

Innate Immune Responses to Fungal Allergens

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Abstract

Purpose of Review In this review, we describe innate immunity to fungi and the ability of pattern recognition receptors (PRRs) to recognize fungal-associated molecular patterns (FAMPs) and danger-associated molecular patterns (DAMPs). **Recent Findings** Protective responses against fungal antigens can be divided into two parts: innate immunity and adaptive immunity. Detection of foreign substance by the innate immune system is mediated by a variety of genetically encoded receptors known as pattern recognition receptors (PRRs). These PRRs bind to PAMPs (pathogen-associated molecular patterns) and more specifically to fungal-associated molecular patterns or FAMPs on target microorganisms. They also bind to DAMPs (damage-associated molecular patterns) which are substances released due to tissue and cell damage. PRRs can be divided into several families including Toll-like receptors (TLRs), nucleotide-oligomerization domain (NOD)-like receptors (NLRs), and C-type lectin receptors. **Summary** Fungal PRRs can respond to internal and external components found in fungi. In addition, a number of fungal products, including some fungal allergens, seem to mimic or represent DAMPs. Collectively, activation of these fungal PRRs alerts the innate immune system to the presence of fungal exposure and can promote both innate and adaptive immune responses.

Keywords Innate immunity · Fungal immunity · Fungus

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Introduction

Fungi are eukaryotic organisms that can be multicellular or single-celled (e.g., yeasts). They contain many processes that are similar to humans in that they utilize oxygen, metabolize carbohydrates, and excrete carbon dioxide along with other volatile organic compounds. Fungal cell walls are composed of rigid carbohydrate polymers such as mannans (polymers of mannose), chitin (polymers of N-acetyl-D-glucosamine) and beta-glucans (polymers of D-glucose monomers linked by beta-glycosidic bonds), and various proteins [1•].

Protective responses against fungal antigens can be divided into two parts: innate immunity and adaptive immunity. Innate immunity refers to specific defense mechanisms that can recognize foreign materials and danger signals. Innate mechanisms include physical barriers such as skin and mucous membranes, chemical mediators in the blood and tissues, and a variety of cells specifically designed to attack foreign substances in the body which function as an early response surveillance system [2••].

The adaptive immune system refers to antigen-specific responses. These are of necessity more complex in that the antigen first must be processed and recognized as foreign. Following that initial recognition, an array of immune cells targeted at that antigen proliferates and cause it to be recognized by various inflammatory pathways and cells. In addition, the adaptive immune system has an anamnestic response to previous exposures to an antigen so that a more prompt and enhanced response can occur on re-exposure. Many fungal secretions are able to activate an adaptive immune response leading either to Th1 or Th2 responses.

Detection of foreign substance by the innate immune system is mediated by a variety of genetically encoded receptors known as pattern recognition receptors (PRRs) [3]. These receptors recognize and bind to evolutionary conserved

structures on microorganisms generally referred to as pathogen-associated molecular patterns (PAMPs) or fungal-associated molecular patterns (FAMPs) when referring to fungal substances such as those from *Candida albicans* [4, 5•]. Such patterns are commonly present in microbes and fungi but not in mammals. In addition to detecting invasions by microorganisms, PRRs can also detect patterns associated with tissue damage caused either by trauma or pathogens. The substances released due to tissue and cell damage are referred to as damage-associated molecular patterns or DAMPs [6–8].

Signals generated through PAMPs, DAMPs, and FAMPs induce expression of a variety of cytokines and chemokines, which, in turn modulate innate and adaptive-induced inflammatory responses [9]. The consequences of this depend on the type, location, extent, and duration of these responses. The cumulative effect of these responses along with the genetic background of the host determines the extent of innate response. In this review, we will describe the ability of PRRs to recognize fungal components and the fungal molecules that are recognized (FAMPs and DAMPs).

Innate Immune Mechanisms

Cell-associated PRRs have been divided into several families including Toll-like receptors (TLRs), nucleotide-oligomerization domain (NOD)-like receptors (NLRs), and C-type lectin receptors. In addition, protease-activated receptors (PARs) and sialic acid-binding proteins (sialic acid-binding immunoglobulin-like lectins (siglecs)) are often included in this group.

Fungal PRRs can respond to internal and external components found in fungi. In addition, a number of fungal products, including some fungal allergens, seem to mimic or represent DAMPs. Collectively, activation of these fungal PRRs alerts the innate immune system to the presence of fungal exposure and can promote both innate and adaptive immune responses.

Toll-like Receptors

Toll-like receptors (TLRs) are named after the fruit fly Toll receptors and are the best characterized receptors involved in early innate immune responses. Up to 15 TLRs have been identified in mammals, 12 of which are known to be present in humans [10, 11•]. TLRs generally form heterodimers that binds to PAMPs and FAMPs resulting in a signaling cascade (e.g., MYD88, TRAF, IRAK) that leads to activation of inflammatory components.

TLR1, TLR2, TLR3, TLR4, TLR6, and TLR9 have been implicated in the recognition of FAMPs. The result of activation depends on which TLR or combination of TLRs binds to a particular FAMP [12•].

TLR2 heterodimerizes with TLR1, TOLLIP (toll interacting protein), and others to recognize glycolipids from bacteria and beta-glucan on fungal conidia and hyphae. It acts in combination with MyD88 (myeloid differentiation primary response gene 88) and TIRAP (Toll interleukin receptor adapter protein) and is expressed on the surface of microglia, Schwann cells, monocytes, macrophages, dendritic cells, polymorphonuclear leukocytes, B cells, and T cells including Tregs. TLR2 interacts with phospholipo-mannans (PLMs) on *C. albicans*, unidentified ligands on *Aspergillus fumigatus*, and in combination with TLR1 and TLR6 with glucuronoxylomannan (GXM) from *Cryptococcus*.

TLR4 is activated upon ligation of O-linked mannans from *C. albicans* and *Cryptococcus neoformans*. Its ligands are present on *A. fumigatus* conidia but not hyphae [13]. TLR3 binds to double-stranded RNA from conidia and TLR9 responds to unmethylated CpG motifs from fungal DNA. TLR6 is involved in the recognition of *C. albicans*.

Activation of TLRs can lead to production of cytokines resulting in pro- and anti-inflammatory responses [14]. For example, activation of TLR6 leads to production of IL-23 and IL-17A which promotes TH17 responses. TLR2 leads to activation of oxidative pathways in polymorphonuclear cells with the release of gelatinases and inflammatory cytokines. On the other hand, TLR2 also seems to promote regulatory T (Treg) cells, thus limiting some antifungal adaptive immune responses [15]. TLR2 TLR4 (and cofactor CD14) activation by recognition of fungal conidia ligands seems to enhance TNF- α production and oxidative pathways. TLR activation also can lead to activation of nuclear factor kappa B (NF- κ B) and mitogen-activated protein kinases, which regulate proinflammatory gene transcription and expression.

To date, no genetic defects in TLRs have been found to be associated with an increased susceptibility to infection with fungi in humans. In particular, humans with a defect in MyD88 do not have an increased incidence of fungal infections [16]. On the other hand, immunocompromised hosts with certain polymorphisms associated with TLRs do seem to have an increased susceptibility to fungal diseases, suggesting that there may be unidentified factors that are involved in fungal innate immunity associated with TLRs [17].

Nucleotide-Oligomerization Domain (NOD) /NOD-like Receptors (NLRs)

The NLRs are a family of intracellular receptors that can recognize PAMPs and FAMPs. They can cooperate with Toll-like receptors to regulate inflammatory responses. There currently are 23 known human NLRs that can be divided into 2 groups: the NOD subfamily including NOD1 and NOD2, and the leucine-rich repeat and pyrin domain-containing protein (NLRP) subfamily.

Following recognition, the NLR subfamily (NLR1-12) forms a complex known as an inflammasome that can convert procaspase 1 to caspase 1 which converts TLR-induced pro-IL-1 β into active IL-1 β and activating IL-18. These cytokines have multiple proinflammatory effects. In addition, this inflammasome has an ability to stimulate the production of reactive oxygen species which also leads to activation of IL-1 β , which is important for inflammatory responses to PAMPs and FAMPs [18]. *A. fumigatus* hyphal fragments can induce NLRP3 inflammasome assembly in vitro. This, along with absent in melanoma 2 (AIM2), form a surveillance system that mediates innate responses against *A. fumigatus* infection in mice [19].

C-type Lectin Receptors (CLRs)

C-type lectin receptors are a large family of transmembrane receptors that recognize self and nonself ligands including carbohydrates lipids and proteins. They tend to recognize fungal glucans and mannans. CLRs are organized into 17 groups that mediate a variety of responses including phagocytosis, clearance of apoptotic cells and that modulate the innate and adaptive immune responses in addition to cell-cell adhesion [20]. Type I CLRs include DEC 205 and MMR (macrophage mannose receptor). Type II CLRs include Dectin-1, Dectin-2, Mincle (macrophage-inducible C-type lectin), DC-SIGN (dendritic cell-specific ICAM3-grabbing nonintegrin), and DNGR-1 (DC NK lectin group receptor-1). Soluble CLRs include MBL (mannose-binding lectin).

Dectin-1

Dectin-1 is a CLR that is specific for beta-glucans that are present in the cell walls of *Aspergillus*, *Candida*, and other fungal genera [21]. It has a CRD connected by a stalk to the transmembrane region, followed by a cytoplasmic tail containing an ITAM-like (immunoreceptor tyrosine-based activation motif) pattern. Dectin-1 binds to and promotes phagocytosis of cells that contain beta-1,3-glucans. It has been shown to collaborate with TLR2 to enhance the responses triggered by each receptor, and it can modulate cytokine expression by inducing NFAT through the Ca⁺⁺ – calcineurin-NFAT pathway. Dectin-1 triggers phagocytosis and activation of Src and Syk kinases leading to production of reactive oxygen species (ROS) activation of NF- κ B and secretion of proinflammatory and Th2 cytokines (IL-4 and IL-13). The ROS have a direct microbicidal role in the phagosome and can also increase IL-1 β secretion by activating the NLRP3 inflammasome [22].

Dectin-1-deficient mice have been found to be more susceptible to infection with *C. albicans* and *A. fumigatus* [23].

Dectin-1 deficiency in humans has been also shown to be associated with increased susceptibility to infection with *C. albicans* such as in chronic mucocutaneous candidiasis and recurrent vulvovaginal candidiasis [24].

Dectin-2

Dectin-2 is the primary PRR for fungal infections and the induction of Th17 adaptive immunity. It binds to mannose-type carbohydrates and to fucose and is the functional receptor for alpha-mannans. It belongs to the selective group of CLRs that link pathogen recognition to adaptive immunity. Its activation triggers ROS leading to NLRP3 inflammasome activation and processing of pro-IL-1 β . It also promotes Th2-mediated lung inflammation by inducing IL-33. Dectin-2 has been shown to recognize the fungi *C. albicans*, *A. fumigatus*, *Saccharomyces cerevisiae*, *C. neoformans*, *Histoplasma capsulatum*, *Trichophyton rubrum*, *Microsporum audouinii*, and *Malassezia* spp. Despite this recognition, susceptibility to fungi due to Dectin-2 deficiency has not (yet) been described in humans.

Mincle is part of the Dectin-2 family. It recognizes a variety of PAMPs including some FAMPs. Ligands for Mincle include fungal alpha-mannose. It also senses damaged cells by recognizing endogenous DAMPs [25•]. Mincle is most commonly associated with immunity to mycobacteria; however, it is also able to recognize fungal species including *Candida* and *Malassezia* [26, 27]. Currently, no human defects in Mincle have been associated with increased susceptibility to fungi.

Other CLRs

Dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) is a C-type lectin that binds to various carbohydrate structures including mannans, alpha-mannosyl, and alpha fucosyl residues. It is involved in recognition of viruses (HIV-1, HCV, dengue fever, CMV, Ebola) and other microbes including *Mycobacteria*, *Leishmania*, and *Candida*. Microbes interact with DC-SIGN to activate the Raf-1-acetylation-dependent signaling pathway and modulate TLR signaling. The response to each involves formation of a DC-SIGN signalosome which is necessary for the association of DC-SIGN with Raf-1. This complex leads to various inflammatory responses which depends on the ligand. For example, mannose recognition leads to increased expression of IL-10, IL-12, and IL-6 while stimulation by fucose leads decreased production of IL-6 and IL-12 [28]. Polymorphisms in DC-SIGN have been shown to be associated with an increased susceptibility to invasive pulmonary aspergillosis in humans [29].

Mannose-binding lectin (MBL) is a soluble C-type lectin that plays a crucial role in innate immunity against yeast by increasing complement activation and uptake by polymorphonuclear cells. It binds to mannose and/or N-acetylglucosamine residues on microorganisms leading to opsonization and activation of the lectin complement pathway. MBL is known to play a role in the development of Th17 responses to *C. albicans*; however, MR knockouts do not have an increased susceptibility to infection with *C. albicans* [30].

Protease-Activated Receptors (PARs)

There are four distinct PARs [31]. The best studied is PAR-2 which is overexpressed in the lungs and nasal epithelium of people who have asthma. Activation of PARs results in release of proinflammatory cytokines (IL-1, IL-25, IL-33, thymic stromal lymphopoietin, and GM-CSF). Activation can be endogenous or exogenous such as with proteases from allergens (Der p1, Bla g1, and fungal proteases). *Alternaria* has serine protease activity that can elicit release of IL-33 via a PAR-2 mechanism leading to airways inflammation in mice [32].

Several fungal allergens are proteases that can induce inflammatory responses by altering the permeability of epithelial layers and by the induction of proinflammatory cytokines through protease-activated receptors. They can elicit TH2 responses and also act as adjuvants potentiating responses to themselves and to other allergens. Examples of fungal proteases that also are important allergens include vacuolar serine proteases (Asp f 18, Pen c 2, Pen c 18, Rho m 2), alkaline serine proteases (Asp f 13, Pen b 13, Tri r 2, Cur l 1, Epi p 1, Pen c 1, Tri r 4), metalloproteinase (Asp f 5), and aspartic protease (Asp f 10) (<http://www.allergome.org>).

Sialic Acid-Binding Immunoglobulin-like Lectins (siglecs)

Siglecs are immunoglobulin-like type I transmembrane proteins that bind to sialic acids attached to the terminus of cell surface glycoconjugates. To date, 14 types of siglecs have been described in humans producing a variety of functions depending on their cell surface receptor interactions [33]. Siglecs are primarily expressed on cells of the adaptive immune system (particularly B cells) and are involved in discrimination between self and nonself [34]. They also selectively affect innate immune responses to DAMPs but not to PAMPs or FAMPs and are believed to play a role in discriminating between infections versus tissue injuries. Some siglec receptors seem to be involved in either inhibition or at least dampening of inflammatory responses.

A number of fungal proteins such as heat shock protein 70 (HSP-70) and HSP-90 are highly conserved from bacteria to

plants and animals and they are homologous with human DAMPs [35]. In general, their functions can be divided into intracellular and extracellular and membrane bound. When stimulated by stress conditions, HSPs initiate extensive transcriptional and translational regulation including proteins that regulate cytoskeletal elements. Some act as chaperones for proteins and the small ones act as ubiquitins. They can present peptides via MHC to the immune system and have multiple immunological consequences ranging from induction of Tregs to autoimmune responses seemingly dependent upon their concentration. Intracellularly, HSPs are involved in regulation of redox reactions which are viewed as intracellular messengers. They are also recognized as danger signals by the immune system and are recognized by receptors such as TLR 4, TLR2, CD14, CD91, CD94, Lox-1, SR-a, etc. The danger signals alert to the presence of internal pathological processes.

HSPs also are capable of inducing inflammatory responses by associating with CD24 and receptors for altered advanced glycation end products (RAGEs). CD24 molecules, being highly sialylated, then bind to siglec-10/G which moderates the response. Examples of HSPs identified as fungal allergens include *Alternaria* (Alt a 3), *Cladosporium* (Clad a HSP-70), *Penicillium* (Pen c 19), *Malassezia* (Mal s 10) for HSP-70 and *Cladosporium* (Clad a 12), and *Aspergillus* (Asp f 12) for HSP-90.

Receptor for Altered Glycation Products (RAGE)

RAGE is a 35-kD transmembrane pattern recognition receptor which has the ability to bind to advanced glycation endproducts found in damaged cells including glycoproteins. Binding to its ligands leads to activation of NF- κ B resulting in transcription of proinflammatory cytokines, chemokines, and adhesion molecules.

RAGE is expressed at high levels in alveolar epithelial type I cells. Deletion of RAGE can protect mice from airway remodeling, eosinophilic infiltration, and airway hyperresponsiveness [36]. RAGEs recognize DAMPs and FAMPs. Their activation results in the production of IL-33 which is a key cytokine in activating local TH2 cytokine production. A number of fungal products are involved in sugar metabolism and redox metabolism, so their interaction with RAGEs may trigger induction of Th2 responses [9, 37].

Innate Immune Receptors and the Microbiome

Cells of the innate immune system through their PRRs are a critical aspect of the host–microbiome interface. For example, the activation of TLRs and NLRs is directly coupled to the production of antimicrobial peptides in the gut [38]. Epigenetic alterations in genes associated with the innate

immune system are related to the presence of microbes. For example, when germ-free neonatal mice are initially colonized, a change in the methylation level of chemokine-encoding genes can be detected along with reduced recruitment of NK-T cells, leading to a reduction in colitis and allergic asthma [39].

Through their receptors, innate immune system cells can sense the metabolic profile of microorganisms, including fungi, leading to altered host physiological responses. There is an emerging suspicion that this interaction contributes to complex disease processes [40]. The bilateral interaction between microorganisms and their environment has implications for human health including increased likelihood of developing allergic diseases such as asthma.

Conclusions

Fungal products including those from cell walls and internal excretions can be recognized both by the innate and adaptive immune system and in particular can induce Th17 and Th2 responses. Activation of these systems can lead to adverse health effects. In addition, many fungal allergens also are intracellular proteins that can be involved in DAMP activation (e.g., proteases). Since fungal products activate both innate and adaptive immune responses, it can be difficult to determine which system is the source of inflammation. Given the ubiquity of fungi and their products, they appear to cause harm by various mechanisms which are not necessarily mutually exclusive. While markers such as IgE may be present, they are not necessarily the mechanism of the problem. Further work will be necessary to sort this out; however, until then, it is important to be aware of complexity of immunity to fungi.

Compliance with Ethical Standards

Conflict of Interest Drs. Portnoy, Williams, and Barnes declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Glossary

CLRs	C-type Lectin Receptors
DAMPs	Damage-Associated Molecular Patterns
FAMPs	Fungal-Associated Molecular Patterns
NLRs	NOD-like Receptors
PRRs	Pattern Recognition Receptors
PAMPs	Pathogen-Associated Molecular Patterns
PARs	Protease-Activated Receptors
TLRs	Toll-like receptors

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