The mycobiota of the human body: a spark can start a prairie fire

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ABSTRACT

Mycobiota are inseparable from human health, shaking up the unique position held by bacteria among microorganisms. What is surprising is that this seemingly small species can trigger huge changes in the human body. Dysbiosis and invasion of mycobiota are confirmed to cause disease in different parts of the body. Meanwhile, our body also produces corresponding immune changes upon mycobiota infection. Several recent studies have made a connection between intestinal mycobiota and the human immune system. In this review, we focus on questions related to mycobiota, starting with an introduction of select species, then we summarize the typical diseases caused by mycobiota in different parts of the human body. Moreover, we constructed a framework for the human anti-fungal immune system based on genetics and immunology. Finally, the progression of fungal detection methods is also reviewed.

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Introduction

The mycobiota, a general designation of fungal species, evolved from the branch of a single-celled marine organism and then underwent further evolution consistent with that of animals, the common ancestor is the organism with a single flagellum, which indicated the close connection between two species. Mycobiota play a role in maintaining stability in both terrestrial and aquatic ecological environments, acting as a decomposer, pathogen, and mycorrhizae.

Research on human microorganisms has been extensively concentrated on bacterial species. However, the growing number of mycobiota-related research papers in recent years indicates an expansion in the field of the mycobiota. Accumulating evidences show that many diseases are inextricably linked to mycobiota. Meanwhile, numerous achievements have been made in the research of organism fungal immunity (Figure 1). It is suggested that its latent role in human health is growing recognized. In particular, the latest researches reveal the mechanism of intestinal mycobiota in colorectal carcinogenesis, which is of great significance for the diagnosis and treatment of colorectal tumor. Thus, overviewing mycobiota in the human body is necessary for further breakthroughs.

In this review, we systematically describe the colonization of mycobiota in healthy people and summarize their association with pathology and immunity. In addition to a comprehensive understanding of the relationship between mycobiota and disease, we also conclude methods for detecting mycobiota to provide guidance for relevant researchers.

Mycobiota at healthy state

Advanced detection techniques give us an opportunity to understand the colonization of mycobiota in the healthy human body. The numerical inferiority of the mycobiota have no effect on its irreplaceable role. The colonization of mycobiota in different body sites of a healthy human is characteristic, in general, Candida, Malassezia, Aspergillus, Epicoccum, Saccharomyces, Alternaria, and Cladosporium are common species. As an essential part of the human microbiome, mycobiota are widely distributed in the healthy human body, mainly exist on the skin and nearly all the mucosal surfaces, such as the gastrointestinal tract, oral cavity, skin, and vagina. They
interact with the host as commensalism and contribute greatly to the maintenance of healthy homeostasis in the human body, which depends on the host, environmental and fungal factors. 

**Mycobiota in the gastrointestinal tract (GI)**

Using high-throughput sequencing to explore, we realized the abundance of the mycobiota in the intestine. There are nearly 70 genera and more than 184 species of mycobiota colonized in the human gut, with Candida, Saccharomyces, and Cladosporium species being major. Among the Candida species, Candida albicans (C. albicans), Candida glabrata, Candida dubliniensis, and Candida parapsilosis are the most common species in the gut. Mycobiota are at great risk of instability due to the influence of other factors in the gut. The antibiotic therapy can change the bacterial community, which in turn promoted the colonization of C. albicans in the GI of mice. Additionally, these mice were more likely to be attacked by Aspergillus fumigatus and developed the allergic response. The stomach and gut are tasked with digestion and absorption of food, so that diet can change the composition of intestinal mycobiota to absorb nutrients better. It is significant to have abundant human diet habits and adapt to a new diet quickly. Age and sex can also cause differences in the gastrointestinal fungal population.
than that of adults, it could be attributed to the weak bacterial competition. Due to the role of sex hormones, there are a larger number of mycobiota in the body of female compared to male subjects.

Many studies have discussed the protective benefits of commensal bacteria. Jiang and colleagues emphasized that intestinal mycobiota are also beneficial for human health. Mycobiota can protect people from mucosal injury and reduce the risk of diseases such as colitis and influenza. The role of mycobiota such as *C.albicans* or *Saccharomyces cerevisiae* is shown during the bacterial depletion caused by the use of antibiotics, which suggests the substitution of mycobiota to bacteria.

### Mycobiota in the oral cavity

The oral fungal community of healthy people is quite complex. Up to date, the groundbreaking research by Ghannoum and colleagues have shown that the number of species of mycobiota is considerable. The most common is *Candida*; therefore, *Candida* is commonly used as a standard for cavity cleaning in healthy individuals. *Cladosporium, Aureobasidium*, and *Aspergillus* also occur in the oral cavity. The difference is obvious in the colonization of mycobiota among individuals. Dupuy and colleagues made the supplement in 2014. Their team firstly identifies the existence of *Malassezia* in the oral fungal community. Due to their large cell bodies, hyphae and other characteristics, mycobiota have an unexpected impact on oral health by the interaction of bacteria. For example, *C.albicans* can cause dental caries couple with *Streptococcus mutans* or *Streptococcus oralis*.

### Mycobiota in the respiratory tract

In the past, it was widely accepted that the respiratory tract in a healthy state was aseptic. With further researches, scientists found that there is a microbial community on the bronchus. But the result only shown the colonization of bacteria. As the matter of fact, the fungal colonization in the bronchoalveolar lavage of healthy people is cut no figure. The few fungal abundance in distinct segments of the respiratory tract exists with significant differences, the part near the mouth are more affected by the environment factors, such as *Davidiellaceae, Aspergillus, and Cladosporium*.

### Mycobiota of the skin and vagina

Skin is the first part of human body to touch environmental microorganisms, with a tremendous community of bacteria and mycobiota. Mycobiota mainly conclude *Malassezia, Penicillium*, and *Aspergillus*. *Malassezia* dominates skin mycobiota in different sites of the healthy human body. By contrast, the foot sites such as toenail and plantar heel shown the highest abundance of mycobiota, which suggested that the foot is easier to suffer a fungal infection. The reason is that a moist skin environment and rich protein provide favorable conditions for fungal colonization. With the quantitative analysis, *Malassezia* represents 53% to 80% of total mycobiota on the human skin and impact the health of our skin greatly. When the skin is damaged, the mycobiota fills the wound and slows down the healing.

Vaginal mycobiota are similar to those in the oral area; *C. albicans, C. glabrata* and *C. krusei*, three subtypes of *Candida*, are the major colonizing mycobiota. Mycobiota are generally recognized as healthy microbes in the vagina, but *C.albicans* can colonize in the vagina without causing any symptoms and can be contagious. Bacteria act as inhibitors against fungal invasion, *Lactobacilli* is commensal bacteria in the female vagina and have the ability to prevent the adhesion of *Candida*.

### Mycobiota and disease

Commensal mycobiota are beneficial for human health, but they are also opportunistic pathogens. Mycobiota cause human disease for two reasons, dysbiosis and infection. Here, we provide a summary of mycobiota-related diseases based on the parts of the human body (Figure 1).

### Mycobiota-related diseases in the gastrointestinal tract

**Inflammatory bowel disease (IBD)**

IBD contains two common forms, Crohn’s disease, and ulcerative colitis. The main characteristic pathological change, mucosal inflammation, is
proved that associated with the decreased abundance of gastrointestinal microbiome. With the accumulation of correlative researches, people have begun to realize the effect of mycobiota on IBD. The detection and analysis showed more intuitively that the intestinal fungal abundance of patients with IBD altered greatly compared with healthy individuals, with an increased Basidiomycota/Ascomycota ratio and incremental *C. albicans*. It is might because the absence of bacteria provide a more favorable environment for mycobiota. Additionally, the raising of *Malassezia* was also identified as the supplement. As early as 1990, researchers used immunological methods to test patients with Crohn’s disease and an antibody against fungal cell wall components was found in their serum. The antibody is known as *Anti-S. cerevisiae antibodies* (ASCA). Later, studies provide evidence that intestinal mycobiota trigger the production of systemic antibodies, such as IgG and IgA ASCA, could be used as serological markers of IBD to diagnose and predict the progression of the disease. Dectin-1 and Card9 play a key role in the antifungal immunity. Study by Iliev and colleagues showed that the deficiency of dectin-1 limited the antifungal immunity of dendritic cells and increased the colonization of *C. tropicalis*, which raised the susceptibility of induced colitis. Furthermore, the use of antifungals could allay the inflammation. The results supported powerfully that mycobiota involved in the process of IBD dynamically. However, mycobiota are only closely related to the occurrence and maintenance of inflammation, rather than a directly induced factor of IBD. The previous research of our group clearly identified that the stimulation of *C. tropicalis* could lead to the lack of NF-kB signaling pathway, resulting in reduced secretion of IL-6 and thus affecting the repair of intestinal epithelial cells. On the other hand, taking the genetic mechanism into consideration, the mutation of mycobiota-sensing related genes, Card9 and dectin-1, were associated with the increasing susceptibility of IBD. (Table 1).

**Colorectal carcinogenesis**

Crohn’s disease and ulcerative colitis can increase the risk of colorectal cancer, which is collectively known as colitis-associated colorectal cancer (CAC). The involved mechanism concludes genes, inflammatory molecules, gastrointestinal tract microbiota and extracellular matrix. The effect of intestinal bacteria had been identified. After that, researchers found five fungi phyla in the intestine of patients with adenomas, which shown the advantage of abundance compared with the two phyla from patients with IBD. Moreover, they also identified that *Fusarium* genus of advanced adenomas was much richer than that of non-advanced subjects. It indicated that fungal colonization contribute the progression of adenoma. Subsequently, Gao and colleagues researched the mycobiota of polyp and CAC patients and complemented the contrast of healthy subjects. They verified the higher abundance of mycobiota in polyp and CAC patients with the comparrison of control group, characterized with the enrichment of *Malassezia*, *Talaromyces*, and *Trametes*. In addition, the difference of fungal structure in three groups was also shown in the result. Coker and colleagues creatively demonstrated that patients with colorectal cancer were characterized with the enhancive Basidiomycota: Ascomycota ratio, the changes in the abundance of *Saccharomycetes*, *Pneumocystidomycetes*, and *Malasseziomycetes* classes. Moreover, the antagonistic effects of mycobiota and bacteria in the intestine contribute to the development of colorectal tumors (Figure 2).

How mycobiota affect the development of CAC? Two studies published on *Immunity* found a link between Card9 and the development of colorectal carcinogenesis, which marked the entry of the mycobiota into the stage of colon carcinogenesis. Malik and colleagues aimed at understanding the role of the Syk-Card9 signal axis in colorectal cancer. Learning from comparative experiments on wild-type and Card9-deficient mice, we known that the inflammatory reaction and the maturation of IL-18 induced by Syk-Card9 signaling provide strong support for the protective effects of mycobiota against colitis and colon cancer. Meanwhile, due to the phenomenon that Card9-deficient mice may take on a higher risk of colon cancer, Wang and colleagues provided evidence that the impaired anti-fungal immunity of Card9-deficient mice results in increased mycobiota,
especially _C. tropicalis_, which increase the proliferation of myeloid-derived suppressor cells (MDSCs) and promote the risk of colon cancer. Similar results from two researches suggest that mycobiota induces a series of response to protect against colon cancer (Figure 2). One interesting thing is that Bergmann and colleagues found a conclusion inconsistent with the above results. They proved that Card9 induces the production of IL-1β, thus exacerbating colon cancer. In this study, Card9-deficient mice and wild-type mice were co-housed for 3 weeks before the experiment, which weakens the influence of fungal factors on tumor development. In conclusion, fungal dysbiosis is closely linked to the deterioration of colitis to cancer, which reminds us that regulating the state of intestinal mycobiota can be a way to treat colorectal cancer.

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**Irritable bowel syndrome (IBS)**

IBS has a great impact on human health. The connection with mycobiota was described when it was discovered that the yeast _Candida_ can make allergic patients suffer from IBS. In recent years, increasing research has been conducted on this disease. It is a type of disease that is characterized by abdominal pain caused by stress allergies. Botschuijve and colleagues provided further information, indicating that differences in mycobiota existed between patients with IBS

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**Table 1. Genetic polymorphisms related diseases.**

| Gene     | Immunity impairment                                      | Response to Diseases | References |
|----------|----------------------------------------------------------|----------------------|------------|
| CYBA/CYBB | Damage to NADPH oxidase                                  | CGD                  | 45         |
| NCF1,2,4  | Dectin-1 Reduce the effect of IL-1β and Th17             | CMC                  | 46,47      |
| IL-12B    | Reduce the production of IL-10                          | Resistance to Candida colonization | 48         |
| IL-12R81  | Reduce the response to IL-12 and IL-23                   | Resistance to invasive aspergillosis | 50         |
| IL-17RA   | Reduce the axis of IL-17                                 | Persisting candidemia | 51         |
| IL-17 F   | Increase the production of IL-22                         | CMC                  | 52         |
| IL-22     | Reduced MBL levels                                       | CMC                  | 45         |
| MBL2      | Increase the production of IL-22                         | Resistance to VVC and RVVC | 53         |
| CARD9     | Impair the response of dectin-1/dectin-2                 | Chronic necrotizing pulmonary aspergillosis | 54,55      |
|           | Reduce the production of Th17 cell and TNF               | Onychomycosis        |            |
| NLRP3     | Reduce the production of IL-1β                           | IBD                  | 56         |
| TLR1      | Reduce the production of IL-1β, IL-6 and IL-8             | RVVC                 | 57         |
| TLR3      | Reduce the production of IFN-γ and TNF-α                 | Invasive aspergillosis | 59         |
| TLR4      | Increase NF-kB signal                                    | CMC                  | 60         |
| TLR9      | Increase NF-kB signal                                    | Invasive aspergillosis | 61         |
| AIRE      | Autoimmunity reduce the production of IL-17A, IL-17 F and IL-22 | Autoimmune polyendocrine syndrome type I | 62         |
|           | Impair the response of T cells                           | APEOED               |            |
| DOCK8     | Impair the response of Th17 cell                         | Hyper-IgE syndrome(HIES) | 63,64      |
| STAT3     | Impair the response of T cell(Th17 cell and memory T cell) | CMC                  | 65,66      |
| STAT1     | Reduce the production of IL-17, IL-22 and IFNγ (the response of Th1 and Th17 cells) | Systemic candidiasis | 67         |
| SFTPA2    | Increase the production of IgE and eosinophilia          | ABPA, CCPA           | 68         |

**Abbreviation:** CMC: Chronic mucocutaneous candidiasis; CGD: Chronic Granulomatous Disease; VVC: Vulvovaginal candidiasis; RVVC: Recurrent vulvovaginal candidiasis; APEOED: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CCPA: chronic cavitary pulmonary aspergillosis; ABPA: allergic bronchopulmonary aspergillosis; IBD: Inflammatory bowel disease.
and healthy people; in other words, fungal dysbiosis was related to IBS. The study suggests the mechanism of the disease: in the first phase, after the stress reaction, corticotropin releasing factor was activated, and then mast cells released histamine, which damaged the barrier function.

In the second stage, mycobiota became pathogenic, and the body initiated the immune response depending on dectin-1/Syk, which is the main cause of abdominal pain. Meanwhile, barrier dysfunction and hypersensitivity continued, causing a vicious circle.

**Figure 2.** The influence of mycobiota on IBD and colorectal carcinogenesis.

**a.** Depend on the studies of model mice, we can know that DSS induces local inflammation in mice. Under normal circumstances, Fungi penetrates the epithelial cell layer and activate immune responses based on dectin-1 and Card9, lymphocytes (Th17 cell) have a further protective role to play in preventing the process of inflammation. However, without the function of dectin-1 and Card9, the growth of fungi may out of control and promote inflammatory cell infiltration, this make mice take on high risk of IBD. In addition, there are two points we need to take notice, firstly, Fungi have nothing to do with inflammation, they just drive the process; the lack of Card9 can be more serious than dectin-1, it is because that Card9 can receive signals from other receptors.

**b.** According to recent researches, fungi may influence colorectal carcinogenesis in two pathways. On the one hand, it will involve the immune system. SYK-Card9 signaling pathway is the main mechanism that mediates fungal immunity, its deficiency can lead to two disastrous results. Firstly, the maturation process of IL-18, a key inflammatory factor, is inhibited. Moreover, impaired immunity can promote the proliferation of MDSCs, which is a catalyst for tumor formation. On the other hand, Competitive antagonism between intestinal fungi and bacteria may also effect the development of colon cancer. Abbreviation: DSS: Dextran sulfate sodium; IBD: Inflammatory bowel disease; CLR: C-type lectin receptors; SYK: Spleen tyrosine kinase; MDSCs: Myeloid-derived suppressor cells.
**Mycobiota-related diseases in the respiratory system**

**Oropharyngeal candidiasis (OPC)**
As mentioned, the dominant fungal species in the mouth is *C.albicans*, which causes OPC (also known as thrush) in the absence of immunity. In the core oral mycobiome of Human Immunodeficiency Virus (HIV) patients and healthy individuals, the researcher identify the enrichment of *Candida* in HIV patients, leading to a higher risk of oral candidiasis caused by an opportunistic fungal infection. Apart from *Candida*, *Epicoccum*, and *Alternaria* were also common genera in HIV-infected patients. The occurrence is based on the imbalance between fungal invasiveness and the immune reaction. HIV blocks the function of antigen-presenting cells and CD4 + T cells. The resistance of oral mucosa is also destroyed. In addition, at the gene level, it was found that the transcription of SAPs in HIV-positive mice was higher than that in the negative control group. In this way, the starting point of prevention and treatment of oral candidiasis should be the enhance-ment of immunity and resistance to mycobiota. However, the abuse of antifungals could resulted in the drug-resistance of *Candida*.

**Cystic fibrosis and asthma**
The lungs of healthy people have very little fungal colonization, which is affected by the environmental and oral mycobiota. When pathological changes occur in the lungs, such as cystic fibrosis mycobiota (mainly *Aspergillus fumigatus*), overpopulate due to a mutation of the transcriptional repressor Nrg1. Notably, the fungal dysbiosis is insensitive to antibiotic therapy and can lead to allergic bronchopulmonary mycosis (ABPM) (Box 1). This allergic reaction is a complication of cystic fibrosis, increasing the severity of the disease. There are many serum markers that can be used to diagnose cystic fibrosis complicated with allergic diseases, such as thymus- and activation-regulated chemokine, CD203c, IgE, and so on. Studies have shown that vitamin D3 can be used to prevent allergic airway disease in cystic fibrosis, hindering further health deterioration. Several studies explained that intestinal mycobiota can cause allergic airway disease in the lung through the entero-pulmonary axis mechanism (Figure 3). Allergic airway diseases also account for the severity of asthma. The term for this type of disease is severe asthma with fungal sensitization (SAFS) (Box1). The treatment of SAFS mainly include anti-IgE monoclonal antibodies (omalizumab) and high-dose intravenous corticosteroids rather than conventional treatments.

**Graft-versus-host disease (GVHD)**
According to the result of multivariate analysis, *Candida* spp colonization induce the Th17/IL-23 response through pattern-recognition receptors, which promotes the development of GVHD. The success of lung transplantation is mainly affected by infectious complications. Using bronchoalveolar lavage (BAL) and oropharyngeal wash (OW) to sample lung transplant patients and healthy people, the result clearly show that both BAL and OW samples from patients contain *Candida* at higher abundance than healthy individuals, while *Aspergillus* is also dominant in BAL samples. This provides good evidence that mycobiota threaten lung transplantation by causing infection.
Mycobiota-related metabolic diseases

Intestinal bacteria have been recognized as pathogenic factors affecting obesity and diabetes.\textsuperscript{104,105} Mar Rodriguez and colleagues\textsuperscript{106} emphasized the composition changes of the fungal community in obese subjects for the first time. They studied the mycobiota in fecal samples from obese subjects and control groups. The difference of fungal abundance between two groups was un conspicuous; however, the common genus in obese patients include Candida, Nakaseomyces, and Penicillium while Mucor, Candida and Penicillium were most frequently detected in non-obese individuals. Significantly, It is discovered that phylum Ascomycota et al. were associated with abnormal metabolism and phylum Zygomycota et al. contributed to the defense of metabolic disturbance conversely, which indicates that mycobiota will become therapeutic sites for metabolic diseases. Gosiewski and colleagues\textsuperscript{107} used Quantitative real-time PCR(qPCR) to analyze gut mycobiota, such as Candida, in patients with type 1 diabetes and concluded that the high prevalence of \textit{C.albicans} is one of the characteristics of diabetes.

Other mycobiota-related diseases

Malassezia, the main mycobiota in the skin, can cause different skin infections. Pityriasis versicolor is a form of skin tinea that has a definite connection with \textit{Malassezia}.\textsuperscript{108} The hyphae of \textit{Malassezia} invades the skin, and its metabolites form small-scale pigmented plaques in lipid spills. Balaji and colleagues\textsuperscript{109} detected that cross-reactivity between fungal thioredoxin and human thioredoxin may related to the inflammation in the patients with atopic dermatitis. In addition, \textit{Malassezia} also contributes to dandruff\textsuperscript{110} and folliculitis,\textsuperscript{111} which bring stubborn trouble to the patient. 

\textit{Candida} can also cause skin infection, named chronic mucocutaneous candidiasis (CMC),\textsuperscript{112} marked with the deficiency of IL-17. In the patient’s body, mutations in STAT1 prevent T cells from differentiating into Th17 cells and thus fail to secrete immune effectors such as IL-17, which are the key to skin resistance to \textit{Candida} infection.\textsuperscript{65,68,113} Moreover, patients with autoimmune disease produce antibodies to IL-17, which impair immunity and can also trigger CMC.\textsuperscript{62}

Recent study by Yang and colleagues shows that intestinal mycobiota contributed to the aggravation of alcohol-induced liver disease.\textsuperscript{114} After
drinking alcohol, the burden of intestinal mycobioti

Humicola species, Fusarium and Aspergillus, which

led to an increase of mortality. Moreover, the
development of liver disease depends on dectin-1,
the signal induces the production of IL-1β from
Kupffer cells and promotes liver inflammation.
These findings suggest that the intestinal myco-
bio may become the therapeutic target for alco-
hol-related liver disease.\textsuperscript{115}

Recurrent vulvovaginal candidiasis (RVVC) is
a mucosal fungal infection that seriously affects the
health of women.\textsuperscript{116} C. albicans can act as a symbiont
in the vagina of most healthy women, causing inflam-
mation through promoting epithelial cells to produce
cytokines and chemokines\textsuperscript{117} when the body is com-
promised, such as with HIV infection, pregnancy, diabetes, antibiotic use, and so on. In addition, genetic
cfactors can also increase susceptibility, which is linked
genic polymorphisms of immune molecular-
related gene, such as dectin-1.\textsuperscript{118} Antifungal drugs
such as fluconazole are commonly used in clinic,\textsuperscript{54}
but there is a risk associated with their use in pregnant
women.\textsuperscript{119} Therefore, probiotics and vaccines\textsuperscript{54,120}
are hopeful use instead of to anti-fungal therapy.

Multiple fungal species can be associated with
the central nervous system when the body’s
immune function is defective, mainly Aspergillus
and Cryptococcus.\textsuperscript{121} For example, brain abscesses
are caused by Aspergillus infection in leukemia
patients because of neutropenia. Additionally,
cryptococcal meningitis is related to HIV infec-
tion, which is a great threat to human life.\textsuperscript{122} Meningitis usually originates from a lung infec-
tion, and there is evidence that antifungal treat-
ment for meningitis may exacerbate immune
reconstitution inflammatory syndrome.\textsuperscript{123} Intestinal mycobio
ti may be involved in nervous
system diseases, such as autism spectrum
disorders\textsuperscript{124} and Rett syndrome.\textsuperscript{125}

\textbf{Host immunity and mycobio}
ta

We have long known the damage caused by myco-
bio to the human body and the severity of the
damage warrants vigilance. Furthermore, the poly-
morphisms caused by fungal immunity-related
gene mutations impact the immune response,
which is associated with the susceptibility to fungal
genetic diseases or infectious diseases (Table 1).
Healthy people can live normally in environments
with an abundance of mycobio or harbor mycobio
in their body thanks to a strong immune
system interaction with the commensal mycobio
to achieve balance. This process includes the
immune defense against infection and the reaction
of mycobio to the immune system.

\textbf{Immunity of organisms to fungal infection and
dysbiosis}

The skin and mucosa of the human body are the
most exposed to mycobio. Innate immunity
begins with the perception and recognition of
fungal invasion at these sites (Figure 4). After
that, the downstream signaling pathway begins,
with transduction in the nucleus, triggering
a series of immune effects.

\textbf{Pattern recognition receptors}

Pattern recognition receptors (PRRs) in the
human body consist of C-type lectin receptors
(CLRs), toll-like receptors (TLRs), NOD-like
receptors (NLRs) and RIG-I-like receptors
(RLRs). Research on RLRs is still insufficient, but
we are aware of a function in the recognition of
Candida. PRRs recognize fungal pathogen-
associated molecular patterns (PAMPs) in particu-
lar (Figure 4).

CLRs dominate fungal perception and immunity,
they can activate the Syk-Card9 pathway through
immune receptor tyrosine-based activation motifs
(ITAMs) or FcR (relate to ITAMs), which in turn
activates nuclear factor kappa B(NF-kB) signaling
and a series of inflammatory reactions.\textsuperscript{126} However,
there are differences among receptors (Figure 4),
dectin-1 (also known as Clec7a) is a CLR that is
expressed by many immunological cells. This mole-
cule recognizes β-glucan and then promotes the
production of cytokines to induce inflammation,
thus controlling Candida infection mainly.\textsuperscript{127} The
deficiency of dectin-1 may cause the reduction of
IL-17, the patient may be more likely to develop
recurrent vaginal candidiasis and onychomycosis.\textsuperscript{46}
However, the results of subsequent experiments are
contradictory. Saijo and colleagues\textsuperscript{128} suggested that
the function of neutrophils in killing C. albicans was
not impaired when dectin-1 was lacking, which
The reaction between mycobiota and immune system.

**a.** On the cell membrane of the phagocyte, there are many pattern recognition receptors, they sense the fungal infection through recognizing specific components of the cell wall, then the signal goes downstream. The C-type lectin receptors (dectin-1,2,3 and mincle) are based on SYK-Card9 pathway and then reach NF-κB. The toll-like receptors (TLR2,4,6) are coupled with MYD88 pathway mainly.

**b.** The maintenance of immune homeostasis includes resistance and tolerance. The resistance is divided into two parts. Firstly, phagocytic-centered innate immune system. The neutrophil could not only produce IL-6, IL-23 but also cooperate with macrophages and monocytes to cause inflammation. Dendritic cells could deliver information to T cells through MHC and TCR. Secondly, adaptive immune effects include antibodies produced by B cells and specific lymphokines produced by different subtypes of T cells; The tolerance is mainly relying on the remission of inflammation by Treg cells. The two kinds of actions coordinate with each other to reach the balance state of the body's immune system. Abbreviation: TCR: T cell receptor; MHC: Major histocompatibility complex; PRRs: Pattern recognition receptors; IDO: Indoleamine-2,3-dioxygenase
indicated that dectin-1 had no obvious effect on invasive fungal infection. This led to speculation until studies found that the response of dectin-1 was species specific, only involving C. albicans yeast but not filaments, depending on the nature of the β-glucan in the cell wall of the yeast. Apart from the isolation of infection, experimental evidence has shown the role of dectin-1 in fungal dysbiosis. Researchers have shown that dectin-1 inhibits the excessive growth of Candida in the gastrointestinal tract to coordinate the ecological environment of the intestine and avoid colitis. Interestingly, Iliev and colleagues found the role of dectin-1 was explained in the opposite way. They demonstrated that dectin-1 signals, while resistant to mycobacteria, also inhibited the growth of Lactobacillus in the gastrointestinal tract and affected the infiltration of Treg cells, which undermined the body’s ability to protect against colitis. In addition, dectin-1 also assists the function of TLRs (TLR2, TLR4). Dectin-2, dectin-3, and Mincle have a secondary role in fungal immunity and connect to the downstream Sky-Card9-Bcl10-Malt1 pathway through FcRγ. Unlike dectin-1, dectin-2 can reduce systemic Candida infection by stimulating the differentiation of Th17 cells. Additionally, the recognition of dectin-2 by α-mannan is essential to trigger the immune response of the human body against Malassezia, which is also associated with Mincle via the recognition of lipophilic components in vitro. The effect of dectin-3 is similar to that of dectin-2, which enhances the immune control of fungal invasion. Dectin-2 and dectin-3 cooperate with each other to form heterodimers, which promote the production of proinflammatory factors (IL-1β, IL-6). Research has shown that this type of complex improves the ability to sense mycobacteria pathogens. Mincle could kill mycobacteria by promoting phagocytosis and TNF production, although this function is not widely accepted. A recent study provided more information about dectin-3, scholars found that the composition of the gut mycobacteria is altered in model mice with dectin-3 deletion and the dysbiosis causes a higher risk of colitis induced by dextran sodium sulfate. This finding indicates the role of dectin-3 in maintaining the homeostasis of the colon microenvironment. Mannose receptor (MR) recognizes α-mannan, mediating the sensing of mycobacteria on the surface of a macrophage. A characteristic of MR is that it can build a bridge for the immune effect of Th17 cells induced by C. albicans in human peripheral blood mononuclear cells without anti-CD3 or anti-CD28 antibodies, which assist IL-17 in fungal resistance. Importantly, MR requires the assistance of other CLRs, such as dectin-1 and TLR2. It is worth emphasizing that the absence of MR leads to the susceptibility to C. neoformans and is ineffective against infection by C. albicans and P. carinii. CD23 is a newly discovered CLR, JNK1 (also known as MAPK8) can down-regulate the body’s antifungal immunity. According to an experiment with mice, we concluded that inactivating the activity of JNK1 could increase the level of CD23 and promote the production of nitric oxide, which contributes to stronger immunity against fungal pathogens. Therefore, we expect that the JNK1 inhibitor may bring hope for antifungal therapy. Later, an article revealed the mechanism of antifungal immunity of CD23: it connects the NF-κB signal pathway through the FcRγ subunit and upregulates the production of nitric oxide from macrophages. Notably, this applies to defense against C. albicans and A. fumigatus, but not C. neoformans.

TLRs such as TLR2, TLR4, and TLR9 are essential parts of PRRs that participate in sensing mycobacteria. In addition, the polymorphisms of TLR4 and TLR9 could affect human susceptibility to mycobacteria (Table 1). After the recognition of fungal PAMPs, protease-activated receptors (PARs) are activated, and then PARs and TLRs influence each other and impact fungal immunity. The results of studies have shown that PAR1 enhances immune inflammation in Candida infection with the help of TLR2, while PAR2 cooperates with TLR4, downregulating the response to Aspergillus. TLR2 can also maintain the balance between Th17 cells and Treg cells, with the depression of Th17 cells. The downstream of Toll-like receptor is linked with MYD88. Using in vivo experiments, we found that the IL-1 R/MyD88 pathway is essential for the defense against C. albicans and that the TLR4/MyD88 pathway protects us from succumbing to Aspergillus fumigatus.

The function of NLRs is shown in the NLRP3 inflammasome. The signal transduction of fungal infection is dependent on Sky, which can endow NLRP3 activity and produce the precursor of IL-
Then, the role of NLRP3 becomes relevant, which activates caspase1 for processing IL-1β. This process is significant for the defense against mycobiota. NLRC4, which controls the activity of IL-17 and IL-1β, is also required in resisting mucosal candida infection.

The role of cells and molecules

The roles of cells and molecules are divided into two parts: innate immunity and adaptive immunity. These two parts work together to build harmonious and unified anti-fungal immune homeostasis (Figure 4).

Neutrophil is the most powerful phagocyte, and this type of cell has the ability to kill mycobiota through oxidative and nonoxidative mechanisms. For oxidative methods, neutrophils can first produce mycobiotacidal peroxide through NADPH oxidase and myeloperoxidase, which is known as a respiratory burst. The deficiency of protection from NADPH oxidase has been proven to be linked with chronic granulomatous disease, a hereditary disease marked by chronic inflammation and lethal fungal infection. Secondly, another system is based on reactive nitrogen intermediates, which are guided by inducible nitric oxide synthase (iNOS or NOS2). For the nonoxidative system, nuclear members are functional proteins or polypeptides, including antimicrobial peptides and hydrolases. All of these pose a powerful threat to fungal invasion. Additionally, some proteases in neutrophils have been reported to have a role in neutrophil extracellular traps, which are able to catch mycobiota. Otherwise, the neutrophils can also provide a source of IL-17, assisted by IL-6 and IL-23.

The cytotoxicity of epithelial cells is not strong and mainly functions as a barrier. Themacrophage is not able to kill fungal spores but can control their growth and help pathogens become exposed to anti-fungal drugs. Due to the experiments on CX3CR1 deficient mice, we underline the potent protection from renal resident macrophages in the early stage of systemic Candida infection, which relies on CX3CR1. The latest study found that CX3CR1+ mononuclear phagocytes (MNPs) have an impact on antifungal immunity. CX3CR1+ MNPs could trigger patient defenses such as Th17 cells and antibodies to reduce fungal colonization during bowel disease depending on CLR signaling pathways, and even better, these cells can regulate the intestinal fungal community and prevent imbalances. Monocytes play a major assisting role; they can kill fungal spores or transport them into lymph nodes in the form of dendritic cells, triggering adaptive immunity. In addition, mononuclear cells can also provide assistance to neutrophils in preventing the progression of disseminated candida infection, but overreaction can lead to immune-related pathology in the kidneys.

In the innate anti-fungal immunity, except for the effects of the abovementioned cells, the role of other cells and molecules should not be ignored. Innate immune cells include epithelial cells, natural killer cells and dendritic cells, while molecules contain chemokine, complement, and newly discovered Casitas B lymphoma-b (CBLB) molecules (Table 2).

Adaptive immunity against mycobiota is supported by T lymphocytes and antibodies produced from B lymphocytes. T lymphocytes include CD4+ and CD8+ T cells. Some studies have authenticated that CD8+ T cells are able to supplement CD4+ T cells’ functional deficiency in the case of immunodeficiency and other antifungal activities. Here, we only focus on CD4+ T cells, such as Th1, Th2, and Th17 cells.

It has been reported that T cells of different subtypes have specific functions. Th1 cells can be activated by cytokines (IL-12) produced downstream of PRRs, although the guidance of dendritic cells (DCs) is found to have an effect when the body suffers from systemic infection, then performing functions such as the production of IFNγ and enhancing the anti-fungal ability of innate immune cells like phagocytes. To employ a different role, the function of Th2 cells is more likely to soften the immune system. These cells can be regarded as the target of negative regulation in an organism’s anti-fungal immunity, maintaining a balance. Thus, the activation of the Th2 cell response requires Th1 cell inhibition as a cost, which causes susceptibility to Candida infection. IL-4 is a trigger factor of the Th2-type response, and this upregulated response of Th2 cells may cause people to suffer from diseases.

Th17 cells are the main force of specific immunity against fungal infection in organisms. Th17 cells can receive stimulatory signals from multiple cytokines (IL-23, IL-6, and IL-1β), with an article highlighting...
the role of IL-6 produced by the Langerhans cell combined with CLRs. The upstream events may lead back to a few signaling pathways that were previously discussed; the well-known mechanism is combined with Card9, which is the center of anti-fungal immunity. For example, in the response to Aspergillus fumigatus infection, researchers found that Card9 accepts the signal from dectin-1 and impels CD4 + T cells toward the direction of Th17 cell differentiation, which is based on the inhibition of Th1 cell formation. After activation, Th17 cells can produce cytokines based on IL-22 and IL-17. Accumulating evidence has shown that IL-17 predominates the protective response with the second role of IL-22 when the body encounters OPC and RVVC. It suggests that Th17 cells have a role in the immunity of mucosal fungal infection specifically.

Treg cells are another important subtype of T cells. The effects of Treg cells and monoclonal antibodies have complemented the antifungal adaptive immunity so that the organism can mount a better response to fungal-induced lesions (Table 2).

**Effects of mycobiota on organism immunity**

**The evasive fungal pathogen response to the immune system**

The recognition of PAMPs is the basis for the immune system to monitor fungal pathogens. Therefore, many mycobiota utilize this point for immune escape. For example, the polysaccharide layer of Cryptococcus neoformans and the protein layer from Aspergillus fumigatus can hide PAMPs. Additionally, the morphology of mycobiota may play the same role, such as the hyphae of Candida. Damage to recognition is also realized by other pathways, including the activation of complements and the inhibition of phagocyte function. After being identified, mycobiota still struggle to survive by various methods, including the destruction of the mature of phagocytes, escape, and the resistance to unfavorable environments, which are used by different species of mycobiota.

Furthermore, fungal pathogen Pneumocystis carinii causes infection and initiates the Syk pathway triggered by Dectin-1. This response promotes MR shedding, which gives functionality to MR (in the form of sMR) based on metalloproteinase. Soluble MR (sMR) is widely thought to help mycobiota avoid clearance by host immunity. Interestingly, the Mincle receptor is a powerful weapon for mycobiota, but toxic factors of mycobiota could reduce the activation of Interferon Regulatory Factor (IRF1), which is associated with the pathway induced by E3 ligase Mdm2. The alteration could damage the ability to resist fungal infection by blocking the production of IL-12, which weakens Th1 cells activity but increases that of Th2 cells.

**Impact of mycobiota on the immune system**

More and more studies show that mycobiota have the effect on human immune system. In early times, researchers found the benefits of Saccharomyces boulardii, a type of probiotic mycobiota, which can regulate the immune system against the invasion of C. difficile and relieve intestinal inflammation.
albicans was found to affect immune components such as TLR4, Dectin-1 and build patient defense in the gut and lung. There is also evidence that mycobiota regulate lymphocyte recirculation. Fungal flora can induce Raldh β” dendritic cells gathering in peripheral lymph nodes. Without this process, lymphocyte adhesion molecules (necessary in recirculation) would have no response. To survive under the surveillance of the immune system, apart from the help from Treg cells mentioned above, mycobiota could also accommodate immune sensitivity. C. albicans can activate the tolerance of macrophage and DCs increase the impression of indoleamine-2,3-dioxygenase. It is widely accepted that it can induce the enrichment of Treg cells and the depletion of Th17 cells. All of these may help mycobiota adapt to immunity better. In addition, the contribution of cytokines cannot be ignored, and TGF-β and IL-10 are used by Malassezia to avoid excessive inflammatory responses. MDSCs are usually believed to promote tumor formation depending on the nature of hyper proliferation. According to further study, people began to realize the effect they play in the interaction between fungal pathogens and hosts. A murine study further provides evidence that the recognition between fungal pathogens and dectin-1 drives the neutrophilic subtype of MDSCs to obstruct the activity of Natural killer cells and Th17 cells through cooperation with caspase-8, IL-1β and ROS, thereby preventing the human body from suffering severe inflammation. It is also proved that C. tropicalis induce MDSCs differentiation from bone marrow cells, which promote the development of CAC. In short, MDSCs can be used by mycobiota as a medium to achieve the regulation of the immune system.

Except for the primary immune response, some researchers found that the innate immune system that has been exposed to fungal pathogens can provide a faster and stronger defense against reinfection, which is called ‘trained immunity’ (Box2) for fungal pathogens. This revolutionizes our perception of innate immunity. It was found that C. albicans can enhance the resistance of monocytes to secondary infection in the body by means of dectin-1 and it’s epigenetic modification. Recently, Tso and colleagues had shown that the mechanism of fungal pathogen evolution involves a symbiotic relationship with the host gastrointestinal tract. The use of antibodies selects a fungal strain with hyphal deficiency, which has low toxicity and high immunogenicity. This fungal pathogen’s adaptation to the intestinal tract enhances the protective power depending on the innate immune system. The effect is impermanent, but it can relieve a crisis of adaptive immune deficiency, such as Acquired immune deficiency syndrome (AIDS). It can also give us an advantage when searching for proper vaccines for infection protection, for example, Bacillus Calmette-Guerin is a well-known anti-tuberculosis vaccine that also has protective effects on fatal systemic fungal infections, which has been demonstrated to have an association with the change of metabolic pathways.

**Methods for detecting mycobiota**

Hospital AIDS and transplant patients as well as intensive care patients have a high risk of fungal infection. In addition, drug-resistance due to inappropriate anti-fungal treatment can also lead to a challenging disaster for humans. To realize more accurate and fast detection, we must rely on convenient and advanced methods and techniques(Figure 5).

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**Box 2: Trained immunity**

People have always held the view that, among the immune responses, including nonspecific (innate) and specific (adaptive) responses, only the latter can preserve memory to provide a stronger protection against reinfection. However, several studies have shown that plants and invertebrates, which only have innate immunity, are on-alert when they reencounter the same or different pathogens. This phenomenon is named systemic acquired resistance. Targeted in-depth studies have deepened our understanding of this phenomenon. Previous invasion trained the innate immune system to offer better protection when reinfection occurred. Thus, the concept of ‘trained immunity’ is widely known. According to a study on vertebrates, we also found the existence of trained immunity in their bodies, which has the characteristic of adaptability, but not specificity.

On the basis of experimental studies, β-glucan (mycobiota), peptidoglycan or lipopolysaccharide (bacteria) and other microbial pathogens could trigger responses targeted on innate immune cells, mainly macrophages, monocytes and natural killer cells. Compared with adaptive immunity, trained innate immunity contains many differences such as temporal and nonspecific characteristics, which are attributed to the dependence on epigenetic or transcriptional changes rather than genetic variation. However, there are still some adverse effects and labile factors exist.
Histopathological and immunological methods

Traditional diagnostic methods for fungal diseases depend on histopathological examination (selective culture, microscopic examination, biochemical detection). This method provides a reliable standard for Candida infection but more damage to the patient due to the length of the detection time, including disease deterioration and economic losses. There are differences in detection methods for different types of fungal infections; however, false positivity, confusion, and invalidation may occur in the morphological diagnosis of fungal infection.

The immunological method is a technique for detecting fungal antigens, mainly components of the fungal cell wall, such as β-d-glucan. Some laboratory researchers used radioimmunoassay to detect fungal mannan, which has diagnostic significance for systemic candidiasis. The Cand-Tec latex agglutination test also has a related application. Enzyme-linked immunosorbent assay (ELISA) is used in the diagnosis of penicilliosis by detecting the antibody Mp1p. It has been proven that ELISA is better than the latex agglutination test in aspergillus infection identification. Nevertheless, antigen detection
is influenced by many factors, such as immune complexes and detection thresholds, which are limited; therefore, prospective improvements are required.

**Molecular biological methods**

The above methods cannot address the complexity of the fungal community. Therefore, molecular biological methods have entered the stage of fungal detection. Polymerase chain reaction (PCR) is a basic technology related to fungal DNA detection. Although traditional PCR technology has advantages of being quick and intuitive, the low DNA content of fungal pathogens has led to the fact that this technique cannot meet the required sensitivity. Thus, some improved technologies were born. qPCR allowed us to access real-time detection, enhancing sensitivity and specificity. This instant feedback signal was accomplished by fluorescent probes such as Taqman. Isothermal PCR eliminates the thermal cycle step, simplifying the PCR technology greatly. Loop-mediated isothermal amplification has an absolute advantage. Use of PCR necessitates attention to some points: DNA extraction should be performed with attention to DNA quality and should avoid contamination; in regard to the design of various primers, the target is usually directed to the fungal rDNA operon region. Researchers have harmonized the biomarkers used to identify fungal species. Based on the considerable sequences and analyses, The taxonomic and phylogenetic classification based on sequence analysis of the ITS genomic region has become a crucial component of fungal ecology and diversity studies.

After using PCR to amplify specific regions, sequencing is the next step. Currently, metagenome sequencing opens the door to a new world for fungal detection. Next-generation sequencing (NGS) is the second generation high-throughput sequencing technology, replacing Sanger sequencing. NGS is supported by high-throughput sequencing platforms such as 454-pyrosequencing technology and the Illumina MiSeq sequencing platform. The sequence results should be compared according to a common database (like GenBank). Although there are some shortcomings with searching, it has provided an effective method for the identification of mycobiota.

The methods of DNA analysis for mycobiota help us to familiarize ourselves with fungal colony changes associated with related diseases. For example, the microscopic pathological changes of patients with ulcerative colitis were studied by denatured gradient gel electrophoresis analysis. Moreover, clinical studies have shown that microarray technology can be used in the pathological analysis of mycosis. Because the structures and characteristics of mycobiota are diverse, we often need to use different methods for specific fungal species to achieve accurate judgments, except for common approaches such as β-glucan assays. For example, it is most appropriate to detect germ tube antibodies for *Candida* spp. while detecting galactomannan for *Aspergillus* spp.

Over time, the rapid development of new molecular identification methods has opened the understanding of the fungal world. Whole Genome Sequencing is applied in human oral mycobiota. Other technologies such as Mass spectrometry, Fluorescence in situ Hybridization and Magnetic resonance help us have a more thorough understanding of mycobiota.

**Conclusions**

Earlier, when it came to the microbiome of the human body, the first thing people considered was bacterial species. However, in recent years, the role of the mycobiota has gradually appeared, reflecting a position that cannot be ignored. Through reviewing these studies, we have realized that the effects of mycobiota have penetrated all aspects of human pathology, with a gradual expansion of scope. This tells us that the door to the new world of mycobiota has opened and that more novel problems are in need of our solutions: how to transfer the model of colon cancer into clinical practice; whether the functional similarity between bacteria and symbiotic mycobiota can be extended to other aspects; what should we do to preserve the benefits of mycobiota for the immune system and minimize the damage?

The rapid rise of fungal research also provides a new approach to the treatment of clinical-related diseases. It is worthwhile to note that we should consider fungal species in the internal
microenvironment rather than in isolation. Only in this way can we systemically understand the responses and apply them in actual disease treatments for the benefit of more people.

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