Immune Response to Fungal Pathogens

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Fungi rarely cause disease in individuals with normal immunity. However, fungi present in the normal biota of the skin, mucous membranes, intestinal tract, and fungi in the environment that are normally non-pathogenic, can cause life-threatening infections in individuals with suppressed immunity. In the past decades, the prevalence of opportunistic fungal infections has increased, and these are associated with lowered immunity due to chemotherapy, HIV infection, and aging. The development of traditional antifungal agents has not kept pace with the increasing prevalence of invasive fungal infections, and the resistance to antifungal agents has become a major problem. Fortunately, study of the molecular and cellular mechanisms of the host immune response to fungi is increasing day-by-day. These studies indicate that fungal-specific mechanisms exist in the human body, including maintenance of immunological homeostasis in tissues, destruction of homeostasis by fungal infections, elimination of fungi by the host immune response, and recovery of homeostasis. Research into the mechanisms of fungal infection in humans suggests a new treatment paradigm that goes beyond traditional antifungal agents. Vaccines against fungi and immunotherapy using the host immune mechanism against fungi have recently been developed and are nearing use in the clinic.

**Key Words:** Adaptive immunity, Fungal infection, Innate immunity

**INTRODUCTION**

Fungi are heterotrophic eukaryotes that are morphologically classified into their yeast and filamentous forms. Fungi are widely distributed in the environment, and while the majority of fungi are harmless to humans, some do cause various forms of disease, from superficial infestation and allergic diseases to life-threatening internal organ infections.

The prevalence of fungal diseases has been increasing since the late 20th century due to an increase in the elderly population and an increase in patients with reduced immunity due to diabetes, AIDS, organ transplantation, and cancer. The host's immune response to fungi not only determines the clinical form of the fungal disease, but also greatly affects the host's susceptibility to the disease and the severity of the disease. The host's defense mechanisms against fungi are very complex, ranging from innate immune responses that cause non-specific immediate responses to pathogen infestations to highly specific acquired immune responses induced during infection.

Recently, a great deal of new information has been discovered regarding innate immune responses and regulatory T cells involving antimicrobial peptides and pattern recognition receptors. There has been considerable research on the inter-
actions between different constituent cells and fungi, which have greatly increased the knowledge of human antifungal immune responses. The aim of this review is to provide an overview of the human immune response to fungi.

Fungal Recognition by the Innate Immune System

Innate immune mechanisms in humans respond to a variety of fungal pathogens in a fast and conserved manner. Constitutive mechanisms of innate immunity exist at the sites of interaction with the fungus and include the barrier function of the skin and the mucosal epithelial surfaces of the respiratory, gastrointestinal, and urogenital tract. Microbial antagonism and the complement system also provide defense mechanisms and opsonic recognition of fungi. For example, complement receptor 3 (CR3: heterodimer of CD11b and CD18) recognizes complement deposited on β-(1,6)-glucan on the fungal surface. In addition, the host cell may contain pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), C-type lectin receptors (CLRs), and galectin family proteins that detect pathogen-associated molecular patterns (PAMPs) in fungi. PRRs on phagocytic cells initiate downstream intracellular events that provoke activation of the immune system and elimination of fungi, with specific immune responses generated according to the cell types involved.

Those cell types include innate phagocytic cells such as neutrophils, monocytes, and macrophages, which are mostly involved in innate immunity to fungal species through phagocytosis or other direct killing mechanisms. On the other hand, dendritic cells (DCs) uptake fungi to induce DC maturation, so that mature DCs stimulate naive T cells to become effector T helper cells. In this way, early recognition and inflammation against the fungus offer critical signals that drive adaptive immunity.

Fungal cell walls show a combination of different components depending on the species, growth stage, and surrounding environment. Fungal cell walls play an important role in the recognition phase because they are the main source of PAMP, which is recognized by PRR in mammalian cells. The three major cell wall components found in most medically important fungi are β-glucans, chitin, and mannans. During the course of fungal infection, a number of host PRRs are stimulated by fungal cell walls, which contain a variety of carbohydrate groups recognized by PRRs such as C-type lectin receptors (CLRs). For example, mannose receptor and DC-SIGN bring the mannose-binding lectin (DC-SIGN), macrophage mannose receptor 1, langerin, and mannose-binding lectin. The main PRR is dectin 1, which detect β-glucans in fungal cell wall and induce the inflammatory cytokines and chemokines. This immune response is accomplished by two main cascades: the spleen tyrosine kinase (SYK)-caspase recruitment domain containing protein 9 (CARD9) pathway and the RAF pathway. These two pathways combine to promote or regulate the host immune responses to fungi, and ultimately activate nuclear factor-κB (NF-κB). Although it is not yet clear how CARD9 induces the activation of NF-κB following fungal infection, recent studies have shown that CARD9 serves as a link between dectin 2 and NF-κB activation via IkB kinase ubiquitination, and also as a link between dectin 1 and ERK activation by turning on the RAF system. The SYK-CARD9 pathway also stimulates the NLRP3 (NOD-, LRR and pyrin domain-containing inflammasome) and the inflammasome promotes interleukin-1β and interleukin 18 by caspase 1.

In a manner similar to dectin 1, dectin 2 recognizes high-mannose structures, mannose receptor, and DC-SIGN recognize branched N-linked mannans to activate downstream immune responses. Dectin 2 binds mainly to hyphae with higher affinity than yeast, so that pairs with the Fc receptor γ chain (FçRγ) to provoke the production of inflammatory cytokines. Mannose receptor and DC-SIGN bring the mannosylated fungal antigen to DCs, which is linked to antigen processing and presentation to T cells. Dectin 3 functions as a PRR by recognizing α-mannans. Dectin 3 and dectin 2 undergo heterodimerization, and this dimer can recognize α-mannans leading to higher sensitivity in recognition of Candida albicans than either dectin 2 or dectin 3 alone, and leading to strong activation of NF-κB-dependent immune responses against fungi. This is supported by a previous report suggesting that dectin 3 deficiency results in lowered NF-κB activation.
and cytokine production against *Candida tropicalis* in the gut. Another major group of PRR is the TLRs. The main subtypes of TLRs, which are involved in the detection of fungal components, are TLR 2, TLR 4 and TLR 9. These subtypes detect the phospholipomannan, zymosan, fungal DNA and O-linked mannan. There are several studies that have shown that mice lacking TLR signaling are highly susceptible to various fungal infections, but the exact immunologic role of TLRs in fungal infection remains unclear. This ambiguity might be due to the diversity in fungal species, routes of infection, and pathogen-receptor coordination. Even though there is a debate about the relationship between TLR function and susceptibility to fungal infection, recent human studies have shown that TLR polymorphism is associated with the higher susceptibility to the specific fungal species. For example, TLR 4 polymorphism is associated with the higher susceptibility to candidal sepsis, and TLR 9 polymorphism is associated with allergic bronchopulmonary aspergillosis (ABPA). Similar to CLRs, TLRs also promote the antigen-presentation of fungal component to DCs, which promote T cell responses to fungi. With regard to immunological cascades, the stimulation of TLRs by fungal antigens induces downstream signaling of the protease-activated receptors (PARs). PARs, which are G protein-coupled receptors, are activated by fungal proteases as well as host proteases that are activated by fungal-host immune reaction. Once TLRs detect the fungal antigens, PARs are activated and are able to detect various virulence factors associated with host tissue injury. There are two types of PARs; PAR 1 mediates pro-inflammatory responses, whereas PAR 2 mediates anti-inflammatory responses. So, TLR and PAR signaling cascades affect each other to regulate immune responses to the fungi. Although little is known about the cytoplasmic receptors that respond to fungi, NOD-like receptors (NLRs) are known to recognize fungi and, if activated, promote the secretion of IL-1β and IL-18 via production of the inflammasome (ABPA). For example, in mice that lack IL-1 receptor type I (IL-1RI) signaling, different susceptibility patterns by aberrant activation of IL-18 or caspase 1 have been identified. However, mice lacking NLRP3 show increased sensitivity to *Candida* infections. Defective activation of NLRP3 is known to be linked to increased *C. albicans* colonization and the deterioration of Crohn’s disease. These observations demonstrate how commensal fungi such as *C. albicans* become pathogenic under certain circumstances.

Mammalian PRRs recognize not only PAMPs, but also by-products of cells that have been destroyed by external pathogens, such as nucleic acids, which are called damage-associated molecular patterns (DAMPs). Although specific signaling pathways that regulate immune responses induced by PAMPs and DAMPs have been identified, unexpectedly, the fact that molecular pathways recognizing PAMPs and DAMPs converge to common specific pathways has been also identified. This raises the questions of whether the host immune system distinguishes between these two types of molecular patterns, and how they do so. It is not clear to what extent these two different molecular patterns, PAMPs and DAMPs, contribute to the mechanisms of inflammation, immune homeostasis, and repair that occur during the course of fungal infection. However, a mechanism has recently been proposed to explain how host immunity can distinguish immune responses from PAMPs and DAMPs. A key molecule is alarmin S100 B, which distinguishes host-specific immune response from PAMPs from those from DAMPs by spatiotemporally integrating the signal from TLRs with the receptors for the advanced glycation end-product (RAGE). When a nucleic acid, a type of DAMP, binds to a TLR2 ligand derived from a fungus, S100B inhibits the inflammation induced by TLRs. Thereafter, intracellular TLR3 and TLR9 are activated, leading to downregulation of the immune response. Thus, the interaction of RAGE with TLRs represents a regulatory circuit in the response to fungal infection: the endogenous danger signal protects the host from excessive inflammation due to fungal infection, and terminates the inflammation by DAMPs sensing mechanism. This suggests the interesting possibility that the host may have developed PAMPs to modulate excessive immune responses by DAMPs.

**DENDRITIC CELLS**

Dendritic cells (DCs) are specialized antigen presenting cells that take up antigens, integrate local inflammation signals, and migrate to lymph nodes, which drain the affected area, effectively leading to adaptive fungal immune responses. For example, analysis of DCs activated by fungi through whole-genome transcriptional analysis suggests that there are specific transcription programs that result from fungal infection. The fact that this group of specific DCs has a variety of programs, and the fact that the characteristic intracellular signaling system is paired with different PRRs, suggests that there is a great plasticity of the DC system and the T cell immune response. The immune response of DCs to different adaptive fungi is also affected by cooperation and specialization between DC subgroups. Inflammatory DCs induce Th17 and Th2 cell responses via the TLR adaptor MYD88, while tolerogenic DCs promote differentiation into regulatory T (Treg) and Th1 cell responses via the TLR adaptor TRAM.
cells via TLR Adaptor Molecule 1 (TICAM). In addition, signal transducer and activator of transcription 3 (STAT3) affects the balance between canonical and non-canonical activation of NF-κB, by inducing expressing an enzyme called indoleamine 2,3-dioxygenase (IDO), which plays a key role in the plasticity of DCs and in the formation of functional specialization. Various signaling systems of functionally independent DCs ultimately control the balance between CD4⁺ T cells and Treg cells and determine whether fungi cause infection or maintain commensalism.

DCs direct a specific T cell immune response through a variety of factors, including the nature of the fungal pathogen, the site of infection, and the susceptibility of the host. For example, the DC subset present in the skin (skin-resident T cell) triggers a characteristic T-helper immune response. In previous studies of *C. albicans* infection models, langerhans cells are necessary and sufficient to induce differentiation into Th17 cells, but dermal DCs expressing Langerin are required to induce differentiation into Th1 cells and cytotoxic T cells, which has been shown to interfere with the Th17 response.

Morphological characteristics of fungi also affect the differentiation of T helper cells. The yeast forms of *C. albicans* can induce a Th17 response by langerhans cells, which results in IL-6 production through interacting with dectin-1. In contrast, the filamentous form has a morphological characteristic that prevents interaction with dectin-1, causing a Th1 response. In addition, IL-23 production is increased from dermal DCs by stimulation of nociceptive sensory nerves to protect against skin infections of *C. albicans*, which promotes IL-17 production by dermal γδ T cells and subsequent antifungal action of neutrophils.

**LYMPHOCYTES**

There are three main T cell subtypes involved in fungal infection of humans: Th1, Th2, and Th17 cells. Th1 cells are highly associated with protective immunity to fungal species. As with any T cell response, differentiation into Th1 cells is determined by the DC’s response to the combination of TLR and CLR signals induced by the fungal infection. By indirectly assisting the production of opsonizing antibodies and the production of IFNγ, a representative cytokine, Th1 cells play a fundamental and essential role in the activation of phagocytes in infected areas. Thus, the inability of T cells to properly transmit activation signals to phagocytes in infected areas can lead to uncontrollable infections or prevent proper treatment efficacy by antifungal agents. The adaptive immune response to commensal fungi, called delayed-type hypersensitivity, acts as a defense against fungi in the host with normal immune function, and there is a relatively favorable prognosis when this reaction occurs. For example, the antibodies to the cryptococcal antigen is found in immunocompetent host in high prevalence, which indicates the Th1 immune response occurs after the initial infection, thereby causing the growth of the fungi and acquired immunity against the fungus.

Th2 cells are differentiated from naive T cells in their production of IL-4 and IL-13, which buffer the fungal defense effect by the Th1 cell immune response by secreting IL-5 and lead to the activation of macrophages in the other direction than Th1 cell response. As opposed to Th1 cells, immune responses by Th2 cells are involved in fungal infection, fungal allergic reactions, and recurrence of fungal infections. In atopic dermatitis patients and newborns, delayed hypersensitivity reaction by Th1 cell responses is suppressed, which is associated with increased levels of IgE, IgA, and IgG against fungi. In addition, ABPA is known to occur when Th2 cell reactivity is increased in cystic fibrosis patients. However, some studies have shown that humoral immune responses by Th2 cells play a protective role against fungi, as do Th1 cells, and together with these responses resolve the excess fungal levels inside macrophages and affects gene expression in fungi.

Th17 cells play a major immune response in the mucosal fungal infection. IL-17, the most important cytokine in mucosal fungal infections, is produced by Th17 cells and γδT cells to protect mucosal and skin from *Candida* infections. Th17 cells are also activated by the signaling systems of SYK-CARD9, MYD88, and mannose receptors, which promote the activation of neutrophils and defensin production in mucosa. This promotes Th1 cell immune responses and suppresses Th2 cell immune responses against fungal infections in various parts of the body. Indeed, previous experimental studies have shown that in mucosal candidiasis infection, Th17 cells assist the response of Th1 cells, and that not only Th1 but also Th17 cell responses are defective in patients with chronic mucocutaneous candidiasis. However, there are still many conflicting opinions on whether IL-17 and IL-17 receptor interactions are essential for the activation of Th17 cells. This indicates that the extent of infection, the site of infection, and the microenvironment of the fungal infection site determine whether the Th17 cell immune response is activated. On the other hand, in *Candida* infection, the Th17 immune response is inhibited by *Candida* species, and if the Th17 immune response is not inhibited properly, complete resolution of the fungal infection is not achieved and chronic inflammation occurs. A mechanism that connects inflammation and chronic fungal disease could be excessive Th17...
immune response, which impedes proper fungal defense and ensures that fungi remain at the site of infection. Taken together, the Th17 immune response is thought to be associated with chronic fungal disease, in which continued fungal secretion of antigens disrupts the host’s immune system41. In addition to Th1, Th2 and Th17 cells, Treg cells play a major role in the defense against fungal infections. In the course of fungal infection, the ultimate goal of the immune response is to completely eliminate pathogenic fungi while minimizing damage to the host tissue by the immune response. Many clinical studies of fungal infection have shown an inverse relationship between IFNγ and IL-10 production. High levels of IL-10 in patients with chronic Candida infection inhibit IFNγ production, and high levels of IL-10 have been observed in severe fungal infections, such as aspergillosis in patients with neutropenia, and in various endemic mycoses. Those studies indicate that there is a link between high levels of IL-10 and susceptibility to fungal infections42. Despite these facts, IL-10 production is thought to be a consequence, rather than a cause, of infection. This implies that IL-10 is the product of a homeostatic immune response to control the inflammatory response in cases of chronic fungal infections that cause poorly controlled, persistent inflammation42. The anti-inflammatory activity of Treg cells in fungal infections has been demonstrated in human and mouse experiments. In studies of fungal infections, inflammatory responses and immune tolerance are shown to be regulated with close cooperation between different subgroups of Treg cells. However, the immune response of Treg cells has the potential to limit the effects of protective immune responses, not only by reducing host damage, but also by leading to chronic fungal infection and eventually to an immunosuppressed state43. Thus, by regulating the magnitude and quality of innate and adaptive immune responses, Treg cells induce a variety of immune responses, ranging from apparent immunosuppressive conditions to protective tolerance, which ensures the survival of the host without completely eliminating pathogenic fungi. This indicates that the host immune response and fungi interact with each other to determine whether the fungi are present as normal biota or as a pathogen.

In addition to the above-mentioned types of T cells, attention has recently focused on the role of tissue-resident memory T cells (TRM), which is another important subgroup of T cells discovered in the early 2000s. In a physiological environment, TRM cells live in epidermal barrier tissue and are involved in interactions between the external environment and the host. TRM cells induce a rapid immune response against antigens that penetrate the epidermal barrier independently of the recruitment of T cells in the blood44,45, and activate the rapid protective immune system as one of the representative features of adaptive immune system46. This is because TRM cells form a specific population against certain pathogens which is previously encountered in the barrier tissue, and thus have different T cell receptor repertoire depending on the type of epidermal barrier tissue46.

In particular, CD4+ TRM cells in papillary dermis contain populations specific for viruses, fungi, and protozoa. It is known to include a population that is specific to C. albicans, which has similar immunophenotype as Th17 cells, as well as HSV and Leishmania spp47,49. In addition, CD4+ TRM cells, like CD8+ TRM cells, face the challenge of pathogens, promote rapid activation of the immune system, and serve to quickly remove pathogens from the skin49. In support of this fact, local skin infections caused by external pathogens resulted in a sharp increase in the number of CD8+ TRM cells, as well as CD4+ TRM cells, in infected areas, whereas a decrease in the number of TRM cells resulted in unaffected sites, thus providing global defense49.

For example, a recent study using a mice model showed that long-lived populations of Th17 CD4+ TRM cells increase after cutaneous C. albicans infection, which are responsible for the defense of local infection. On the other hand, migratory T cells do not reside in the skin, and do not share the Th17 immunophenotype, suggesting that there is a clear role-sharing between TRM and migratory T cells49.

Natural killer (NK) cells represent the prototype of lymphocytes in innate immunity. NK cells, together with Th1 cells, are classified as group 1 T cells, and their commonality is that they secrete IFNγ as a major cytokine. NK cells kill various pathogenic fungi directly by secreting perforin. For example, the action of perforin on C. neoformans requires PI3K-dependent ERK1/2 signaling in NK cells50. NK cells secrete GM-SCF and IFNγ, which are involved in promotion of neutrophil action51. Recently, studies have been conducted on the mechanism by which NK cells recognize fungi. NKp30 receptors are involved in the recognition of Candida and Cryptococcus and kill them by releasing perforin52. In addition, NKP46 was involved in the recognition and killing of Candida glabrata53, and CD56 was found to be involved in NK cell activation and inflammatory cytokine secretion by Aspergillus54. Recently, studies are underway to attempt to prophylaxis or treat invasive fungal infections using fungal recognition mechanism of NK cells.

**THERAPEUTIC IMPLICATION OF HOST-FUNGAL INTERACTION**

Fungi are organisms composed of eukaryotes, unlike bac-
teria and viruses, so they are very similar in structure and function to mammalian cells. For this reason, the development of antifungal drugs is complicated and the cost is high enough to hamper the development antifungal therapeutics. However, with an increasing understanding of fungal and host interactions, immunological therapeutic approaches are currently under investigation. The first attempted treatment focused on recombinant cytokines. For instance, a method has been employed, with varying degrees of success, to synthesize GM-CSF or G-CSF and administer it into the body to increase the population of myeloid lymphocytes and to promote antifungal action of neutrophils. Treatment with IFN-γ was developed to promote the phagocytic function of macrophages and to restore a defective Th1 cell immune response, and these have been introduced as an adjuvant therapy to chronic granulomatous disease and cryptococcal meningitis.

Cellular immunotherapy is recognized as a new approach to treating fungal infections. With injection of anti-Aspergillus T cells, the survival rate of hematopoietic stem cell transplant patients is improved. In addition, genetically engineered T cells expressing antigen receptors with specificities similar to those for dectin-1 are known to be effective in the treatment of aspergillosis in animal models. Innate immune cell therapy is also in the spotlight as an effective alternative therapy. In animal models, dendritic cells treated with Aspergillus conidia or inoculated with RNA of conidia have been shown to activate antigen-specific Th1 cell immune responses. Most of the above-described treatments using immune cells are in the preclinical phase. However, Aspergillus-specific T cells were used to treat hematopoietic stem cell transplantation patients, which resulted in higher T cell responses and elevated levels of IFN-γ and IL-10.

Due to the difficulty of developing antifungal agents, there is also a effort underway to prevent invasive fungal infection by inoculating immunosuppressed patients with vaccines against fungi. However, immunosuppressed patients may fail to produce an appropriate immune response to the vaccine due to lowered function of the immune system, and there is a question about the efficacy and safety of this approach. To overcome this problem, vaccines are being developed that engage elements of the immune system that are relatively intact. Yet, there is no fungal vaccine available in the clinical field. However, recent studies using fungal cell wall molecules have been published. For example, a vaccine consisting of laminarin and diphertheria toxoid, centered on β-glucan, led to acquired immunity against Candida or Aspergillius in animal experiments. In another animal experiment, it was shown that a subcutaneous vaccine composed of glucan particles extracted from Cryptococcus induce a robust Th1 and Th17 immune response to prevent cryptococcosis. Most recently, a phase I study of a vaccine composed of recombinant Candida-derived proteins showed acquired immunity against Candida and is the most anticipated fungal vaccine for humans.

CONCLUSIONS AND FUTURE PERSPECTIVES

As the number of immunosuppressed patients increases, not only the mucocutaneous fungal infection, but also the incidence and prevalence of invasive fungal infections are increasing. However, the pace of development of therapeutic agents for fungal infections is not keeping up with the increasing prevalence. Over the last few decades, in-depth research on innate and acquired immune responses to fungi has been undertaken, and attempts have been made to establish various treatment techniques using the immune response, as described above.

The enhancement of antifungal effects through the host natural immune response is emerging as a treatment option for future fungal infections. There are questions about the safety and effectiveness of the drugs under investigation, but clinical studies are underway on immunosuppressive patients. An alternative approach is to modulate the key regulators of the immune response. For example, immune responses to fungi, whether innate or acquired, are caused by major fungal recognition systems, such as TLRs, MYD88, and microRNAs. Modulations to these molecules might be able to increase antifungal resistance.

In summary, the above-mentioned immune responses and related studies provide an optimistic prospect for future anti-fungal immunotherapy. Recent research on fungal immunity by fungal immunologists has enhanced the understanding of various aspects of the regulation of antifungal immune responses from the organism level to the molecular level, along with innate immune recognition, inflammatory responses, and adaptive immunity.

The results of ongoing studies will reveal more diverse fungal receptors and immune responses in the future, and animal model experiments and human genetic studies will also be integrated into each other, broadening our understanding of fungal infection. Studies on how fungal composition, diversity, and metabolism affect immune homeostasis and inflammatory diseases are ongoing, and these studies will give us deeper understanding not only about fungal infections, but also inflammatory diseases that involve immune responses against fungi, including atopic dermatitis, Crohn’s disease, and ulcerative colitis.
ACKNOWLEDGEMENT

The authors declare that there is no acknowledgement.

CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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