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Immunity to Fungal Infections: Review Article

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Abstract: Most fungi to which we are regularly exposed through the air or because they are part of our normal microbiota do not usually cause disease in immunocompetent individuals. However, some fungi rarely become pathogenic if host defenses breached or compromised with symptoms ranging from mild superficial infections to severe systemic diseases that are associated with a high degree of morbidity and mortality. Protective immunity against fungal pathogens achieved by the integration of two distinct arms of the immune system, the innate and adaptive responses. Innate and adaptive immune responses intimately linked and controlled by sets of molecules and receptors that act to generate the most effective form of immunity for protection against fungal pathogens. The way to respond primarily determined by interactions between pathogens and cells of the immune system of the host, but the actions of T cells will feedback into this dynamic equilibrium to regulate the balance between tolerogenic and inflammatory responses. However, the host responses against different fungal infections are as diverse and distinct as the different fungal diseases themselves. Clinical and basic research during the last decade has brought exciting new insights into the pathogenesis of fungi and revealed important molecular and cellular players in host-fungal interactions and host defense. However, commensal and normally non-pathogenic environmental fungi can cause life-threatening infections in immunocompromised individuals. Therefore, the objective of this review is to insight the mammalian immune responses against fungi infections.

Key words: Fungi · Infection · Immune Responses

INTRODUCTION

Fungi tend to be either unicellular (yeast-like) spherical, such as Candida species, or multicellular and filamentous, like Aspergillus. Some fungi live commensally on the topologically external surfaces of the body, while others live most of their lives in the soil as a mass (mycelium) of thread-like processes (hyphae). Dimorphic fungi adopt a yeast-like form at one stage in their life cycle and a hyphal form at another stage. Fungal cells have a cell wall like bacteria but also cell membrane-like mammalian cells [1]. However, the fungal cell wall lacks the peptidoglycans, teichoic acids and lipopolysaccharide components of the bacterial wall and the main component of the fungal cell membrane is ergosterol rather than the cholesterol found in mammalian cell membranes.

The correlation between the incidence of fungal infection and clinical fungal-related disease has risen dramatically in the last two decades, which would suggest an increasing pool of susceptible, immunocompromised individuals [2]. However, immunocompromised individuals can suffer from acute infections that sometimes go on to become persistent. Invasion of blood vessels by a growing fungus chokes off the blood supply to the host tissue, damaging or killing it [2]. The exceptions are the dermatophytes, filamentous fungi that infect the skin, hair and nails [2]. These organisms, which include species of Epidermophyton, Microsporum and Trichophyton, cannot penetrate the living, cellular tissue of a healthy host and so are restricted to parts of the body that lack living cells, such as the keratinized outer layer of skin. Important fungal pathogens are *Blastomyces dermatitidis, Histoplasma capsulatum, Candida species, Aspergillus species, Cryptococcus neoformans and Pneumocystis carinii* [1]. Blastomycosis occurs when conidia of the yeast-like fungus *B. dermatitidis* inhaled through the aerosol. This organism replicates extracellularly to cause a pulmonary infection that spreads through the blood to the skin, bones and male urogenital tract, but not the gut. In contrast, *H. capsulatum* is an intracellularly

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replicating yeast-like fungus that causes histoplasmosis. Inhaled microconidia develop into Histoplasma that take up residence preferentially in local respiratory macrophages [2].

A progressive pulmonary disease resembling tuberculosis can spread to the secondary lymphoid organs, mucosae, gut and adrenal glands. Candida species such as *C. albicans* and *C. tropicalis* lurk in the normal flora at the mucosae (but not in the skin) and cause disease only if these mucosal barriers are broken or compromised [1]. A deficiency of neutrophils in the host (neutropenia) leaves the host especially vulnerable to candidiasis. Such Candida infections are usually superficial in nature (such as vaginitis and cystitis) but can progress to infections of the eye, skin and brain [3].

Inhalation of spores of Aspergillus species causes a variety of diseases and can induce allergic responses. Conidia of three species, *A. fumigatus*, *A. flavus* and *A. niger*, are particularly pathogenic for humans, causing invasive pulmonary infections that can be fatal if allowed to entrench [2, 3]. Aspergillus species also produce mycotoxins that damage hepatocytes, macrophages and CTLs. *C. neoformans* is a yeast-like fungus often present in pigeon droppings. When a host inhales unencapsulated spores of Cryptococcus, the parasite enters the lung and synthesizes a protective capsule that inhibits phagocytosis. If the infection becomes established, the result may be cryptococcosis, a syndrome of pulmonary infection accompanied by meningitis [3, 4].

The mechanistic aspects of immune responses (innate or adaptive) vary depending on the fungal species encountered [5] the target organism and the site of infection. Survival within phagocytes from where fungi can later disperse throughout their host is one particular elegant strategy [1, 6]. To maintain a stable host-fungi interaction, the immune response segregated into an innate first-line defense, which latterly strengthened by a second-tier, adaptive response.

Decades ago, fungal immunology research largely focused on defining the molecular interactions between pathogen-associated molecular patterns (PAMPs) and their cognate pattern recognition receptors (PRRs) and was beginning to understand how immune cells could interact with fungi as some of the molecules involved in fungal recognition were discovered. Dendritic cells (DCs) found to act at different levels in the immune response against fungi [4]. They are not only able to mount an immediate innate immune response by producing inflammatory mediators; they could also influence subsequent adaptive immune responses, including tolerance to commensal organisms. In fact, fungi are associated with an extensive variety of diseases in mammals, ranging from cutaneous lesions and acute self-limiting pulmonary manifestations in immunocompetent individuals to inflammatory diseases and severe life-threating infections in immunocompromised patients [7]. Therefore, the objective of this review is to insight the mammalian immune responses against fungi infections.

Evasion Strategies: Invasive fungal infections caused by Candida species or Aspergillus fumigatus and other filamentous moulds are devastating in immune compromised patients [7]. Many fungi adopt different forms at different stages in their life cycles, making immune defense necessarily more complex. The structure of the fungal cell wall and membrane means that fungi generally can avoid complement-mediated lysis. In addition, many fungi have developed strategies to offset the effector actions of neutrophils, macrophages, CTLs and NK cells [8]. If fungal pathogens overcome the initial epithelial barrier and (start to) invade the host tissue, they may get in contact with immune cells in the tissue and/or depending on the route and degree of invasion in the circulation [8].

Table: Fungal mechanisms to evade the host immune

Immune system element thwarted	Fungal mechanisms
PPR recognition	Have no LPS or peptide glycan in cell wall
Specificity of T and B cells	Have a multi stage life cycle
Complement	Block access to the cell membrane via cell wall
Phagocytosis	Block phagocytosis via polysaccharide capsule
T and B cell function	Induce immune deviation to Th2
Block NF-KB activation	Increase NO production to decrease lymphocyte proliferation
	Block phagocytosis
	Inhibit neutrophils migration
	Decrease IL-12 and B7 expression by monocytes
	Activate regulatory T- cell via polysaccharide capsule component
	Produce melanin to decrease Th1 and Th2 responses
	Block TNF production

Innate Immunity: Any invader that breaches the physical barrier of skin or mucosa greeted by the innate immune system; second line of defense. Immunologists refer this system asinnate, which is a defense mechanism that all mammalians naturally seem to have. The innate immune system has evolved to sense conserved microbial structures, so-called pathogen- associated molecular patterns (PAMPs) via germline-encoded PRRs. Ligand binding by PRRs induces the activation of signaling cascades inside the cell that leads to gene expression in the nucleus. The production of cytokines, chemokines, complement units and antimicrobial factors by innate immune cells results in the activation and recruitment of effector cells to the site of infection and in the elimination of pathogens, respectively [7]. Innate immune cells including neutrophils, monocytes/macrophages and dendritic cells rapidly detect the presence of fungi and induce an antimicrobial response. Neutrophils, macrophages and DCs are all critical to the antifungal response [9-11]. The release of inflammatory cytokines, as well as reactive oxygen intermediates and antimicrobial peptides, can then clear the fungi in target organs [6]. Fungal recognition is mediated by a variety of surface-bound and soluble pattern recognition receptors (PRRs) recognizing fungal cell wall components and nucleic acids including Toll like receptors (TLRs), C-type lectins (Dectin-1, Dectin-2, Mincle, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, mannose-binding lectin 2 (MBL2) and long pentraxin 3 (PTX3)) [12-22].

PRRs in Fungal Recognition: PRRs are the first line of defence in antifungal immunity. Upon recognition of surface-expressed PAMPs such as β-glucan and α-mannan, CLRs initiate inflammatory innate responses that in turn polarize a Th17 adaptive immune response, which is generally beneficial to fungal control and clearance [23]. The primary fungal PAMPs recognized by the innate immune system of the host are components of the cell wall. The fungal cell wall is composed of skeletal and matrix components, which resemble mesh and mortar in concrete buildings [23]. The skeletal structures at the base of the cell wall consist of chitin, which is a β-(1, 4)-linked polymer of N-acetylglucosamine and β-1, 3- and β-1, 6-glucans that are stabilized by intermolecular hydrogen bonds. The fungal cell wall matrix is composed of mannoproteins, namely, heavily glycosylated proteins with mannose-containing polysaccharides (mannans). These mannoproteins attached to β-1, 3-glucans or chitin by a linker structure. Important differences in cell wall composition and conformation exist between different fungal species [24]. B-1, 3-glucan, which is usually hidden by other carbohydrates, is one of the most potent fungal PAMPs. The sequestration of β-1, 3-glucan by less immune-stimulatory cell wall components evolved as a potent immune evasion strategy in many pathogenic fungi [25-29].

C-Type Lectin Receptors (CLR): The main PRRs involved in fungal recognition belong to the family of myeloid C-type lectin receptors (CLRs) that are highly expressed by dendritic cells (DCs), neutrophils and macrophages. CLRs are classified by the presence of one or several C-type lectin-like domains (CTLDs), many of which bind to carbohydrates such as those in the fungal cell wall [30]. The family of CLRs encompasses soluble molecules such as the mannose-binding protein (MBP) or surfactant protein D that activate the complement cascade, endocytic receptors that internalize their ligands such as the mannose receptor (MR) and signaling receptors that act as bona fide PRRs to initiate innate and adaptive immunity, while others have immunomodulatory activities [30-32]. The prototypic signaling CLR is dectin-1. It binds to β-(1, 3)-glucans in the fungal cell wall. Dectin-1 contains an ITAM-like motif, also called hemITAM, in its cytoplasmic domain [33-36]. Selective signaling via dectin-1 results in the induction of high levels of TNF, IL-6 and IL-23, but little IL-12 and is thus qualitatively distinct from TLR- mediated signaling [37]. Dectin-1 signaling can also engage phospholipase Cγ2 (PLCγ2)-dependent nuclear factor of activated T cell (NFAT) activation, resulting in the production of IL-2 and IL-10 [38]. Moreover, dectin-1 signaling leads to the induction of IL-1β via the activation of caspase-1, which mediates cleavage of pro- IL- 1β into mature IL-1β [39, 40]. Dectin-1 signaling was implicated in the response to many pathogenic fungi and its host-protective role was demonstrated in mouse models with *C. albicans* [41], *A. fumigatus* [42-44] and Pneumocystis [45-47]. Dectin-2 and mincle are two additional Syk-coupled CLRs that recognize fungal α-mannan structures [48]. Unlike dectin-1, they lack the hemiTAM motif in their cytoplasmic tail. Instead, they assemble with FcRγ, an ITAM-containing adaptor for signaling [49]. In addition, dectin-2 and mincle have recently been shown to associate with MCL (also called dectin-3) for enhanced ligand binding [50-53].

Mannose-Binding Lectin: The mannose receptor (MR) is a PRR primarily present on the surface of macrophages and dendritic cells and thus there are 2 MLB isomers in

the mouse; MBL1 and MBL2, while humans only have MBL2. Mannose-binding lectin (MBL) is a soluble lectin belonging to the collectin family and consists of a CRD that is attached to a collagen region via α-helical coil domain [4]. It is produced by the liver and secreted into the blood, where, after binding to microbial carbohydrate surfaces, it can activate the lectin pathway of the complement cascade, enhancing the phagocytosis of microorganisms and modulating inflammatory responses [54-57].

Toll-Like Receptors (TLRs): Ligands and Cellular Responses Intensive research in this area in the last few years has identified several fungal PAMPs recognized by TLRs; however, the primary structures of the fungal ligands have not yet been fully resolved. Some studies have suggested that mannosylated structures derived from Candida, Cryptococcus and Scedosporium can directly interact with specific TLRs, including TLR1, TLR2, TLR4 and TLR6, triggering inflammatory responses [58]. Besides CLRs, certain TLRs are also implicated in fungal recognition, including TLR2, TLR4, TLR7 and TLR9. The family of TLRs is the best-characterized family of PRRs. TLRs is membrane-bound receptors composed of leucine-rich repeats for ligand recognition and a conserved Toll/IL-1R-domain in the cytoplasmic domain. The latter mediates signaling via MyD88 (and/or TRIF in some cases) to couple to NF-êB activation (or IRF activation in case of TRIF-mediated signaling) and the induction of pro-inflammatory target genes. TLR2 and TLR4 are expressed at the cell surface, where they recognize fungal phospholipomannan and O-mannan structures, respectively [59, 60]. The endosomal TLRs TLR7 and TLR9 have also been implicated in fungal recognition, namely, in sensing of nucleic acids and induction of IL-12 and/or type I interferons in response to C. neoformans, A. fumigatus and C. albicans [61]. Moreover, TLRs contribute to antifungal immunity by modulating the response induced by other PRRs [62].

Inflammasome Activation by Fungal Pathogens: Besides other cytokines and chemokines, many fungal pathogens induce the production of IL-1β. Biosynthesis of bioactive IL-1β requires two independent signals. The first regulates transcription and translation of pro-IL-1β and the second induces the proteolytic cleavage of pro-IL-1β into the active IL-1β [63]. Fungi trigger both steps of IL-1β synthesis. Importantly they induce proteolytic cleavage by caspase-1 via the assembly of Inflammasome with distinct subunit composition. *C. albicans* stimulates the assembly of a canonical inflammasome composed of the NOD-like receptor NLRP3 and ASC to provide a scaffold for caspase-1 activation. The importance of the NLRP3 inflammasome in antifungal immunity was demonstrated in NLRP3-deficient mice, which display an increased susceptibility to systemic and superficial candidiasis [64]. Activation of the NLRP3 inflammasome by C. albicans depends on yeast-to-hyphal transition, which may reflect the dependence on β-glucan exposure at the fungal cell surface [65-67] and the secretion of secreted aspartyl proteinase (SAP) 2 and SAP6 [68]. In addition, IL-1β can be processed by neutrophil-derived proteinase-3 [68] and by C. albicans- derived aspartyl proteases [69-70]. IL-1β is closely related to IL-1α, which signals through the same receptor. IL-1α also depends on processing for becoming bioactive, but it is not a substrate of caspase- 1 [63]. However, the NLRP3 inflammasome and caspase-1 is implicated indirectly in the secretion of IL-1α [71] by catalysing the processing of IL-1β, which was proposed to bind to intracellular IL-1a and to serve as a shuttle for IL-1α release [72]. Cell surface-bound IL-1α can be cleaved by calpain I and II at the cell membrane and secreted pro-IL-1α can be processed by extracellular proteases [73]. IL-1α, which is constitutively expressed in some cells such as keratinocytes, is also released upon cytolytic cell death. In addition that caspase-1 has a critical function in the processing of IL-1β; caspase- 1 activation can also induce pyroptosis, an inflammatory form of programmed cell death [74]. Pyroptosis results in DNA fragmentation and chromatin condensation. However, in contrast to apoptosis, which is a non-lytic mechanism, pyroptosis involves cell swelling, pore-mediated lysis and release of intracellular components, which usually are not exposed to the extracellular compartment, including cytoplasmic cytokines such as IL-1α and IL-1β ATP, HMGB1 and nucleic acids. Due to their inflammatory properties when released in the extracellular environment, these molecules were also called damage-associated molecular patterns (DAMPs) [75] that for some of them, cellular receptors were identified that promote inflammatory responses.

Roles of Defensins in Fungal Innate Immunity: They are cationic, microbicide peptides active against many Gram-negative and Gram-positive bacteria, fungi and enveloped viruses composed of three pairs of intermolecular disulphide bonds which are classified in to alpha, beta and theta [76]. Defensin exist in the mammalian white blood cells such as macrophages, granulocytes, NK cells and only beta defensins are located in the epithelial cell

[77]. They interact with the membrane of invading fungi microbes that are negative due to lipopolysaccharide and acid encapsulated by the cell membrane that the peptides have higher affinity to the binding site compared to Ca2+ and Mg2+ ions. Therefore, the peptides exchange place with those ions, thus affecting the stability of the membrane by passing across the membrane due to changes in the electric potential and aggregate in to dimers [78]. Finally pore complex will be created as a result of breaking the hydrogen bonds between the amino acids in the terminal end of the strands connecting defensins monomers causing membrane depolarization and cell lysis [79]. Defensins not only have the ability to strengthen the innate immune system but can also enhance the adaptive immune system by chemo taxis of monocytes, T-lymphocytes, dendritic cells and mast cells to the infection site that improves the capacity of macrophage phagocytosis [80].

Adaptive Antifungal Mechanisms

Humoral Defense: Other than the secretory IgA that defends the mucosae, antibodies are thought to contribute in only a limited way to defense against fungi. Antibody-mediated opsonisation may promote phagocytosis and thus contribute to the presentation of fungal antigens that activates Th1 cells [81]. Antibody-mediated immunity is generally thought to play a minor role for natural protection from fungal infections. Although antibodies are generated in response to commensal or environmental fungi and can be detected in the serum, their specificities are not usually protective to the host [81]. More recently, it has become clear that depending on the specificity and isotype, certain antibodies can modulate the course of fungal infections and thereby benefit or harm the host [82]. Antibody- mediated immunity is now viewed as a promising therapeutic approach against fungal infections and several protective antibodies to fungi have now been developed [82, 83]. Anti-cell wall mannoprotein antibodies can block adhesion of *C. albicans* [84, 85]. In contrast, antibodies directed against *C. neoformans* glucuronoxylomannan (GXM) protect via enhancing cellular immunity including phagocytosis and antibody-mediated cellular cytotoxicity [82, 83, 86].

Complement: While fungal cells can activate the complement cascade, they are generally resistant to complement-mediated lysis. However, they are subject to phagocytosis when opsonised by complement products. Fungi also express analogues of complement receptors that facilitate adherence to host cells and may also promote phagocytosis. Pro-inflammatory cytokines induced by products of complement activation also contribute to anti-fungal defense [8]. Complement activation plays a central role during bloodstream infections [87]. Fungal pathogens rapidly activate the complement via multiple pathways including the alternative complement pathway [88]. Rapid activation of the C3 convertase leads to C. albicans opsonization by C3b binding to β-(1, 6)-glucan [89], which facilitates phagocytosis by neutrophils in a CR3-dependent manner [90]. Importantly, complement activation also results in the induction of anaphylatoxins C3a and C5a with important immune stimulatory activities, in particular on neutrophils and monocytes, which are abundant in the circulation and they can act as chemo attractants for these cells in tissues [90].

Cell Mediated Immunity: After ligand binding, dectin-1 can induce several cellular responses, including phagocytosis, respiratory burst and chemokine and cytokine production [1]. Cell-mediated innate immunity is the primary means by which fungi infections are controlled. Neutrophils and macrophages both carry out vigorous phagocytosis and produce powerful anti-fungal defensins. These defensins induce an osmotic imbalance in pathogens such as Candida and Cryptococcus that kills them. Neutrophils and macrophages also secrete copious quantities of IL-1, IL-12 and TNF. IL-12 stimulation activates NK cells that contribute to fungal cell killing via cytokine secretion (rather than natural cytotoxicity) [2]. IFN produced first by activated NK cells and later by activated Th1 cells also hyper activates macrophages, which can initiate granuloma formation. Interestingly, a fungus present in its unicellular yeast-like form tends to provoke a protective Th1 response, whereas its hyphal form tends to induce a non-protective Th2 response. There is some evidence that either distinct subsets of DCs, or distinct receptors on DCs, respond to the two different fungal morphologies [1]. These DCs then proceed with phagocytosis and antigen processing and presentation and influencing Th1/Th2 differentiation in the direction best suited to eliminate the particular form of the fungus present. The Th1 response induced by exposure to airborne fungal spores, or invasion by skin or mucosal fungal flora that have a yeast-like form, is mediated by cells producing copious quantities of IL-2 and IFN [2]. Th2 responses are comparatively rare during infections with yeast-like fungi.

Antigenic Specificity of Antifungal CD4+ T Cells: T cells carry antigen receptors that recognize antigenic peptides presented in the context of MHC class II molecules on antigen-presenting cells. Each T cell carries antigen receptors of a different specificity and thereby the overall T cell population displays thereby a nearly unlimited diversity of different antigenic specificities [91]. The T cell repertoire is generated through somatic recombination of germline-encoded gene segments. Antigen recognition by CD4+ T cells is limited to peptide antigens that are presented in the context of MHC class II molecules [91]. To become fully functional, naïve T cells require stimulation by cognate antigen-MHC-II complexes that are presented by antigen-presenting cells to induce their activation and clonal expansion, which precedes their differentiation into effector T cells [86, 90]. Only a few fungal T cell epitopes were identified to date. These include the C. albicans-derived pALS3236-253 and pADH126-140 epitopes, which are functionally conserved in diverse non-albicans species of Candida [91-95].

Immunization and Treatment Against Fungal Infections: Currently, there are no proven fungal vaccines available in clinical practice due to several challenges. Among several challenges in the development of working fungal vaccines, most of immune-compromised individuals (vulnerable groups) are unable to mount effective and strong immune response [96]. Additionally, the complexity of the eukaryotic fungal cells with a double layer of protection with inner layer of plasma membrane and outer layer of cell wall similar as mammalian cells caused major setback in the development of any vaccine or therapeutic drugs [97]. However, there are some exciting studies in recent years using fungal components of the cell wall and plasma membrane make theoretically possible to develop a universal vaccine [98]. For instance, a glycoconjugate vaccine composed of β-glucan, laminarin and the diphtheria toxoid can mount a strong immune response and confer protection against infection with Candida or Aspergillus in mice [99]. Preclinical studies of vaccines containing attenuated fungi have shown promising results. Forinstance, in2006, Pep1 was shown to be a cell wall dominant antigen that was protective in mice challenged with C. posadasii by applying immunoproteomic and bioinformatic tools, researchers then identified five peptides from Pep1 that were predicted to have high afnity to MHC-II and these peptides were able to induce IFN-γ by peptide-exposed lymphocytes [100]. In addition, subcutaneous vaccination with glucan particles containing Cryptococcus alkaline extracts canprotect mice against cryptococcosis due to the induction of robust Th1 and Th17 immunity [101]. In recent researches there are more than two subunit vaccines containing recombinant C. Albicans derived proteins found to confer immunogenicity in phase I clinical trials as the most promising candidates for a human vaccine [102]. Finally, due to the similarity between fungal and mammalian cells significantly complicating drug development and therapeutic approaches to combat fungal disease. However, advances in our understanding of the interplay between fungi and the host have led to the exploration and design of innovative immunotherapeutic approaches. Initial therapeutic strategies were only focused on the use of recombinant cytokines and Monoclonal antibodies have been recently evolved [97].

CONCLUSION

Different aspects of the innate and adaptive immune response to fungi have been intensely investigated. Furthermore, novel analytic techniques capable of detecting immune responses elicited by fungi have proven to be a promising area of scientific research. The pool of immunocompromised individuals is rapidly expanding, indicating that there would be an urgent need to develop novel and more potent antifungal drugs. This option would be especially relevant for immunocompromised hosts, although the safety and efficacy of novel antifungal remain questionable. A better understanding of the role of the host-pathogen interaction will lead to further development of potential novel antifungal therapies.

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