. These types of food can also be incorporated more frequently into the daily diet. This change aims to prevent the occurrence of intestinal inflammation and thus aids in preventing certain intestinal diseases.

Probiotic fungi

Natural strains

In recent years, interest in the use of fungi as probiotics has notably increased among researchers. Yeasts have consistently been a primary focus in this domain. For probiotics, antibiotic resistance is a significant advantage that enhances their survival in the host's gut and promotes symbiotic stability [99]. Although yeasts are unaffected by antibiotics, a favorable trait, this characteristic also carries associated risks, primarily the potential transfer of resistance genes to pathogenic bacteria. Studies have indicated that gene transfer between yeasts and bacteria is rare, thus mitigating concerns regarding the transfer of resistance genes to pathogenic bacteria; consequently, using yeast as a probiotic is considered safe in this context [100]. *S. boulardii* is a widely utilized probiotic yeast currently used for the treatment of gastrointestinal diseases [101]. It plays a role in the formation of intestinal physiological protective barriers, in the regulation of the gastrointestinal microbiome, in immunomodulation, metabolic regulation, and in competition with pathogens, demonstrating good probiotic characteristics [102, 103]. It interacts with epithelial cells, dendritic cells, monocytes, macrophages, and lymphocytes, and regulates the metabolites produced by the intestinal microbiome, thereby exerting both immunoregulatory and anti-inflammatory functions [102]. Therefore, *S. boulardii* is frequently used in the treatment of inflammatory bowel diseases [104]. In addition to *S. boulardii*, the most widely recognized yeast used as a probiotic, there are many other fungi with probiotic potential, including *S. cerevesiae*, *Pichia guilliermondii*, *C. orthopsilosis*, *C. tropicalis*, *M. caribacca*, *D. hansenii*, *K. marxianus*, *K. lactis*, and others [105–110].

Moreover, recent studies suggest that *C. metapsilosis* M2006B may be an emerging intestinal probiotic fungus for preventing and treating IBD. Huo and his team's research [111] demonstrated that colonization of *C. metapsilosis* M2006B could alleviate colitis induced by DSS, TNBS, or IL-10 deficiency by activating the farnesoid X receptor (FXR). Additionally, it was found that *C. metapsilosis* M2006B could alleviate DSS-induced colitis in germ-free mice or mice treated with antibiotics, indicating that its effect is independent of the intestinal microbiota. The research eventually revealed two acyclic sesquiterpenoids (F4 and F5) as the main active metabolites of the fungus, which act as FXR agonists to alleviate colitis.

Numerous studies have demonstrated that using fungal probiotics for regulating the intestinal microbiome and alleviating intestinal inflammation can potentially prevent and treat intestinal diseases, representing an emerging field with significant potential that warrants further exploration by researchers.

Engineered strains: self-tunable engineered yeast probiotics

Research has also concentrated on fungal-related bioengineering therapies, introducing new yeast-based technologies that can be used to suppress intestinal inflammation. Scott et al. [112] used directed evolution and synthetic biology approaches to develop an engineered brewer's yeast probiotic. They employed a multi-round iterative selection process, utilizing flow cytometry, to isolate human *P2Y2* receptors that exhibited the desired enhancement in EATP sensitivity, thereby achieving a targeted mutation. This engineered yeast is capable of sensing the concentration of extracellular ATP (EATP) in the lumen through the high-affinity extracellular ATP receptor *P2Y2* and responds by releasing the EATP-degrading enzyme APY-Rase, thus degrading key molecules involved in the body's inflammation and suppressing intestinal inflammation in mouse models. The research team also conducted experimental validation using healthy mice and mice with TNBS-induced colitis. The engineered yeast probiotic was applied to both groups of mice. Subsequently, fecal samples were collected from each group. These samples underwent 16 S rRNA sequencing and β-diversity analysis, which helped detect differences in the microbiome composition among the samples. The results confirmed the probiotic's suppressive effect on experimental intestinal inflammation in mice.

Sun and colleagues [113] addressed the current absence of specific treatments for ulcerative colitis by developing a high-lactic acid-producing engineered yeast strain, *Saccharomyces cerevisiae* SyBE 39. The research team enhanced lactic acid production by over fivefold relative to the wild-type yeast through gene knockout and the introduction of exogenous genes. The team employed this engineered yeast in a DSS-induced mouse model of ulcerative colitis for therapeutic experiments and observed that SyBE 39 markedly alleviated clinical symptoms in mice, ameliorated tissue pathology, repaired the intestinal barrier, and suppressed the expression of proinflammatory cytokines. Additional mechanistic studies demonstrated three key functions of SyBE 39. First, it promoted the conversion of macrophages to the M2 phenotype, which is associated with anti-inflammatory effects. Second, it inhibited the activation of the NLRP3

inflammasome by facilitating lactate uptake through monocarboxylate transporters, thereby reducing inflammatory cell death in intestinal macrophages. Third, SyBE 39 can also modulate the intestinal microbiome, augment probiotic levels, and enhance the production of short-chain fatty acids. These diverse mechanisms highlight the potential of SyBE 39 as a multifunctional therapeutic agent in treating inflammatory conditions of the intestine. Self-tunable engineered fungal probiotics offer novel therapeutic research avenues for numerous intestinal inflammation-related diseases.

Fecal microbiota transplantation

Fecal Microbiota Transplantation (FMT) represents an emerging therapeutic approach that involves transplanting functional microbial communities from the feces of healthy individuals into the intestines of patients to cultivate a new intestinal microbiota, thereby exerting therapeutic effects on various diseases. Several studies have demonstrated the beneficial effects of FMT on IBD [93, 94]. Zhang and colleagues' study [94] demonstrated that FMT can regulate intestinal microbiota, increase the production of short-chain fatty acids, inhibit the activation of the NF-κB pathway, and thus exert a significant anti-inflammatory and antioxidant effect, significantly improving the clinical symptoms of IBD mice, such as weight loss, elevated DAI scores, and reducing the pathological damage to the intestinal tissue. The study revealed that FMT could enhance the relative abundance of beneficial intestinal bacteria such as *Lactobacillus* and *Odoribacter*, and suppress pathogens such as *Helicobacter* and *Clostridium*, thereby modulating the composition of the intestinal microbiota and restoring the balance of the microbial community. FMT was found to increase the levels of short-chain fatty acids produced by intestinal microbiota, such as acetic acid, propionic acid, and butyric acid. Short-chain fatty acids not only provide energy for intestinal epithelial cells but also improve the function of the intestinal mucosal barrier. In addition, short-chain fatty acids activate the Nrf2 signaling pathway, elevate the expression of antioxidant enzymes CAT and SOD, thereby boosting antioxidant capacity and mitigating oxidative stress damage. Furthermore, short-chain fatty acids inhibit the activation of the NF-κB signaling pathway, which promotes the expression of pro-inflammatory cytokines such as TNF-α and IL-1β; thus, FMT reduces the production of these cytokines by targeting this pathway. Paramsothy and colleagues [114] observed that FMT was somewhat effective in treating UC patients, noting that shifts in the abundance of *C. albicans* in fecal samples before and after the treatment correlated with clinical responses. Specifically, in patients exhibiting a higher abundance of *C. albicans* in their feces before FMT, a stable level of Immunoglobulin G (IgG) antibodies and a reduced abundance of *C. albicans* post-treatment were associated with an alleviation of the condition. This suggests that the mechanism of action of FMT may partially involve reducing the abundance of *C. albicans* and controlling the pro-inflammatory immune responses induced by fungi during intestinal inflammation.

In recent years, the use of FMT in preventing and treating CRC has progressively expanded [115]. However, current research predominantly concentrates on the bacterial components of feces, often neglecting the significant roles of fungi, archaea, and viruses. Studies have demonstrated that fungi, along with their interactions with bacteria, are crucial in the development of CRC [36]. Moreover, fungi may serve as predictors of the therapeutic outcomes in fecal microbiota transplantation. The study by Leonardi et al. [116] showed that in patients with ulcerative colitis who received FMT treatment, an increase in the abundance of *Candida* was positively correlated with clinical response and increased bacterial diversity. A decrease in the abundance of *Candida* after FMT indicated an improvement in the condition. Therefore, it is essential for future FMT studies to more thoroughly consider the diverse microbial components in the donor microbiota, as fungi and other microbes may also influence the treatment's efficacy. Comprehensive monitoring and assessment of bacteria, fungi, archaea, and viruses in FMT donor samples, along with studying their disease relationships, will enhance our understanding of FMT's bioactive components and optimize its efficacy. Exploring the composition of fungi and their interactions with other microbes holds great promise as a future research direction in FMT.

Conclusion and future perspective

Fungi are a crucial component of the human gut microbiota, contributing significantly to maintaining gut health and regulating intestinal inflammation alongside other gut microorganisms. Intestinal inflammation is a pivotal factor in various gastrointestinal diseases and plays a vital role in the pathogenesis and disease progression of conditions such as IBD and CRC. Therefore, this review provides a summary of the changes in gut fungi during intestinal inflammation, the potential regulatory mechanisms of fungi on intestinal inflammation, the interactions among bacteria and fungi in gut diseases, and the fungal-based therapeutic approaches for intestinal inflammatory diseases. It highlights the frequently overlooked link between gut fungi and intestinal inflammation and diseases, providing insightful perspectives on research directions that warrant future attention. Recent studies on the relationship between fungi and the development of intestinal inflammation have explored multiple aspects, including the impact on host immunity, host

gene expression, and the colonization, composition, and metabolism of other gut microbes. For example, regarding host immunity, fungi are known to influence the production and function of various inflammatory immune cells through multiple mechanisms, thereby both promoting and inhibiting inflammatory responses. In terms of gene expression, fungi affect downstream signaling pathways and gene expression through activation of pattern recognition receptors on the surface of intestinal epithelial cells, among other methods. In terms of microbiota, a complex interplay exists between fungi and bacteria; fungi indirectly regulate the host gut by influencing the colonization and abundance of specific bacteria. However, certain aspects remain unclear, such as the specific mechanisms that link fungal alterations to the onset of inflammation. It is still uncertain whether changes in fungi precede and cause intestinal inflammation primarily, whether the intestinal inflammatory environment in gut diseases modifies the composition of gut fungi and thereby worsens the inflammation, or if both factors are equally influential. Additionally, the specific mechanisms through which bacteria modulate the interaction between fungi and the development of intestinal inflammation warrant further investigation. Moreover, the application of fungi in diagnosing gut diseases remains largely unexplored. Only anti-*Saccharomyces cerevisiae* antibodies (ASCA) have been extensively utilized in diagnosing CD in IBD [117]. However, numerous studies indicate that their diagnostic efficacy for IBD is suboptimal [117–121]. These insights underscore the need for researchers to concentrate on a more comprehensive exploration of gut fungi, aiming to elucidate the diverse mechanisms of fungi in gut diseases, and to devise more effective strategies and broader options for the prevention, diagnosis, and treatment of numerous gut diseases.

Acknowledgements
We extend our gratitude to Professor Xiaomin Yu and Xiaotian Huang from Nanchang University for their guidance and valuable suggestions in writing this paper. We also appreciate the drawing tools provided by Figdraw.

Author contributions
Y.H prepared the initial draft and subsequent edits, literature review, and illustration design; X.Y and X.H reviewed topics and illustration concepts, content and framework design, and manuscript draft review.

Funding
This work was supported by the National Natural Science Foundation of China (NSFC 32260024, 32060040), The Jiangxi Natural Science Foundation (20232BAB216091, 20202BAB206062), The Double-Thousand Talent Program of Jiangxi Province (jxsq2023201019).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Received: 16 August 2024 / Accepted: 27 September 2024
Published online: 15 October 2024

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