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Innate Defense against Fungal Pathogens

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Human fungal infections have been on the rise in recent years and proved increasingly difficult to treat as a result of the lack of diagnostics, effective antifungal therapies, and vaccines. Most pathogenic fungi do not cause disease unless there is a disturbance in immune homeostasis, which can be caused by modern medical interventions, disease-induced immunosuppression, and naturally occurring human mutations. The innate immune system is well equipped to recognize and destroy pathogenic fungi through specialized cells expressing a broad range of pattern recognition receptors (PRRs). This review will outline the cells and PRRs required for effective antifungal immunity, with a special focus on the major antifungal cytokine IL-17 and recently characterized antifungal inflammasomes.

Human fungal pathogens are responsible for more than a million life-threatening infections annually, which can be associated with mortality rates reaching 95% (Brown et al. 2012). Fungal infections are difficult to treat and control because of rising problems of antifungal drug resistance and the lack of diagnostics, novel antifungal drugs, and vaccines. Fortunately, the majority of pathogenic fungi are opportunistic pathogens (Table 1) and, as such, do not normally cause disease unless there are alternations in immune defense. The use of immunosuppressive drugs, the human immunodeficiency virus (HIV) epidemic, and modern clinical interventions result in such alternations and have contributed substantially to the recent increases of systemically infected patients. Fungi also cause nonlethal skin and mucosal infections that are equally difficult to treat and often recurring.

The innate immune system is the first line of defense against pathogens and broadly protects against invading microorganisms. Genetically inherited receptors, called pattern recognition receptors (PRRs), are used by innate cells for recognition of conserved pathogen-associated molecular patterns. Signaling downstream from PRRs activates cellular responses and killing mechanisms, and also helps initiate and shape adaptive immune responses. Adaptive immunity, unlike innate, is activated by specific antigens recognized by noninherited

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Table 1. Species of pathogenic fungi that cause disease in humans, the barrier tissue breached and organs infected, and the PRRs needed for protective immunity

	Selected disease(s)	Barriers breached/site of infection	Selected PRRs involved in protective immunity	Selected references
Ascomycota				
Candida albicans	Disseminated candidiasis	Blood, kidneys, brain, heart	TLR-2/TLR-4/TLR-6	Ferwerda et al. 2009 Saijo et al. 2010
	Vulvovaginal candidiasis	Vagina	Dectin-1	Wells et al. 2008
	Mucosal candidiasis	GI tract, oral mucosa	Dectin-2 CR3, DC-SIGN	
Candida glabrata	Disseminated candidiasis	Blood, kidneys, brain, heart	Mincle, MR	
Aspergillus fumigatus	Invasive pulmonary aspergillosis	Lung, blood	TLR-9/TLR-3 Dectin-1, Dectin-2	Ramirez-Ortiz et al. 2011
	Allergic bronchopulmonary aspergillosis	Lung	CR3 DC-SIGN	Werner et al. 2009 Sainz et al. 2012
Pneumocystis carinii	Pneumonia	Lung	Dectin-1	Saijo et al. 2007
Blastomyces dermatitidis	Blastomycosis (pneumonia)	Lung	??	Wüthrich et al. 2011
Histoplasma capsulatum	Histoplasmosis (pneumonia)	Lung	??	Wüthrich et al. 2011
Paracoccidioides brasiliensis	Paracoccidioidomycosis	Lung	TLR-2/TLR-4	Loures et al. 2011
Coccidioides immitus *Coccidioides posadasii*	Coccidioidomycosis (Valley fever)	Lung, blood	Dectin-1	Viriyakosol et al. 2013
Fonsecaea pedrosi	Chromoblastomycosis	Skin	TLRs Mincle	Da Glória Sousa et al. 2011
Basidiomycota				
Cryptococcus neoformans	Cryptococcosis/ cryptococcal meningitis	Lung, brain/CNS	MR TLR-2 CR3	Dan et al. 2008
Cryptococcus gattii				
Trichosporon rubrum	Onychomycosis	Skin/nails	??	
Malassezia sympodialis	Atopic dermatitis Atopic eczema	Skin	Mincle Dectin-2	Ishikawa et al. 2013

CNS, central nervous system; CR3, complement receptor 3; GI, gastrointestinal; MR, mannose receptor; PRRs, pattern recognition receptors; TLR, Toll-like receptor.

T-cell/B-cell receptors and has a faster response time with each subsequent challenge (immune memory) (Wüthrich et al. 2012).

The vast predominance of fungi in the environment results in continual human exposure. It is estimated that we inhale several hundred *Aspergillus fumigatus* spores a day (Rivera et al. 2011), and many humans are also colonized with commensal fungi (e.g., *Candida albicans*) (Iliev et al. 2012). For this reason, our innate system is equipped to recognize fungal particles and maintain commensal relationships, but also destroy the pathogenic fungi that we are exposed to. This review will outline the cells and recognition receptors in innate antifungal immunity, with a special focus on IL-17 defenses and inflammasomes, both recently identified as major players in antifungal defense.

CELLS AND BARRIERS

Cells of the Innate Immune System

Cells considered part of the innate immune system are characterized by the presence of inherited receptors with broad specificity (see next section) and a rapid response time. This section will discuss the predominant cell types used for antifungal defense: neutrophils, macrophages, dendritic cells (DCs), natural killer (NK) cells, innate-like lymphocytes, and epithelial cells (ECs). However, it is important to appreciate that there are several other cellular populations that may contribute in antifungal responses, although they remain poorly characterized or unstudied in the context of fungal infections.

Neutrophils

Neutrophils are highly phagocytic granulocytic polymorphonuclear cells that have been well characterized as a result of their importance in antimicrobial immunity. The classic mechanism of killing by neutrophils is through the production of reactive oxygen species (ROS), which kill phagocytosed microbes when the granules that contain them fuse with the phagosome. Nonoxidative mechanisms include the release of neutrophil-specific degrading enzymes, elastase and cathepsin-G, which were shown to be nonredundant in *A. fumigatus* immunity (Tkalcevic et al. 2000). Other methods of killing include the formation of neutrophil extracellular traps (NETs), external lattices made up of DNA, histones, and antimicrobial proteins (Byrd et al. 2013). NETs have been described in human neutrophils exposed to *A. fumigatus* (McCormick et al. 2010), *C. albicans* (Urban et al. 2006), and *Cryptococcus neoformans* (Urban et al. 2009). The relative importance of NETs in vivo has still to be determined, although a key component of NETs, calprotectin, was recently shown to have efficacy against *C. albicans* in vivo, and animals deficient in calprotectin were more susceptible to infection (Urban et al. 2009).

Neutrophils have also been shown to play detrimental roles during fungal infection through immunopathology. Neutrophil-depleted animals were shown to survive for longer and have lower burdens of *C. neoformans* following pulmonary infection (Mednick et al. 2003), whereas $CCR1^{-/-}$ animals, which have defective neutrophil recruitment to the kidney during disseminated candidiasis, had improved survival and outcome (Lionakis et al. 2012). This may, however, not translate to human medicine in which neutrophil frequency and function appear to be hugely important for host defense. A reduction in circulating neutrophils is cited as a high risk factor for developing invasive candidiasis (Byrd et al. 2013), and chronic granulomatous disease patients, whose neutrophils are unable to make ROS, are more likely to be diagnosed with invasive aspergillosis (De Luca et al. 2012).

Monocytes/Macrophages

Monocytes are blood-borne cells that differentiate into macrophages within tissues, which they infiltrate following an inflammatory signal. Once within tissues, macrophages further develop into a distinct functional phenotype, which is determined by the cytokine milieu. Proinflammatory cytokines, particularly interferon γ (IFN-γ), drive a classically activated (M1) phenotype, whereas anti-inflammatory cytokines (e.g., TGF-β) drive alternatively activated (M2) macrophages (Mosser and Edwards 2008). Macrophage phenotype can have a profound effect on antifungal immunity. In experimental pulmonary cryptococcosis (caused by *C. neoformans*), susceptibility is associated with M2 phenotypes, whereas protective vaccine strains induce M1 cells that correlated with enhanced survival rates to subsequent lethal challenges (Hardison et al. 2012). Macrophages are also able to switch between M1/M2 phenotypes, and this plasticity was recently shown to be crucial in the protection against another respiratory fungal pathogen, *Paracoccidioides brasiliensis*. Using resistant and susceptible strains of mice, both M1 and M2 cells were shown to control fungal growth, although their protective value was only evident at different stages of infection (Feriotti et al. 2013).

A recent major development in the field of innate immunology was the demonstration of "trained immunity," a term given to describe short-term immunological memory carried by innate cells (Netea et al. 2011; Netea 2013). Innate cells shown to participate in this phenomenon include NK cells and monocytes. Trained immunity was recently shown to protect against fungal infection; monocytes stimulated in vitro with β-glucans, a component of fungal cell walls, were shown to protect animals deficient in an adaptive immune system against lethal systemic candidiasis infections, and this protection was attributed to epigenetic reprogramming (Netea et al. 2011; Quintin et al. 2012; Netea 2013).

DCs

DCs are important innate cells involved in the initiation of immune responses through to the generation of adaptive immunity via antigen presentation (discussed in detail elsewhere in the literature). DCs have attracted particular attention in their potential as effective targets for novel therapeutic and vaccine strategies. Recent studies have shown how use of nonpathogenic yeast (Kiflmariam et al. 2013) and complexes targeting innate antifungal receptors expressed by DCs (Carter et al. 2006; Lipinski et al. 2013) can induce effective antifungal immunity. However, to take full advantage of this novel approach it still needs to be understood which DC subtypes are needed for antifungal protection and the mechanisms involved. DC subtypes are based on phenotype, anatomical location, and other functional characteristics. The different DC subtypes that contribute to antifungal immunity are still being determined, although it has recently been suggested that plasmacytoid dendritic cells (pDCs), typically considered as antiviral cells, may play a protective role to pulmonary fungal pathogens. Animals resistant to *P. brasiliensis* infection were shown to generate a mixed lung DC population, including pDCs, which susceptible mice lacked (Pina et al. 2013). Furthermore, animals depleted in pDCs were shown to be hypersusceptible to invasive aspergillosis, which correlated to the toxicity and protective cytokine responses exerted against the fungi by pDCs in vitro (Ramirez-Ortiz et al. 2011). In addition to understanding the roles of functional subtypes of DCs, it is also important to understand how fungi interact with DCs once engulfed. For example, *C. gattii* is efficiently killed by DCs; however, it does not appear to stimulate proper maturation, and thus immunity is compromised and may explain the ability of this organism to infect otherwise healthy hosts (Huston et al. 2013).

NK Cells

NK cells are primarily known for their antiviral and -tumor properties, for which they were first identified. NK cells in both mice and humans have been described to have antifungal activity against a range of fungi including *C. albicans*, *A. fumigatus* (Schmidt et al. 2013b), *C. neoformans* (Islam et al. 2013), *Pneumocystis murina* (Kelly et al. 2013), and *P. brasiliensis* (Longhi et al. 2012). NK cells exert their effect through the direct killing of yeast using perforin, killing infected host cells, and secretion of proinflammatory cytokines (Schmidt et al. 2013b). However, the role of NK cells is complicated and poorly understood; many articles have suggested influential roles of NK cells on other cell types (reviewed extensively by Schmidt et al. 2013b), and a further complicating factor is the observation of an active suppression of NK-mediated killing by some fungal species (Schmidt et al. 2013a).

Innate-Like Lymphocytes

Lymphocytes, such as T-helper cells, cytotoxic T-, and B-cells are considered part of the adaptive immune system and will not be discussed here. However, there are cells of lymphoid origin that are considered part of the innate system, as they possess more innate-like qualities than their adaptive relatives. These cells include γδ T cells, recently discovered innate lymphoid cells (ILCs), and invariant natural killer (iNK) T cells.

γδ T cells are characterized by the expression of an invariant T-cell receptor (TCR),

made up of the γ and δ chains, and thought to be particularly important in mucosal defenses, as they are found primarily in the gut and make large amounts of IL-17 (Gladiator et al. 2013), a cytokine crucial for antifungal mucosal defenses (see below). Similarly, ILCs are also found primarily in mucosal surfaces and thought to play important roles in fungal allergic asthma (see next section). The contribution of ILCs in fungal infections is a new area with results that are difficult to reconcile currently. The confusing nomenclature of ILCs has also made this difficult and, thus in this work, we will use the grouping system proposed by Spits et al. (2013) in which ILC-1 are predominantly IFN-γ producing, ILC-2 are IL-4/13 producing, and ILC-3 are IL-17 producing. Using this system, ILC-3 was shown to potentially play important roles in mucosal candidiasis (Gladiator et al. 2013; see below), whereas ILC-2 were shown to have a detrimental role in *C. neoformans* immunity (Flaczyk et al. 2013), suggesting a dependence on anatomical location and fungal species.

iNK T cells are a rare population of lymphocytes expressing an invariant TCR that recognizes lipid antigens in the major histocompatibility complex (MHC) molecule CD1d. Animals deficient in CD1d, and therefore unable to initiate NK T-cell responses, were recently shown to have an increased susceptibility to *A. fumigatus* infections (Cohen et al. 2011). The investigators of this article were not able to identify a fungal lipid responsible for the phenotype, instead suggesting the involvement of self lipids. However, another group has recently identified an *Aspergillus*-derived lipid, termed asperamide B, which could be used to induce airway hyperreactivity and activation of iNK T cells in vivo (Albacker et al. 2013).

ECs

ECs are the first point of contact with microbes and, although not typically considered immune cells, there have been several recent examples of ECs contributing to the innate immune response, primarily through the production of chemokines, such as IL-8. Vaginal ECs have been shown to produce inflammatory chemokines in response to *C. albicans* (Yano et al. 2012), whereas corneal and bronchial ECs both produce inflammatory cytokines in response to *A. fumigatus* (Guo and Wu 2009; Sun et al. 2012). Mechanisms driving EC chemokine production include the ligation of TLRs (Guo and Wu 2009) and stimulation with antimicrobial peptides (Wagener et al. 2013). ECs are also important in maintaining commensal populations and initiating a proinflammatory response following a switch to a pathogenic phenotype; Moyes and colleagues showed that oral ECs only switched on inflammatory pathways following stimulation with the pathogenic hyphal form of *C. albicans* and not the commensal yeast form, and that this biphasic response was controlled by mitogen-associated protein or mitogen-activated protein kinase signaling and fungal burden (Moyes et al. 2010). Characterization of PRR expression in ECs has so far been limited to TLR family members, although expression of C-type lectin receptors (CLRs) is less well defined (Weindl et al. 2010). However, it was recently shown that Dectin-1, a critical antifungal PRR (see below), can be induced on human bronchial ECs exposed to *A. fumigatus*, which was required for the induction of ROS and inflammatory chemokines (Sun et al. 2012).

Innate Immune Regulation in Barrier Tissues

The skin and mucosal surfaces act as physical barriers between the environment and deep tissues. Many of the cell types described above are found in abundance within barrier tissues and are important in surveillance, maintaining commensal relationships, and protection from invasion. This section will outline the most recent developments in the regulation of antifungal immunity within barrier tissues.

Skin

Human skin is readily colonized by fungi, predominantly *Malassezia* species (Findley et al. 2013). *Malassezia* are pathogenic yeast that are associated with exacerbating various skin diseases, including atopic eczema and atopic dermatitis (AD), in which barrier function and im-

mune regulation is compromised (Saunders et al. 2012). In these diseases, *Malassezia*-derived products have been shown to influence host responses, including the generation of cross-reactive T cells that exacerbated AD (Balaji et al. 2011), and down-regulation of human DC maturation and proinflammatory cytokine production (Vlachos et al. 2012). Other pathogenic fungi that target the skin include *Trichophyton* species, which cause common infections of the skin and nails (onychomycosis), and also *C. albicans*. *C. albicans* infections of the skin were recently shown to be controlled by different DC subsets resident in the skin, Langerhans cells, and Langerin^{+} dermal DCs, which were each responsible for driving Th17 and Th1 adaptive immunity, respectively (Igyarto et al. 2011).

Respiratory Tract

Inhalation is a common route of exposure to fungal spores in the environment. In immune-compromised patients, these spores may begin to germinate, resulting in lethal invasive infection, such as invasive pulmonary aspergillosis (IPA) and other fungal pneumonias (Table 1). More commonly, the inhalation of fungal spores results in sensitization and exacerbation of allergy and asthma. Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder to *A. fumigatus*, leading to severe asthma symptoms and affects nearly five million people worldwide (Agarwal et al. 2013; Denning et al. 2013). ABPA pathogenesis is poorly understood, although recent insights have identified some mechanisms that may help future development of therapies. For example, Dectin-1 recognition of *A. fumigatus* was recently shown to enhance immunopathology through IL-22 (Lilly et al. 2012), whereas C3aR$^{-/-}$ mice presented with reduced allergic symptoms when sensitized with *A. fumigatus* chitin (Roy et al. 2013). Other fungi that have been shown to exacerbate asthma are *C. neoformans* and *Alternaria alternata*, which induce trademark symptoms of allergy including eosinophilia and Th2 polarization (Goldman et al. 2006; Doherty et al. 2012). Recently, ILC-2 cells have been shown to play major roles in allergic responses to *Alternaria* through the production of IL-5 and IL-13 (Bartemes et al. 2012; Doherty et al. 2012). It is hoped that their further characterization may help identify mechanisms of allergic hyperresponsiveness to fungal allergens and novel therapeutic targets.

Gastrointestinal Tract

Fungi have been described as both commensals and pathogens in the human gastrointestinal (GI) tract. The most commonly described human fungal commensal is *C. albicans*, which initiates a distinct commensalism transcriptional program to optimize growth within the GI tract (Pande et al. 2013). However, high levels of colonization have been associated with enhanced severity of ulcerative colitis and Crohn's disease (Kumamoto 2011), and many cases of systemic candidiasis are thought to originate from commensal populations in the gut (Odds et al. 2006; Miranda et al. 2009). It has therefore been recognized that a better understanding of relationships with fungal commensals is important to delineating disease pathogenesis. It has recently been shown that the mammalian intestinal microbiota has diverse fungal species and is in greater abundance than previously appreciated (Iliev et al. 2012). Analysis of the murine fungal microbiome by Iliev and colleagues identified several fungal species belonging to the genera of *Candida*, *Saccharomyces*, and *Trichosporon* (Iliev et al. 2012). These fungi interacted with the innate immune system via the PRRs Dectin-1 (Iliev et al. 2012) and SIGNR3 (Eriksson et al. 2013), and absence of these interactions could enhance severity of a murine model of colitis because of loss of fungal recognition and barrier integrity (Iliev et al. 2012; Eriksson et al. 2013). Similarly, humans with a Dectin-1 genetic polymorphism were found to be associated with more severe forms of colitis, possibly caused by the disturbance of fungal recognition in the GI tract (Iliev et al. 2012). Interestingly, although Dectin-1 has been shown to be essential for the protection against invasive infections of the gut, it does not appear to play a role in the maintenance of commensal fungal populations in the GI tract (Vautier et al. 2012).

Genital-Urinary Tract

The most common fungal pathogen colonizing the genital-urinary tract is *C. albicans* (Jaeger et al. 2013). Vulvovaginal candidiasis (VVC) is thought to affect 75% of adult woman at least once in their lifetime, and 8% of these women are estimated to be recurrent sufferers (RVVC) (Jaeger et al. 2013). Interestingly, recurrent infections can occur in women with no other known medical complaints and it is still unclear why vaginal candidiasis occurs more often in some individuals. Recent developments have, however, shed some light on mechanisms conferring enhanced susceptibility to RVVC. Animals deficient in IDO1, an enzyme promoting tolerant T-cell responses and production of tolerogenic kynurenines, were shown to have increased susceptibility to VVC and treatment with kynurenines could alleviate disease (De Luca et al. 2013). S100 alarmin proteins have also been shown to mediate an immunopathogenic response in susceptible patients, which was interestingly independent of Th17 cells that are known for their anti-*Candida* properties and a role in the induction of S100 alarmins (Yano et al. 2012). The balance between tolerogenic and protective responses appears to be critical, however, as mice deficient in IL-22, a protective inflammatory cytokine, were also more susceptible to VVC (De Luca et al. 2013). Human polymorphisms reflect the delicate nature of this balance; a polymorphism in the IL-4 gene was found in significantly higher frequency in RVVC sufferers compared with healthy controls, which correlated to enhanced levels of anti-inflammatory IL-4 resulting in a reduction in nitric oxide levels and fungal killing (Jaeger et al. 2013).

INNATE RECOGNITION

The initiation of an immune response begins with the innate recognition of the pathogen by PRRs, which drive early protective mechanisms that are critical to host defense (Fig. 1). There are several families of PRRs that are grouped based on phylogeny, structure, and function. Toll-like receptors (TLRs) and CLRs are the key families involved in antifungal immunity, and we will discuss selected members from these families based on their identified major roles in antifungal responses. Although we discuss PRRs as individual entities, it is important to remember that these PRRs do not work alone and collaborative responses and redundancy are common in mammalian immunology. Indeed, animals and humans lacking signaling adaptors shared by several PRRs tend to show more severe phenotypes than the single PRR deficiencies (Gross et al. 2006; Glocker et al. 2009).

TLRs

TLRs initiate intracellular signaling pathways using MyD88 or the TRIF adaptor proteins, which ultimately activate transcription factors NF-κB and the interferon-regulatory factors (O'Neill et al. 2013). TLR-dependent cellular responses that promote antifungal immunity include the production of type I interferons (IFNs) (Bourgeois et al. 2011) and proinflammatory cytokines TNF-α and IL-12 (Ramirez-Ortiz et al. 2008, 2011), and the promotion of adaptive immunity (Carvalho et al. 2012).

MyD88-deficient mice, which have defective TLR responses from multiple family members, have shown a role for TLRs in immunity to a range of pathogenic fungi including *C. albicans* (Marr et al. 2003), *A. fumigatus* (Bretz et al. 2008), and *C. neoformans* (Biondo et al. 2005). This does not appear to be the case in humans, however. MyD88-deficient humans are highly susceptible to bacterial infections but not fungal (von Bernuth et al. 2008), although associations with systemic candidiasis and TLR-1/4 polymorphisms have been described (Van der Graaf et al. 2006; Plantinga et al. 2012). This is in contrast to patients deficient in the CLR-signaling adaptor, CARD9, who have a high risk of developing severe fungal infections (Glocker et al. 2009). Indeed, one of the primary roles of TLRs in fungal immunity is thought to be modulation of CLR-dependent responses and several examples of TLR/CLR collaboration have been described (Netea et al. 2006). TLR-2, which recognizes fungal glycolipids (Bauer et al. 2008), has a well-documented relationship with Dectin-1 in which synergy promotes phagocytosis and cy-

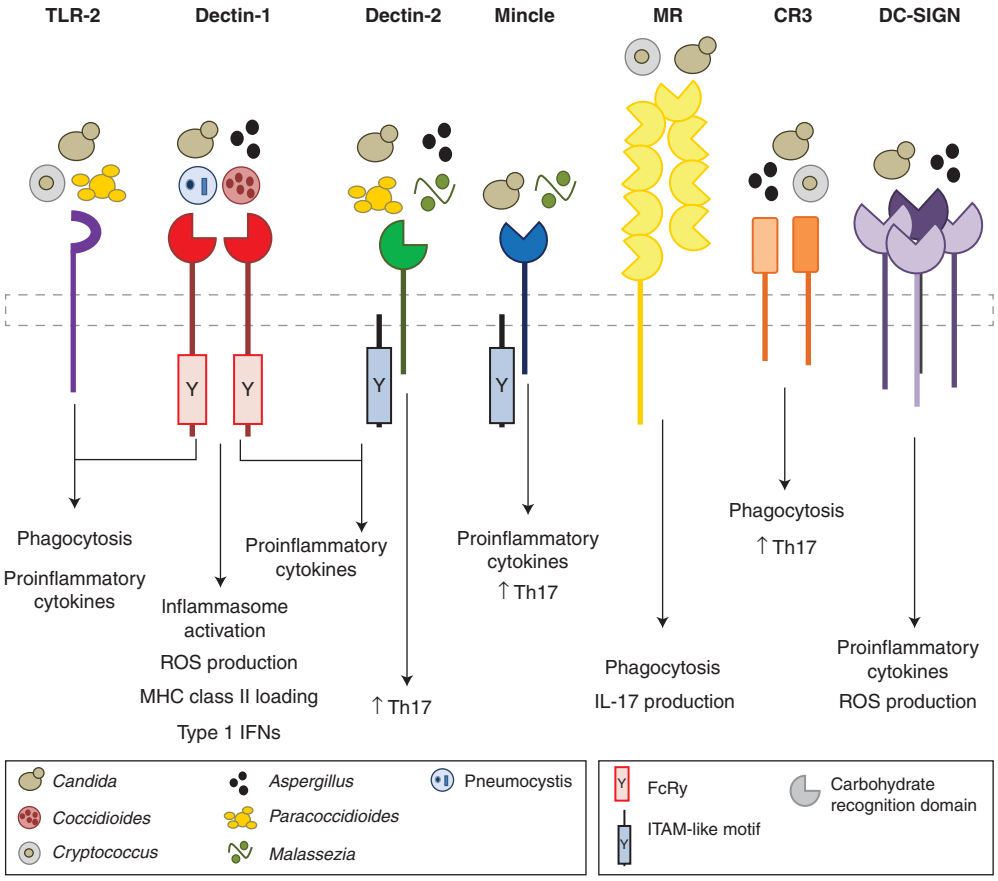

Figure 1. The PRRs discussed herein are depicted showing the fungal species they recognize and downstream effector functions they mediate following recognition. Receptor collaboration between Dectin-1 and TLR-2, and Dectin-1 and Dectin-2, is also indicated by conjoining arrows. See main text for all references.

tokine production (Drummond et al. 2011), and cross-regulation between signaling pathways results in specifically tailored responses (Dennehy et al. 2009). Indeed, the lack of TLR/CLR collaboration can have a profound effect on the outcome of infection. *Fonsecaea pedrosoi* infections, which cause chromoblastomycosis, could be resolved in vivo through the external application of TLR agonists, which repaired defective TLR recognition, and required cooperative CLR recognition and downstream signaling (Da Glória Sousa et al. 2011).

Dectin-1

Dectin-1 is the best-described antifungal CLR that recognizes exposed β-glucans (Brown and Gordon 2001) in the cell walls of numerous pathogenic fungi, including *C. albicans*, *A. fumigatus*, and *Pneumocystis carinii* (Drummond and Brown 2011). Dectin-1 is expressed primarily by myeloid cells and drives complex intracellular signaling pathways of which the best characterized is the Syk-CARD9 pathway (Drummond et al. 2011; Hardison and Brown 2012). Signaling then leads to a multitude of cellular responses, including phagocytosis, cytokine production, the respiratory burst, and activation of inflammasomes. The intracellular signaling pathways downstream from Dectin-1 have been reviewed extensively elsewhere (Drummond et al. 2011; Hardison and Brown 2012). Briefly, the tyrosine in the immunoreceptor tyrosine-based activation motif-like mo-

tif (YXXL) is phosphorylated by Src-family kinases on β-glucan binding. This phosphorylation event allows recruitment of Syk kinase and the formation of a molecular scaffold composed of CARD9, Bcl10, and MALT1. The signaling cascade that follows is responsible for the activation and translocation of several transcription factors into the nucleus (NF-κB, AP1, NFAT), leading to cytokine production and gene transcription.

Innate recognition and the downstream functions of Dectin-1 have significant functional consequences to in vivo antifungal immunity. Dectin-1-deficient mice show accelerated mortality when systemically infected with *C. albicans* (Taylor et al. 2007) and *A. fumigatus* (Werner et al. 2009), whereas increased burdens have been reported with *P. carinii* (Saijo et al. 2007) and *Coccidioides immitus* (Viriyakosol et al. 2013). The human Dectin-1 polymorphism (Y238X), which renders patients Dectin-1 deficient (Ferwerda et al. 2009), has also been linked to an increased susceptibility to mucosal candidiasis, and an increased risk of invasive aspergillosis following transplant surgery (Cunha et al. 2010; Chai et al. 2011). Other recently identified downstream functions of Dectin-1 include modulation of the autophagy pathway to promote antigen presentation of fungal antigens on MHC Class II (Ma et al. 2012) and production of type I IFNs needed for efficient renal infiltration during murine systemic candidiasis (Del Fresno et al. 2013).

Dectin-2

Members of the Dectin-2 family have a single carbohydrate recognition domain and lack intracellular tails with signaling motifs, although there are some members that are exceptions (e.g., DCIR) (Kerscher et al. 2013). Dectin-2 is the best-characterized member of this cluster, and has been shown to bind a number of fungal species including *C. albicans*, *P. brasiliensis*, *A. fumigatus* (Kerscher et al. 2013), and *Malassezia* (Ishikawa et al. 2013). Dectin-2 binds high-mannose-containing structures and, accordingly, α-mannose and a mannose-rich glycoprotein were recently identified as ligands (Saijo et al. 2010; Ishikawa et al. 2013). Dectin-2 associates with FcRγ to drive intracellular signaling pathways, of which the best characterized is the Syk-CARD9 pathway, shared with Dectin-1 (Drummond et al. 2011; Hardison and Brown 2012). Protective roles for Dectin-2 in antifungal defense have been best characterized for *C. albicans*, in which Dectin-2-dependent $CD4^+$ T-cell Th17 polarization (Robinson et al. 2009) was recently shown to contribute to fungal clearance as Dectin-$2^{-/-}$ animals had reduced survival and greater fungal burdens when systemically challenged (Saijo et al. 2010).

Mincle

Mincle is another member of the Dectin-2 family and, like Dectin-2, associates with FcRγ and signals through Syk-CARD9. Using deficient mouse models, Mincle has been shown to play protective roles during infections with *C. albicans* (Wells et al. 2008) and *Malassezia* (Yamasaki et al. 2009). The specific ligands that activate Mincle are currently unidentified for *C. albicans*, whereas *Malassezia*-derived glycero-glycolipid and mannitol-linked fatty acids were recently described to activate Mincle-dependent cytokine production (Ishikawa et al. 2013). Cytokine production appears to be the main protective mechanism downstream from Mincle, as phagocytosis is unaffected in the absence of this PRR (Wells et al. 2008). Other potential roles for Mincle include the modulation of adaptive immunity, which has been described in antimycobacterial responses (Schoenen et al. 2010), although this has yet to be shown during fungal infections.

Mannose Receptor (CD206)

The mannose receptor (MR) recognizes a broad range of pathogenic microbes including bacteria, parasites, viruses, and fungi through terminally mannosylated molecules (Drummond and Brown 2013). Several antifungal activities downstream from the MR have been shown, including the production of IL-17 from human peripheral blood mononuclear cells (PBMCs) stimulated with *C. albicans* mannans (van de

Veerdonk et al. 2009), phagocytosis of *C. albicans* yeast in DCs (Donini et al. 2007), and are also hypothesized to be involved with sampling of phagosomes because of the late-stage recruitment pattern (Heinsbroek et al. 2008). Despite these roles in antifungal immunity, the MR appears to be redundant for a number of fungal infections (Hardison and Brown 2012) except *C. neoformans* in which $MR^{-/-}$ mice were shown to be highly susceptible because of defective $CD4^+$ T-cell responses (Dan et al. 2008).

Complement Receptor 3

Complement receptor 3 (CR3) is an integrin made up of CD11b and CD18, and is part of the evolutionary ancient complement system that marks and attacks foreign microbes using functionally diverse complement proteins released by a proteolytic cascade (Sandor et al. 2013). CR3 is involved with leukocyte adhesion, phagocytosis, and chemotaxis using mechanisms that can either be dependent or independent on other components of the complement system (van Bruggen et al. 2009). CR3 has been shown to bind β-glucan-containing particles (van Bruggen et al. 2009) and may act as the primary β-glucan phagocytic receptor in human neutrophils that, unlike murine neutrophils, were not dependent on Dectin-1 for β-glucan phagocytosis (van Bruggen et al. 2009). CR3 may also prove to be an important link between the innate and adaptive immune systems through functions independent of β-glucan recognition. CR3 was shown to help drive Th1 and Th17 responses during *A. fumigatus* infections (Gresnigt et al. 2013), and has also been described to promote antibody-mediated complement-independent phagocytosis (Taborda and Casadevall 2002).

DC-SIGN

DC-SIGN is a human CLR expressed on myeloid cells that binds fucose/mannose-containing glycans. There are eight murine homologs (named SIGNR), which have been used to study the probable antifungal activities of DC-SIGN. In vitro assays have shown SIGNR1 recognition of *C. albicans* leading to cytokine production (Takahara et al. 2012) and activation of the respiratory burst (Takahara et al. 2011), although some of these functions seemed to depend on Dectin-1 signaling, suggesting a collaborative effort (Takahara et al. 2011). The phenotype of SIGNR1-deficient mice following fungal infection has not yet been reported and, therefore, only in vivo roles to bacteria and parasites have been described so far (Lanoue et al. 2004; Saunders et al. 2009). However, it has been shown in a small cohort of patients that polymorphisms in DC-SIGN are associated with developing IPA, although the mechanism remains to be defined (Sainz et al. 2012).

IL-17 DEFENSES

Immunity to fungal infections is traditionally considered in the purview of adaptive immune responses, particularly because of the incidence of fungal diseases in HIV/acquired immunodeficiency syndrome patients, such as *Pneumocystis* pneumonia, oral candidiasis, and cryptococcal meningitis (Glocker and Grimbacher 2010). This concept was reinforced by the discovery that the cytokine IL-17 is critical for immunity to fungal infections, particularly mucosal candidiasis (Huppler et al. 2012). Although IL-17 is classically associated with $CD4^+$ Th17 cells, in recent years there has been an increasing appreciation of the importance of innate lymphoid sources of IL-17 (Cua and Tato 2010; Spits et al. 2013; Walker et al. 2013). These sources include NK T cells, γδ T cells, $CD4^-CD8^-TCR\beta^+$ cells, and "natural" Th17 cells that do not require activation by a specific antigen and are therefore considered innate. Nonetheless, these innate "type 17" cells bear several similarities to conventional Th17 cells in that they express CCR6, IL-7Rα, IL-23R, and the master transcription factor ROR-γt. However, it is thought that they do not necessarily require a TCR for their development as some cell types have been identified in $Rag1^{-/-}$ mice, which do not have an adaptive immune system (Cua and Tato 2010). There is also literature proposing that certain myeloid cells may be additional sources of

IL-17 (e.g., mast cells, neutrophils, and macrophages) (Hueber et al. 2010; Lin et al. 2011; Werner et al. 2011); however, this remains controversial as many cases can be explained by receptor-mediated uptake of cytokine rather than de novo production. Intestinal Paneth cells were also reported to express IL-17 (Takahashi et al. 2008), which may play a key role in maintaining commensal populations of fungi in the GI tract.

In fungal settings, innate IL-17-producing cells have been most closely examined in the context of mucosal candidiasis in which IL-17 is crucial to defense. Humans with defects at various points along the Th17 pathway are susceptible to mucosal, but usually not disseminated, candidiasis (Hernández-Santos and Gaffen 2012). Although many of these defects are associated with reduced adaptive Th17 responses, innate immunity has also been shown to be compromised. In patients with hyper-IgE/Job's syndrome, who have mutations in STAT3 resulting in reduced IL-6/23 signaling, a reduction in salivary antimicrobial peptides was found that correlated to reduced antifungal activity of the saliva, and may explain why these patients have increased growth of *C. albicans* in the oral cavity (Conti et al. 2011). In mice, *C. albicans* is not a commensal organism (Suegara et al. 1979; Iliev et al. 2012) permitting evaluation of both innate and adaptive responses. The use of mouse models has therefore provided key insights to IL-17 regulation and production in response to *C. albicans*. For example, in dermal *Candida* infections, the γδ T cell population was shown to be the dominant source of IL-17, which contributed to the resolution of skin lesions (Kagami et al. 2010; Hirota et al. 2011; Igyarto et al. 2011). In oropharyngeal candidiasis (OPC), there is also a powerful innate response as the organism is cleared within 3–4 days of infection without notable involvement in the draining lymph node or induction of adaptive immunity, yet IL-17 is crucial for protection (Kamai et al. 2001; Conti et al. 2009; Hernández-Santos et al. 2013). One report suggests that ILC-3 cells may be the source of protective IL-17 in OPC based on a claim that Rag1$^{-/-}$ mice are resistant to disease (Gladiator et al. 2013). However, it was not shown in that report that ILC-3 cells were actually producing IL-17, and Rag1$^{-/-}$ mice have been shown to be very susceptible to OPC in other systems (Pandiyan et al. 2011; Hernández-Santos et al. 2013). In disseminated candidiasis, IL-17 also protects against infection (Huang et al. 2004; Saijo et al. 2010; van de Veerdonk et al. 2010), although it is unclear whether the dominant source is adaptive or innate. However, as most disseminated candidiasis models are studied in a time frame compatible with development of adaptive immunity, indirect evidence suggests that adaptive responses are important.

INFLAMMASOMES

Inflammasomes are a recently described family of proteins originally characterized for their crucial role in the induction of inflammation, which contain a carboxy-terminal leucine rich repeat, a central nucleotide oligomerization domain, and an amino-terminal effector domain used to categorize inflammasomes into one of three classes: pyrin-containing NOD-like receptors (NLRPs), CARD-containing NOD-like receptors (NLRCs), and a baculovirus inhibitor of apoptosis protein repeat (BIR) domain-containing class. Caspase-1, a proteolytic enzyme, is activated following the formation of inflammasomes and is responsible for processing pro-IL-1β. IL-1 functions both locally and systemically (Roh et al. 1986; Gauldie et al. 1987) and is distinct from many other cytokines as its production and release involves a two-step process. The first step is the transcriptional upregulation of IL-1β as an inactive precursor (pro-IL-1β) downstream from Dectin-1 and TLR-2/4 (Netea et al. 2002; Bellocchio et al. 2004; Hise et al. 2009), and the second step is a proteolytic cleavage by caspase-1 releasing active IL-1β (Wilson et al. 1994). Similarly, pro-IL-18 is also cleaved by caspase-1 (Pedra et al. 2007), although this cytokine does not appear to play as predominant a role in fungal immunity as IL-1.

Host responses to numerous fungal pathogens depend on IL-1 receptor signaling (which

can be activated by both IL-1α and IL-1β), including *C. albicans* infections (Bellocchio et al. 2004; Hise et al. 2009), *Fusarium* species causing ocular keratitis (Tarabishy et al. 2012), and *Histoplasma capsulatum* pulmonary disease (Deepe and McGuinness 2006). Interestingly, the dependence on IL-1R signaling appears to be dependent on both the species and site of infection, as it was not required in pulmonary disease caused by *Aspergillus* (Bellocchio et al. 2004; Deepe and McGuinness 2006), but essential in *Aspergillus*-mediated ocular keratitis (Leal et al. 2010).

The best-studied inflammasome to date, NLRP3 (also known as NALP3) was identified as a result of a gain-of-function mutation associated with autoinflammatory diseases characterized by high levels of IL-1β (Aganna et al. 2002; Dowds et al. 2003, 2004; Agostini et al. 2004). NLRP3 is expressed in macrophages, DCs, T cells, B cells, and nonkeratinizing mucosal epithelium (Kummer et al. 2007), and responds to a wide range of stimuli including every class of microorganism (Allen et al. 2009; Craven et al. 2009; Dostert et al. 2009; Harder et al. 2009; Shio et al. 2009; Thomas et al. 2009), and host-derived molecules, such as ATP (Walev et al. 1995; Mariathasan et al. 2006; Petrilli et al. 2007; Qu et al. 2007), uric acid crystals (Martinon et al. 2006), and fibrillar amyloid-β (Halle et al. 2008). Crystalline compounds, such as silica crystals, asbestos, and aluminum salts, are also potent activators (Dostert et al. 2008; Hornung et al. 2008).

The first evidence for a role for NLRP3 in antifungal defenses was established using a murine model of oral candidiasis, in which NLRP3 deficiency resulted in increased susceptibility to mucosal candidiasis, as well as subsequent disseminated infections (Hise et al. 2009). NLRP3 has also been shown to be critical for protection in intravenous models of *Candida* challenge (Gross et al. 2009; Joly et al. 2009). The specific component of *Candida* required for activation of the NLRP3 inflammasome is not yet known; however, several yeast cell-wall preparations, including curdlan (Kumar et al. 2009), zymosan, and mannan (Lamkanfi et al. 2009), have been shown to activate NLRP3, and a recent report identified secreted aspartic proteases from *Candida* as capable of stimulating IL-1β release via NLRP3 (Pietrella et al. 2013). *Aspergillus* hyphal fragments, but not spores, have also been found to invoke the NLRP3 inflammasome to mediate IL-1β release from monocytes (Said-Sadier et al. 2010). Despite extensive research, relatively little is known about the precise molecular events involved in NLRP3 activation. In one study, it was determined that internalization and subsequent lysosomal damage, a characteristic common to crystalline activators, were required for *Candida*-mediated IL-1β release from macrophages (Joly et al. 2009; Pietrella et al. 2013). However, a conflicting report identified no discernible role for lysosomal damage in response to *Candida* in DCs (Gross et al. 2009). It remains to be seen whether these differences are attributable to different *Candida* strains used or point toward differential mechanisms for inflammasome activation in these two cell types. For *Aspergillus*, it was found that K^+ efflux and ROS production was required for IL-1β release from immortalized human monocytes (Said-Sadier et al. 2010). These mechanisms were also found to be important for human PBMC IL-1β release in response to *Candida* (Pietrella et al. 2013).

Limited studies have been performed on the role of other inflammasomes in fungal immunity. A noncanonical inflammasome using caspase-8 was recently shown to be activated directly downstream from Dectin-1 in response to *C. albicans*, and was independent of phagocytosis (Gringhuis et al. 2012). Another inflammasome, NLRC4 (formerly known as IPAF), has been best studied for its role in inflammatory responses to common bacterial pathogens (Miao et al. 2006; Franchi et al. 2007; Suzuki et al. 2007) and was recently shown to mediate a tissue-specific protective response to *C. albicans* (Tomalka et al. 2011). Another inflammasome studied in fungal infection is NLRP10, which was found to have minimal impact on the release of IL-1β in response to *Candida*; however, mortality was increased in *Nlrp10*$^{-/-}$ mice following intravenous challenge because of extensive kidney damage and abrogated Th1 and Th17 T-cell responses (Joly et al. 2012).

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CONCLUDING REMARKS

This work has provided an overview of the essential players in innate antifungal immunity. Although our understanding has recently expanded significantly in certain areas, such as the identification of fungal ligands, there are many aspects of innate immunity that are yet to be defined and understood. For example, further definition of PRR-signaling pathways and the source of innate IL-17, as outlined here, will be paramount to our understanding of early antifungal responses. Furthermore, much work is needed to clarify how individual PRRs work together in the recognition of different fungal pathogens, and how this influences killing and cell behavior. These insights will ultimately help shape the design of future treatments, particularly antifungal vaccines of which there are currently none available. As more advances in our understanding are made, it is likely we will see better diagnostics and treatments to help reduce the mortality of invasive fungal infections.

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