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Antifungal Innate Immunity: A Perspective from the Last 10 Years

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Abstract
Fungal pathogens can rarely cause diseases in immunocompetent individuals. However, commensal and normally nonpathogenic environmental fungi can cause life-threatening infections in immunocompromised individuals. Over the last few decades, there has been a huge increase in the incidence of invasive opportunistic fungal infections along with a worrying increase in antifungal drug resistance. As a consequence, research focused on understanding the molecular and cellular basis of antifungal immunity has expanded tremendously in the last few years. This review will provide an overview of the most exciting recent advances in innate antifungal immunity, discoveries that are helping to pave the way for the development of new strategies that are desperately needed to combat these devastating diseases.

Introduction

The complex interaction between host and microbe is particularly reflected in the pathogenesis of fungal diseases. Most fungi are ubiquitous in the environment, and our immune system has co-evolved and adapted to their presence over millions of years. Fungi can colonize almost every niche within the human body. Certain fungi, such as *Candida albicans* are commensal, whereas others, such as *Aspergillus fumigatus,* are environmental opportunists, which can cause devastating invasive diseases when immune homeostasis is disrupted. 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. Over 3 million people acquire life-threatening invasive fungal infections every year. Opportunistic invasive fungal infections are a significant cause of morbidity and mortality in immunocompromised individuals, and their occurrence has increased dramatically as a result of modern immunosuppressive medical interventions and HIV/AIDS. Our armamentarium to combat these infections is limited, and there is an urgent need to develop more effective antifungal drugs and vaccines. In addition, we need improved methods of diagnosis for optimal management of these infections.

Ten years ago, fungal immunology research was largely focused on defining the molecular interactions between pathogen-associated molecular patterns (PAMPs) and their cognate pattern recognition receptors (PRRs),

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and we were beginning to understand how immune cells could interact with fungi as some of the molecules involved in fungal recognition were discovered. Dendritic cells (DCs) were found to act at different levels in the immune response against fungi. They were 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. This model has moved DCs to the center stage in many fields, including fungal infections, as promising targets for immunotherapeutic intervention. These cellular and molecular studies lead to the conclusion that understanding the initial stages of how innate immune responses are activated will result in the construction of better vaccines and immunomodulatory strategies effective at eliciting protective immunity against fungi.

The discoveries in the last 10 years have been particularly exciting. The identification of mutations or polymorphisms in patients as well as the development and use of knockout mouse models has substantially enhanced our understanding of the underlying mechanisms and functions of numerous PRRs in antifungal immunity in areas such as intracellular signaling, induction and/or regulation of cellular responses, and shaping of adaptive immunity. Novel myeloid and lymphoid-derived cell subsets have been discovered and their roles in antifungal immunity determined. In this review, we will cover the most exciting advances in innate antifungal immunity that have occurred over the last decade, with a specific focus on PRRs and the cells involved. We will also provide a brief overview of how our expanded understanding is being translated into novel therapeutic approaches.

PRRs in Fungal Recognition

Sensing of fungal-associated molecular patterns such as cell wall constituents (i.e., carbohydrate polymers and glycoproteins) and intracellular components (i.e., DNA) relies on the expression of a plethora of PRRs in immune and nonimmune cells. After recognition, PRRs can mediate various cellular functions, from fungal uptake and killing to the production of cytokines and chemokines, which could influence the resultant immune responses.

Great advances have been made in our understanding of how fungi interact with the immune system. The discovery of Toll-like receptors (TLR) as key receptors in immunity, followed by the identification of dectin-1 as a β-glucan receptor, paved the way to the discovery of new receptors involved in fungal recognition and their subsequent cellular responses. In addition, we have gained new insights into their signaling pathways, mechanisms of regulation as well as crosstalk communication. PRRs can be classified into several families based on their structure and function, including the C-type lectin receptors (CLRs), TLRs, nucleotide binding and oligomerization domain (NOD)-like receptors (NLRs), and retinoic acid-inducible gene (RIG)-like receptors (RLRs), which will be discussed in the sections below.

C-Type Lectin Receptors

CLRs comprise a superfamily of proteins that can recognize diverse self and nonself molecules, and thus CLRs can regulate a wide range of physiological and pathological processes. They are constituted of soluble and membrane-bound proteins characterized by the presence of at least 1 C-type lectin domain (CTLD), some of which act as carbohydrate recognition domains (CRD). Conserved residues in the CRD allow recognition of diverse sugar structures, including the EPN (Glu-Pro-Asn) and QPD (Gln-Pro-Asp) motifs which confer specificity for mannose and galactose, respectively. However, other CTLDs lack these components and can recognize a broader range of ligands, including protein and lipids. Structurally, most membrane-bound CLRs consist of a cytoplasmic tail, a transmembrane region, and at least 1 CTLD in the extracellular domain. Others have multiple CTLDs, such as the mannose receptor (MR), which has 8 extracellular CTLDs.

Fungal cell walls contain numerous glycans, glycolipids, and glycoproteins that are not found in mammals, and these structures are recognized by several CLRs discussed in the sections below.

Dectin-1

Dectin-1 (clec7a), also known as the β-glucan receptor – as it was first described – is the best-characterized receptor involved in antifungal immunity. It is a type II transmembrane protein that can recognize β-1,3-glucans in the cell wall of diverse pathogenic fungi in a Ca^{2+}-independent manner. Expression of dectin-1 was originally thought to be primarily restricted to myeloid cells, including DCs, monocytes, macrophages, and neutrophils, although human B cells and subsets of T cells also express

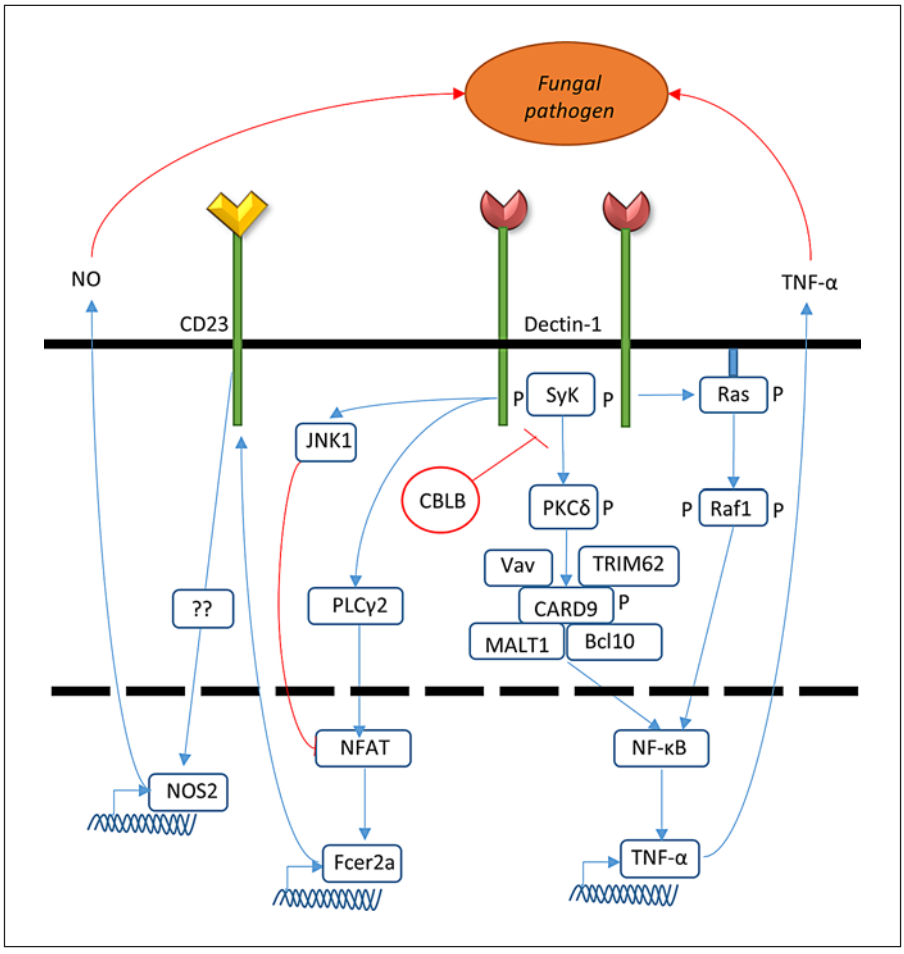

Fig. 1. Novel insights into the dectin-1 signaling pathway. Following dectin-1 engagement, Src-dependent phosphorylation of the dectin-1 ITAM results in Syk activation. The E3 ubiquitin ligase CBLB ubiquitinates dectin-1 and Syk inhibiting downstream immune responses. Downstream of Syk, PKCδ phosphorylates CARD9 and promotes the assembly of the CARD9/Bcl10/MALT1 complex, which subsequently activates the canonical NF-κB pathway to induce proinflammatory cytokines. Dectin-1 also activates NF-κB via the Raf-1 signaling cascade. Vav proteins and the ubiquitin ligase TRIM62 are newly identified molecules that can regulate CARD9 activation. CD23 is a recently described CLR that is upregulated upon dectin-1 engagement and leads to nitric oxide production. Activatory signals are in blue, inhibitory signals are in red.

this receptor [1]. More recently, expression of dectin-1 has been described in human mast cells, keratinocytes, and epithelial cells [2–4].

Intracellular Signaling

Signaling from dectin-1 is known to involve the immunoreceptor tyrosine-based activation motif (ITAM)-containing cytoplasmic domain, which is phosphorylated by a Src family kinase allowing the recruitment of the Syk kinase leading to several cellular responses, described below [1]. Subsequent studies led to the identification of caspase-associated recruitment domain 9 (CARD9) as a key downstream transducer of dectin-1 and other CLR signaling. The Syk pathway leads to activation of a molecular scaffold composed of CARD9, Bcl10, and MALT1, through PKCδ, culminating in the recruitment of several transcription factors, including the NF-κB [5]. Signaling via dectin-1 has shown to induce additional intracellular pathways, including the Raf-1 kinase pathway, and the canonical (NLRP3/caspase 1) and noncanonical (MALT1/caspase 8) inflammasomes [6]. In the last few years, great advances have been made in understanding the mechanisms that regulate dectin-1 signaling (Fig. 1). Recently, 3 complementary studies showed that the E3 ubiquitin ligase CBLB targets dectin-1, dectin-2, macrophage C-type lectin (MCL) (described in more detail below), and their adaptor molecule Syk for degradation, and thus exerts a strong anti-inflammatory effect [7–9]. The authors showed that treatment strategies involving the inhibition of CBLB led to increased inflammatory responses and improved the outcome of experimental candidiasis, which provides evidence that CBLB might represent a therapeutic target in fungal disease. Furthermore, it has been found that another ubiquitin ligase TRIM62 as well as Vav proteins regulate CARD9-mediated antifungal immunity, and these molecules are also potential therapeutic targets [10, 11]. Vav proteins are key activators of

the CARD9 pathway by cooperating downstream of dectin-1 to engage CARD9 for NF-κB control and proinflammatory gene transcription, while TRIM62 acts as a CARD9-binding partner facilitating CARD9 polyubiquitination, which is essential for its activity. Moreover, TRIM62- as well as Vav1/2/3-deficient mice exhibit extreme susceptibility to *Candida* infection, suggesting that they have a pivotal role in antifungal immunity [10, 11]. Interestingly, CD23, a novel CLR, which is well known for its function as a low-affinity receptor for IgE, plays an important role in antifungal immunity through recognition of surface components of fungal pathogens, such as α-mannan and β-glucan, leading to upregulation of nitric oxide synthase (NOS2) expression, reactive oxygen species (ROS) production, and fungal killing. JNK1 was shown to negatively regulate CD23 expression through dectin-1-induced NFAT activation, modulating its antifungal role. Importantly, treatment with 2 different JNK inhibitors significantly increased survival of *C. albicans*-infected mice, suggesting their potential use as a novel antifungal therapy (Fig. 1) [12].

Recent studies have shown that monocytes and macrophages can promote lymphocyte-independent protection during systemic *Candida* reinfection (and provide protection against other nonfungal infections) via epigenetic reprogramming at the level of histone H3 methylation resulting in a phenomenon known as innate immunological memory or trained immunity. In particular, β-glucan induces trained immunity in monocytes via a dectin-1/Raf-1/Akt/mTOR/HIF-1α pathway associated with switching glucose metabolism from oxidative phosphorylation to aerobic glycolysis, which defines a novel therapeutic approach for both infectious and inflammatory diseases [13].

Cellular Responses

After ligand binding, dectin-1 can induce several cellular responses, including phagocytosis, respiratory burst, and chemokine and cytokine production [1]. Recent advances have also given us considerable new insights into the cellular functions that are regulated by dectin-1. For instance, it has been shown that dectin-1 can negatively regulate fungal-mediated neutrophil extracellular trap (NET) formation, and dectin-1 deficiency promotes NET-mediated pathology. Mechanistically, phagocytosis mediated via dectin-1 acts as a cellular sensor for microbial size, preventing NETosis by downregulating neutrophil elastase translocation to the nucleus. Upon contact with noningestible pathogens, dectin-1-deficient mice succumb to the infection due to their increased levels of NETosis leading to tissue damage, and treatment with a neutrophil elastase inhibitor could rescue these mice [14]. Dectin-1 has also been implicated in autophagy since signaling through dectin-1 can trigger the recruitment of autophagy-related protein light chain 3 (LC3) to phagosomes containing β-1,3-glucan, which can facilitate MHC-II presentation of fungal-derived antigens [15, 16].

Role in Antifungal Immunity

The most compelling evidence in the last years comes from mouse models, in which absence of this receptor leads to different degrees of susceptibility to infection with many pathogenic fungi including *C. albicans*, *A. fumigatus*, and *Pneumocystis carinii*, and more recently *Candida glabrata, Trichophyton rubrum*, and *Coccidioides immitis*. In these models, dectin-1 was required for fungal recognition and killing by myeloid cells, and subsequent development of T-helper cell-mediated adaptive immune responses and susceptibility was associated with impaired leukocyte responses and inflammatory cell recruitment resulting in increased fungal growth and dissemination [17, 18]. In addition to protection against systemic fungal disease, dectin-1 has a crucial role in protecting the gastrointestinal (GI) tract during systemic candidiasis and in inflammatory bowel disease, and has been shown to modulate gut homeostasis by interacting with fungal components of the microbiota, which will be further discussed in the following section. In addition, dectin-1 and intestinal fungi have recently been linked with the development of alcoholic liver disease. Chronic alcohol administration causes fungal dysbiosis and translocation of fungal β-glucan into the systemic circulation, which induces liver inflammation and alcoholic liver disease in a dectin-1/IL-1β-dependent manner [19]. All these data highlight the crucial role of dectin-1 in modulating fungal-mediated inflammation.

In humans, single nucleotide polymorphisms (SNPs) in dectin-1 have also been linked with increased susceptibility to major fungal infections, including mucosal candidiasis and invasive aspergillosis. The mutated form of dectin-1 (Y238X), showing reduced expression, did not mediate β-glucan binding and was associated with defective cytokine production [20, 21]. Moreover, an SNP in dectin-1 has also been associated with a severe form of ulcerative colitis [22], highlighting the role of dectin-1 in gut homeostasis, as described.

The Dectin-2 Cluster

Research in the last 10 years has also seen the discovery and characterization of a new cluster of CLRs involved in antifungal immunity. The genes encoding these receptors are located in a cluster, near dectin-1, on chromosome 6 in mice and chromosome 12 in humans, and members of this family include clec6a (dectin-2), clec4d (MCL), and clec4e (macrophage-inducible C-type lectin or Mincle), amongst others (which have not yet been implicated in antifungal immunity). Their expression appears to be primarily restricted to myeloid cells, including monocytes, macrophages, neutrophils, and DCs [23].

Ligands and Cellular Responses

Dectin-2 – the prototypical member of this family – contains 1 CRD in the extracellular domain that can recognize α-mannans and O-linked mannoproteins from several fungi, including *Candida, Histoplasma capsulatum*, and *Cryptococcus neoformans*, in a Ca^{2+}-dependent manner. This interaction can modulate cytokine and ROS production, as well as fungal killing [24]. In addition, dectin-2 can induce cysteinyl leukotriene production, which has been shown to be essential for the initiation of airway inflammation and Th2 immunity against house dust mites. Interestingly, it also mediates cysteinyl leukotriene production following recognition of *A. fumigatus*, which could have implications in fungal-mediated asthma exacerbations [25]. MCL has been mainly associated with the recognition of α-mannans from *Candida*, while Mincle, originally described as the receptor for the mycobacterial cell wall glycolipid trehalose-6,6′-dimycolate (TDM), can also interact with mannitol-linked mannosyl fatty acids, glyceroglycolipids, and α-mannose from *Malassezia* leading to cytokine production. More recently, the interaction between Mincle and its newly identified intracellular ligand β-glucosylceramide (GlcCer) was involved in the pathogenesis of Gaucher disease, an inflammatory genetic disorder characterized by the hematopoietic-specific deletion of the degrading enzyme of GlcCer, named glucosylceramidase. Accumulation of GlcCer in specific organs, including the liver and spleen, induces proinflammatory cytokine production and systemic inflammation in a Mincle-dependent manner [26].

Intracellular Signaling

All the receptors of this family couple with the ITAM-containing Fc receptor γ-chain (FcRγ) chain to drive intracellular signaling via the Syk-CARD9 pathway [27]. Signaling through these receptors can often synergize or antagonize that of other CLRs, including dectin-1, TLRs, and inflammasomes [28]. MCL can dimerize with either dectin-2 or Mincle modulating their surface expression and magnifying their signaling activation and subsequent cellular responses, and these interactions will be reviewed in the section below [29, 30].

Role in Antifungal Immunity

In vivo, dectin-2 has been shown to exert a protective role against *C. albicans, C. glabrata*, and *T. rubrum* infections [31] and, together with MCL, they have been suggested to promote Th17 responses to *Fonsecaea pedrosoi* and *Blastomyces dermatitidis,* respectively [32, 33], while Mincle can antagonize these responses [32]. Mice deficient in MCL show impaired vaccine resistance against *B. dermatitidis* infections, and this lack of resistance was associated with a reduced recruitment of Th17 cells to the lung upon recall following experimental challenge [33]. Recent studies, using deficient mouse models, have suggested that Mincle might play a role in host defense during infections with *Pneumocystis* spp. (pneumonia), *C. albicans,* and *Malassezia*. In these models, Mincle deficiency was associated with altered cytokine responses and increased susceptibility to infection [34–36].

In humans, it has been shown in a small cohort of patients that a dectin-2 SNP is associated with susceptibility to pulmonary cryptococcosis [37]. MCL and Mincle have not been linked yet with susceptibility to fungal infections in humans, although SNPs have been associated with other diseases, such as tuberculosis and rheumatoid arthritis.

DC-Specific Intercellular Adhesion Molecule-3-Grabbing Nonintegrin

DC-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) is a type II transmembrane human receptor whose expression is restricted to myeloid cells, including macrophages and DCs [38]. There are 8 murine homologs of DC-SIGN, known as SIGNR, and all of these are located in a gene cluster within chromosome 8.

Ligands and Intracellular Signaling

DC-SIGN forms tetramers with each chain containing 1 extracellular CRD that binds mannosylated and fucosylated structures. The receptor possesses an incomplete ITAM in its cytoplasmic tail that is not thought to be able to directly induce cellular responses. Rather, upon

ligand recognition, signaling from DC-SIGN modulates other signaling pathways, including signals induced from TLRs. For instance, in immature DCs, the cytoplasmic tail of DC-SIGN is bound by the adaptor protein LSP1 and the Raf-1 signalosome, consisting of CNK1, KSR1, and Raf-1. Upon recognition of mannose-containing pathogens, such as *C. albicans*, various proteins are recruited to the signalosome that induce Raf-1 activation, which then results in the phosphorylation and acetylation of the NF-κB subunit p65. p65-p50 complexes are also simultaneously activated by TLRs. Acetylated p65 is more stable and has an enhanced transcriptional rate which leads to an increased activation of its target genes, promoting Th1 and Th17 differentiation. On the other hand, following recognition of fucose-containing pathogens, such as *Schistosoma mansoni*, the Raf-1 signalosome is displaced. LSP1 becomes phosphorylated and enables the assembly of the fucose-specific signalosome consisting of the kinase IKKε and the deubiquitinase CYLD that allows nuclear translocation of ubiquitinated Bcl3. Nuclear Bcl3 then modulates TLR-induced cytokine and chemokine expression profiles to promote Th2 responses [38]. Thus DC-SIGN is able to direct adaptive immune responses based on the nature of the pathogen.

Role in Antifungal Immunity

Due to the absence of in vivo models, most research on DC-SIGN in the last decade has relied on in vitro studies. In addition to its role in the recognition of mannoproteins from *C. albicans*, it has also been suggested to interact with polysaccharides from *Paracoccidioides* extracellular vesicles and to mediate internalization of *Aspergillus* conidia [24, 39]. SIGNR3, the closest murine homolog of DC-SIGN, has been implicated in sensing fungi present in the microbiota [40]. However, more studies are needed to explore the role of these receptors in an in vivo context.

In a small cohort of patients, it was suggested that SNPs of DC-SIGN are correlated with the development of invasive pulmonary aspergillosis and fungal keratitis. Although these results need to be validated in larger cohorts, they suggest that genetic variants of DC-SIGN could influence the risk of developing fungal infections [17].

Mannose Receptor

MR is a type-I transmembrane protein primarily expressed by myeloid cells, including macrophages and DCs, but is also expressed by epithelial and endothelial cells. The extracellular domain of MR consists of 3 regions: a cysteine-rich domain, a fibronectin type II-like domain, and 8 CRDs. The intracellular domain contains a short cytoplasmic tail that lacks any defined signaling motif.

Ligands and Cellular Responses

MR has 2 lectin binding activities involving Ca^{2+}-dependent recognition of carbohydrates terminated in D-mannose, L-fucose, or N-acetyl glucosamine via its CRDs, and Ca^{2+}-independent binding of sulfated acidic glycans through its cysteine-rich domain. MR was the first receptor described to be involved in the recognition of fungi, including *C. albicans, C. neoformans*, and *P. carinii,* and shown to be able to induce their phagocytosis by DCs [23]. However, some authors have suggested that MR is more a binding receptor that requires a partner to trigger phagocytosis in myeloid cells [41]. Later, *C. albicans* was shown to induce IL-17 production from human antigen-presenting cells in an MR-dependent manner. In particular, the dectin-1/TLR2 pathway could amplify MR-induced IL-17 production in the absence of mitogenic stimulation [42]. Together with NOD2 and TLR9, MR was suggested to interact with fungal chitin, diminishing inflammation by increasing IL-10 and reducing proinflammatory cytokine production [43]. Recent studies have further supported the role of MR in controlling inflammation. For instance, MR has been shown to induce T-cell reprogramming and subsequent tolerance via inhibition of CD45 and upregulation of the inhibitory molecule CTLA-4, which was responsible for the impaired cytotoxic activity of T cells [44].

Intracellular Signaling

MR does not have any defined signaling motif in their cytoplasmic domain, and the ability of MR to induce specific signaling is still controversial. Recent work has shown the important role of the FcRγ chain along with the adaptor protein Grb2 in MR-mediated phagocytosis of *Mycobacterium tuberculosis*. MR interaction with the FcRγ chain was shown to be essential for MR surface expression. In addition, MR activation has been suggested to lead to phosphorylation of its cytoplasmic tyrosine and recruitment of Grb2 followed by activation of the Rac/Pak/Cdc-42 signaling cascade. This in turn leads to SHP-1 recruitment to the phagosome, limiting PI3K activity and phagosome-lysosome fusion [45].

Role in Antifungal Immunity

In vivo studies have suggested that MR has a largely redundant role in immunity to most fungal pathogens,

including *C. albicans*. However, mice lacking MR were shown to be more susceptible to *C. neoformans* and experimental blastomycosis. This effect was associated with defective DC maturation and subsequent $CD4^+$ T-cell responses [46, 47].

Additional Mannose-Binding Lectins

Galectins

Galectins are a family of soluble and cell-bound proteins that bind β-galactosides. These proteins are highly conserved and are expressed by diverse cell types, including monocytes, DCs, macrophages, mast cells, B cells and T cells. Galectin-3 contains a CRD preceded by a nonlectin region consisting of short Pro/Gly-rich tandem repeats.

Ligands and Cellular Responses

It was previously shown that galectin-3 on macrophages recognizes β-mannan from *C. albicans* and, in collaboration with TLR2, is able to induce protective antifungal responses via TNF-α secretion [24]. It has also been suggested that galectin-3 can have a dual role in the regulation of neutrophil function, depending on its cellular location. While recombinant galectin-3 was shown to enhance neutrophil phagocytosis of *C. albicans*, it was also found that intracellular galectin-3 can downregulate neutrophil fungicidal activities by physically interacting with Syk and therefore reducing ROS-dependent killing of *C. albicans* [48].

Role in Antifungal Immunity

Mice deficient in galectin-3 have been found to be more susceptible to disseminated candidiasis [24]. More recently, it was also shown to play a role in *C. neoformans* infection, as galectin-3-deficient mice were found to be more susceptible to cryptococcosis than wild-type mice. In addition, galectin-3 was able to inhibit fungal growth and exert a direct lytic effect on *C. neoformans* extracellular vesicles protecting the host from potential fungal virulence factors carried in these vesicles [49].

Mannose-Binding Lectin

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 an α-helical coil domain. 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. There are 2 MLB isomers in the mouse, i.e., MBL1 and MBL2, while humans only have MBL2.

Ligands and Cellular Responses

Fungal binding by MBL triggers a protease cascade though the MBL-associated serine proteases that leads to the activation of the complement pathway (the lectin pathway) and deposition of complement components on the fungal surface. MBL plays an important role in the innate defense against several fungal pathogens, including *C. albicans*. Direct interaction between MBL and mannosylated components of the fungal cell wall results in agglutination as well as complement activation, which can inhibit growth of (but not kill) *Candida*. In addition, during pulmonary inflammation, MBLs can leak into alveoli where they can interact with *A. fumigatus* conidia through D-mannose, L-fucose, and N-acetylglucosamine residues in a Ca^{2+}-dependent manner, leading to complement activation. Furthermore, studies utilizing serum obtained from transgenic animals have indicated that only MBL2, and not MBL1, recognizes *A. fumigatus* [50]. MBL can also mediate complement-independent responses, as activation of MBL2 on human neutrophils can control phagocytosis and subsequent ROS production against *Candida,* independently of complement activation, a response thought to be coupled with dectin-1 recruitment and signaling [24].

Role in Antifungal Immunity

In a murine model of aspergillosis, administration of recombinant human MBL2 protects mice against infection, while MBL deficiency renders them susceptible. This susceptibility was associated with reduced phagocytosis, complement activation, and cytokine production [50]. MBL1 has also been shown to modulate *Candida* colonization in the gut [51]. Furthermore, in humans, SNPs in MBL2 have been implicated in susceptibility to aspergillosis and candidiasis [52].

Toll-Like Receptors

TLRs are type-I integral membrane glycoproteins, each with an extracellular N-terminal ligand recognition domain constructed of tandem copies of a leucine-rich repeat motif that provides ligand specificity, a single

transmembrane helix, and a C-terminal cytoplasmic signaling domain known as Toll IL-1 receptor domain (TIR) (reviewed elsewhere in this series). These receptors homo- or heterodimerize upon ligand binding followed by recruitment and signaling through specific sets of adaptor proteins, including myeloid differentiation primary response 88 (MyD88) and TIR domain-containing adapter-inducer interferon-β (TRIF) [53].

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 [23]. For instance, O-linked mannosyl residues as well as rhamnomannans from *Candida* and *Scedosporium,* respectively, can be recognized by TLR4 leading to the induction of proinflammatory cytokines, such as TNF-α and IL-6, by macrophages. Furthermore, phospholipomannan and glucuronoxylomannan from *Candida* and *Cryptococcus*, respectively, have been reported to interact with TLR2/TLR6 and TLR2/TLR1 heterodimers leading to the production of proinflammatory mediators, including TNF-α and nitric oxide, by macrophages [23].

Role in Antifungal Immunity

TLRs were first identified over 2 decades ago by their ability to control fungal infections in *Drosophila*, which prompted their study in the mammalian host defense against fungal pathogens. Studies have suggested that different TLRs are able to activate specific arms of the antifungal defense mainly in collaboration with CLRs such as dectin-1 and MR. MyD88-deficient mice, which have defective TLR responses from multiple family members, show increased susceptibility to infection with major human fungal pathogens, including *C. albicans*, *A. fumigatus*, *C. neoformans*, and *H. capsulatum* [17]. In addition, TRIF-deficient mice were found to be susceptible to invasive pulmonary aspergillosis [24]. However, some controversy has risen from studies about the role of specific TLRs in antifungal immunity. For instance, TLR2-deficient mice were reported to have increased susceptibility to disseminated candidiasis, which was attributed to a decreased production of proinflammatory cytokines and reduced neutrophil recruitment. However, another study demonstrated that TLR2-deficient mice are more resistant to disseminated candidiasis associated with increased IFN-γ production and monocyte recruitment. These differences have subsequently been attributed to the use of different fungal strains [54].

Recent studies have also shown that intracellular TLRs, including TLR3, TLR7, and TLR9, are involved in antifungal immunity. *A. fumigatus* can activate the phagocytosis-dependent TLR9/BTK/calcineurin/NFAT signaling pathway leading to the production of proinflammatory cytokines, such as TNF-α, neutrophil recruitment, and fungal clearance [55]. TLR3 on migratory CCR7+ DCs has been shown to contribute to CD8+ memory T-cell responses against *A. fumigatus,* through the sensing of fungal RNA and the induction of cross-presentation via MHC-I [56]. Finally, there is some controversy regarding the role of TLR7 in fungal infection. Phagocytosis of *C. glabrata* by DCs induces a deleterious TLR7-dependent type-I IFN response that promotes fungal persistence in host tissues, such as spleen and liver [57]. Another study showed that mice deficient in TLR7 were highly susceptible to systemic *C. albicans* infection, as TLR7 was required on DCs for sensing *Candida*-derived RNA and subsequent IL-12 production [58].

Healthy individuals with defects in MyD88 signaling do not exhibit increased susceptibility to fungal infections [59]. However, polymorphisms in several TLRs, including TLR1, TLR2, TLR3, TLR4, TLR6, and TLR9, have been associated with increased risk of fungal infections in immunocompromised individuals in several studies. This suggests that TLRs are not primarily required for antifungal immunity in humans, but that under conditions of altered immunity their role becomes more apparent [6, 52].

NOD-Like Receptors

NLRs are cytoplasmic receptors formed of an N-terminal effector domain, a central NOD involved in oligomerization and a C-terminal leucine-rich repeat domain involved in ligand binding. There are 4 N-terminal domains that define their subfamilies named NLRA, NLRB, NLRC, and NLRP [53]. Originally associated with bacterial recognition, these receptors have also been linked with fungal immunity, mainly through interactions with other PRRs.

Ligands and Cellular Responses

The best characterized NLR in terms of antifungal immunity is NLRP3, which is a component of the inflamma-

some, characterized by the activation of caspase-1 and the subsequent production of IL-1β and IL-18. NLRP3 is expressed by many cells, including macrophages, DCs, T cells, B cells, and epithelial cells. Several yeast cell wall preparations have been shown to activate NLRP3, as well as secreted proteases from *C. albicans* [60]. In vitro studies have shown the importance of NLRP3 in host defense against *A. fumigatus*. For instance, LAP (LC3-associated phagocytosis), a noncanonical form of fungal autophagy, can regulate inflammation by inhibiting NLRP3 activation. Here, *A. fumigatus* was shown to activate IFN-γ-dependent DAPK1, a death-associated protein kinase, which led to fungal autophagy and proteosomal-mediated NLRP3 degradation, limiting pathogenic inflammatory responses [61]. Fungi can also affect this response, such as *C. neoformans,* whose capsule can prevent NLRP3 activation facilitating intracellular survival [6].

C. albicans and *C. neoformans* have been shown to activate additional canonical and noncanonical inflammasomes, including NLRC4, NLRP10, and caspase-8 [3, 34]. Activation of dectin-1/Syk/CARD9 signaling upon fungal recognition can activate the noncanonical MALT1/ASC/caspase-8 inflammasome. Whereas the CARD9/Bcl10/MALT1 scaffold directed IL-1β transcription, the recruitment of caspase-8 and the adaptor protein apoptosis-associated speck-like protein containing a CARD domain (ASC) into this scaffold induced the processing of pro-IL-1β into its mature form by caspase-8 [62].

Role in Antifungal Immunity

Different components of the inflammasome, including ASC, IL-1R, IL-1β, and caspase-1, have been shown to be involved in antifungal resistance to many pathogens, such as *C. albicans, A. fumigatus, C. neoformans*, and *Paracoccidioides brasiliensis* [6, 63]. Additionally, mice deficient in NLRP3 have shown susceptibility to several fungal pathogens, including mucosal candidiasis and subsequent disseminated infections [17, 24]. In addition to its role in *Candida* infection, NLRP3 has been suggested to be essential for resistance against *P. brasiliensis* through its role in IL-18-dependent inflammatory responses [64]. NLRC4 has also been shown to exert a protective, but tissue-specific, role in oropharyngeal candidiasis. In contrast to NLRP3, NLRC4 is only essential in the stromal compartment where it is involved in neutrophil recruitment and control of fungal dissemination [65]. In humans, a SNP in NLRP3 has been associated with susceptibility to mucosal candidiasis due to impaired production of IL-1β [52].

RIG-Like Receptors

RLRs are intracellular receptors characterized by the presence of a DExD/H box RNA helicase domain with ATPase activity. They are expressed in both immune and nonimmune cell types and regulate signaling pathways that promote type-I and type-III IFN production, and are traditionally associated with antiviral immunity [53].

Role in Antifungal Immunity

DC-derived type-I IFNs have also been shown to play a key role in host responses against *Candida* and *Histoplasma*; however, type-I IFN production upon fungal recognition seems to be dependent on either dectin-1 and/or TLR7/TLR9 signaling pathways [57, 66, 67]. A recent study has shown that type-I and type-III IFNs are critical regulators of the interplay between CCR2+ monocytes and neutrophils, as IFN-α and IFN-λ promote optimal antifungal responses by neutrophils upon *A. fumigatus* challenge [68]. Loss of MDA5, a melanoma differentiation-associated gene and member of the RLR family, has also shown to increase susceptibility to *Candida* infections in mice and humans [69].

Additional β-Glucan Receptors

In addition to dectin-1 and CD23, other receptors such as the complement receptor 3 (CR3) and lactosylceramide have been shown to recognize β-glucans. CR3 is an integrin dimer consisting of CD11b and CD18, and is expressed widely by myeloid cells, including monocytes, macrophages, DCs, neutrophils, and natural killer (NK) cells. This phagocytic receptor has a "lectin-like domain" that can bind β-glucan with high affinity, and it has been suggested to be the primary β-glucan receptor on neutrophils and NK cells [70]. However, CR3 predominantly mediates fungal phagocytosis and killing in a complement-dependent manner. It has also been suggested that CR3 together with CR4 (CD11c/CD18) can participate in a complement-independent phagocytosis of *C. neoformans.* This involves opsonization with specific anticapsular IgA and IgM antibodies that changes the structure of the capsule exposing the CD18 binding site in the glucuronoxylomannan [71].

Recent studies have further supported the role of CR3 in antifungal immunity. CR3 binding to fibronectin and β-glucan can initiate a complex mechanism of integrin interactions in neutrophils that results in cellular aggregation and NETosis [72]. In vivo models have shown that

CR3 helps drive Th1 and Th17 responses during *A. fumigatus* infections and is essential for resistance to infection with *C. albicans* and *C. glabrata* [73, 74].

Scavenger receptors are a family of cell surface glycoproteins that have also been implicated in β-glucan recognition [1]. The macrophage receptor with collagenous structure (MARCO) has been shown to be required against *C. neoformans* infection in a mouse model. MARCO deficiency leads to impaired fungal control, associated with diminished cell recruitment and activation [75]. CD5 is a receptor that belongs to the scavenger-receptor cysteine-rich (SRCR) superfamily and is expressed primarily by B cells and T cells. Intriguingly, it has been shown that a naturally occurring soluble isoform of CD5 can bind to *Schizosaccharomyces pombe*, *C. albicans*, and *C. neoformans* fungal cells and induce their aggregation. It appears that one of the three SRCR repeats present in the CD5 extracellular domain can bind β-glucans, which might subsequently attenuate the immune response to systemic fungal challenge [76]. Using a mouse model, the scavenger receptors SCARF1 and CD36 have been shown to mediate cytokine production and host defense against *C. neoformans* in a β-glucan dependent manner by functioning as coreceptors to facilitate TLR2 signaling [77]. Finally, recent work has identified the receptor tyrosine kinase ephrin type-A receptor 2 (EphA2) as a β-glucan receptor in oral epithelial cells that is critical for mediating protective immunity during oral candidiasis. Binding of EphA2 to *C. albicans* activates STAT3 and MAPK signaling pathways required to induce proinflammatory cytokines, such as IL-17, to control fungal dissemination in a mouse model of oropharyngeal candidiasis [78].

PRR Crosstalk

Encounter with pathogens can lead to the simultaneous engagement of several PRRs, and the signals emanating from these different receptors are integrated to induce appropriate biological responses. Although this is still a poorly understood area, there have been significant advances in the last decade (Fig. 2). One discovery, for example, is that different receptors can form heterodimers. There is strong evidence showing that MCL can dimerize with related CLRs to regulate their levels of expression, expand ligand specificity, and amplify signaling. For instance, MCL can constitutively form heterodimers with dectin-2, which, compared to their respective homodimers, bind α-mannans more efficiently leading to potent Syk-dependent proinflammatory responses upon *C. albicans* infection [29]. In addition, MCLs have been shown to positively regulate Mincle gene expression through ligand binding as well as protein expression, through protein-protein interaction via its stalk region, thereby magnifying Mincle-mediated signaling [30]. There have also been many studies describing synergistic or antagonistic intracellular signaling between PRR in antifungal immunity. Through association with lipid rafts, dectin-1 and CR3, for example, can collaboratively trigger macrophage IL-6 and TNF-α production via the Syk-JNK-AP1 pathway and subsequently induce host defense against disseminated histoplasmosis [79]. More recently, it has been suggested that dectin-1 can also interact with dectin-2 and trigger the Syk-JNK pathway to activate the NLRP3 inflammasome in response to *H. capsulatum* [80].

Following fungal recognition, collaboration between CLRs and TLRs has also been shown to be pivotal in antifungal immunity, and this crosstalk has been particularly evident in the case of the fungus *F. pedrosoi*, an etiologic agent of chromoblastomycosis. This chronic infection of the skin and subcutaneous tissues was shown to result from inadequate innate fungal recognition by CLRs, primarily Mincle, which resulted in a defective inflammatory response. Using a murine model, it was shown that clearance of *F. pedrosoi* infection could be facilitated following cooperative stimulation of the TLR signaling pathway, an approach that was also shown to be effective in treating the disease in humans [81]. Moreover, recognition of this fungus by Mincle could suppress dectin-1- and dectin-2-induced T-cell responses [28]. This antagonistic role of Mincle over other PRRs has also been observed in other contexts, such as with TLR4 and NLRP3 [82]. Other interactions between CLRs and TLRs have also been described, including dectin-1 and TLR2 crosstalk in the recognition and phagocytosis of zymosan, and their ability to synergize in the activation of NF-κB and subsequent cytokine production (Fig. 2) [27].

It is important to mention that there is also evidence suggesting that NLRs could interact with other PRR members, including TLRs. For instance, fungal chitin, through MR, NOD2, and TLR9 activation, can diminish inflammation by increasing IL-10 and reducing proinflammatory cytokine production, as described above [43]. Moreover, it has been shown that IFN-β induced by *Candida parapsilosis* can inhibit fungal clearance by signaling through STAT1/2 to induce IL-27 in a TLR7- and NOD2-dependent manner. Therefore, inhibition of IL-27 could be a potential avenue for therapy in this disease, but further studies are needed [83].

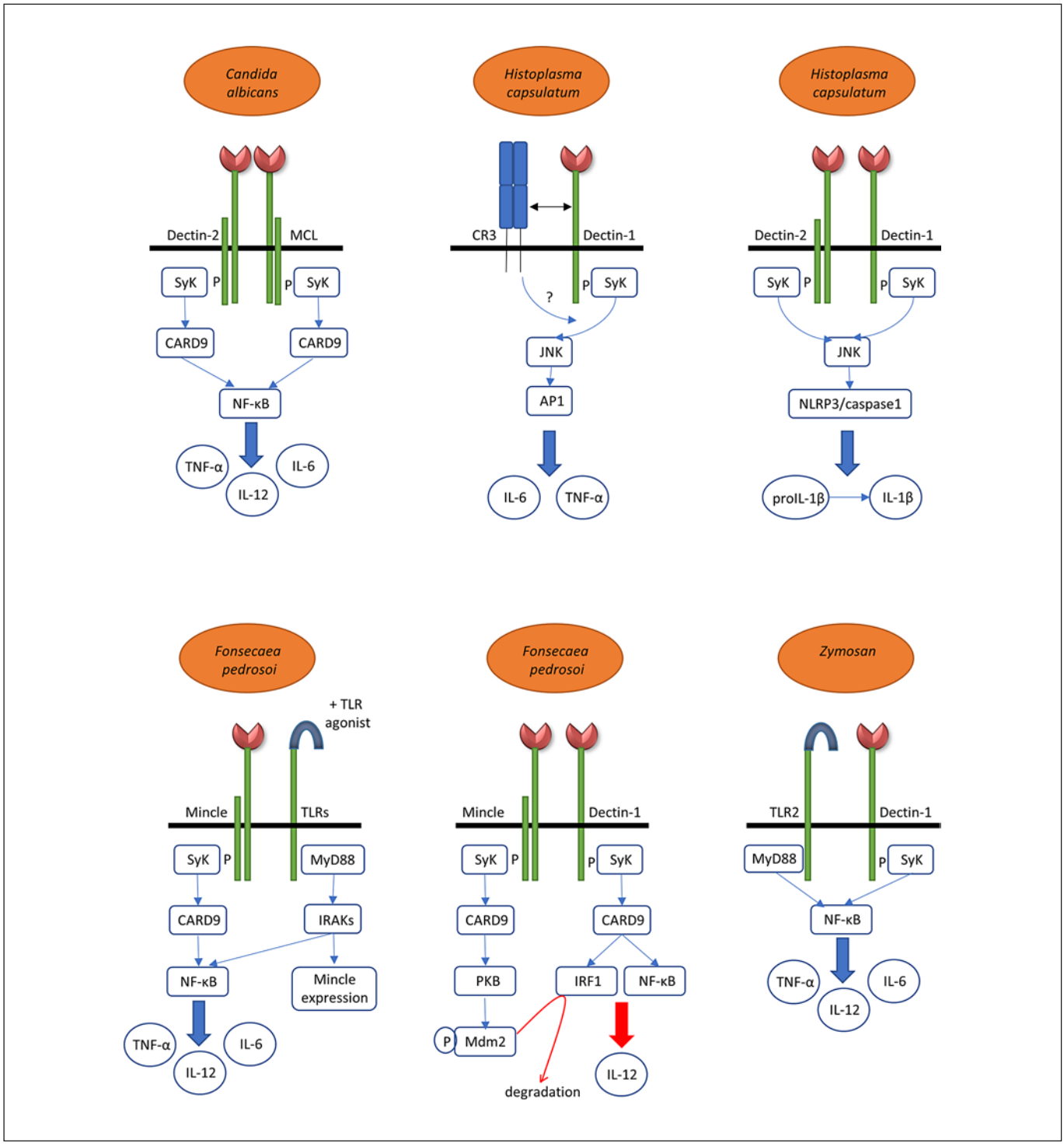

Fig. 2. Crosstalk between different PRRs in antifungal immunity. Dectin-2 and MCL can form heterodimers and amplify proinflammatory cytokine production upon *Candida* infection. Dectin-1 and dectin-2 can synergize to induce the NLRP3 inflammasome against *Histoplasma capsulatum* challenge. In addition, dectin-1 and CR3 can collaboratively trigger proinflammatory cytokine production against histoplasmosis. *Fonsecaea pedrosoi* activates the Mincle signaling pathway but requires costimulation with TLR ligands to induce protective immunity. Mincle can also antagonize dectin-1 signaling upon recognition of *F. pedrosoi*. Finally, dectin-1 and TLR2 interact in the recognition and phagocytosis of zymosan particles leading to proinflammatory cytokine production. Activatory signals are in blue, inhibitory signals are in red.

Innate Cellular Components

Surveillance and elimination of fungal pathogens relies on the sentinel behavior of several cells of the innate immune system and the recruitment of effector cells. Defects in antifungal effector functions of these cells result in susceptibility to many fungal pathogens, including *C. albicans* and *A. fumigatus*. Activation and differentiation of specific T-cell subsets is also a pivotal process, required for the control of systemic fungal infections with pathogens, including *Cryptococcus* and *Pneumocystis*, and protection against mucocutaneous infections. Indeed, the roles of Th1 and Th17 cells, respectively, have been well established in this context [6, 84]. Th1-type cytokines stimulate the effector function of phagocytes, while Th17-related cytokines, such as IL-17 and IL-22, promote the release of antimicrobial peptides by mucosal epithelial cells and induce neutrophil recruitment and activation [6, 17, 84–86]. The role of other adaptive immune cells, such as B cells, is less clear and has been reviewed elsewhere [23, 87]. Here, we are going to focus on recent advances in our understanding of the pivotal role of innate immune cells, including granulocytes, monocytes, macrophages, DCs, and innate lymphoid cells, in antifungal immunity (Fig. 3).

Granulocytes

Neutrophils are the most important innate immune effector cells for the control of many fungal infections. Their importance in fungal infections was originally demonstrated in humans suffering from neutropenia that exhibited a dramatic increase in susceptibility to major fungal pathogens, including *C. albicans* and *A. fumigatus*. Moreover, mutations associated with various aspects of neutrophil recruitment and antimicrobial activity, including CXCR1, NADPH oxidase, and myeloperoxidase, are strongly associated with an increased risk of systemic fungal infections in humans [87]. Neutrophils use oxidative and nonoxidative killing mechanisms against fungal pathogens (Fig. 3). Oxidative mechanisms include ROS production, mediated by the enzymes NADPH oxidase and myeloperoxidase, while nonoxidative mechanisms include the release of granules containing proteins with antimicrobial and degradative properties, including defensins, lysozyme, lactoferrin, gelatinases, elastase and cathepsin-G [41, 88]. NADPH oxidase deficiency results in chronic granulomatous disease, which is associated with increased susceptibility to invasive mold infections [17]. Interestingly, the jagunal homologue 1 (JAGN1) protein has been recently established to be an important factor for survival and differentiation of neutrophils in fungal host defense. Mice deficient in JAGN1 could not mount an efficient neutrophil-dependent immune response against *C. albicans*, characterized by defective migration and impaired formation of cytotoxic granules [89]. Furthermore, C5a receptor signaling in human neutrophils has been linked to the regulation of killing mechanisms during *Candida* infection [90].

Neutrophils also produce NETs against fungi that are too big to be phagocytosed. Originally described in 2004 as a killing mechanism against bacterial infection, NETs are large fibrillar structures composed of DNA, histones, and antimicrobial peptides that bind extracellular pathogens preventing them from spreading and ensuring a high concentration of antimicrobials [91]. NETs have been shown to be induced by several fungi, including *C. albicans*, *A. fumigatus*, and *C. neoformans* [17]. Calprotectin, a key component of NETs, was shown to control the growth of *Candida* and *Aspergillus,* and mice deficient in calprotectin are more susceptible to infection [92]. Additional methods of killing by neutrophils include a ROS-independent mechanism of killing against *Candida* that relies on CR3 ligation and the activation of the PI3K and CARD9 signaling pathways [93] and a mechanism that involves induction of fungal apoptosis [94]. In the latter, the engulfment of *A. fumigatus* spores by neutrophils was shown to induce a programmed cell death response in the fungus, induced by the phagocyte NADPH oxidase and fungal caspases [94].

IL-17 is a potent mediator of neutrophil recruitment, and in addition to lymphocytes, neutrophils have also been proposed to be a source of IL-17, which acts in an autocrine manner to induce further neutrophil recruitment to the site of infection [95]. However, the extent to which IL-17 can control neutrophil function is unclear, since some in vivo studies have suggested that absence of IL-17 does not result in complete neutrophil dysfunction, and their recruitment is not entirely dependent on IL-17 [96]. This suggests that additional IL-17-independent signals can contribute to neutrophil recruitment. For instance, NK cell-derived GM-CSF was shown to be essential for the fungicidal activity of neutrophils. GM-CSF production by NK cells and subsequent activation of neutrophils was orchestrated by DCs through IL-23 production [97]. In addition, IL-15 production by monocytes was shown to drive efficient activation and GM-CSF release from NK cells, which was necessary to boost the killing potential of neutrophils against *Candida* [98].

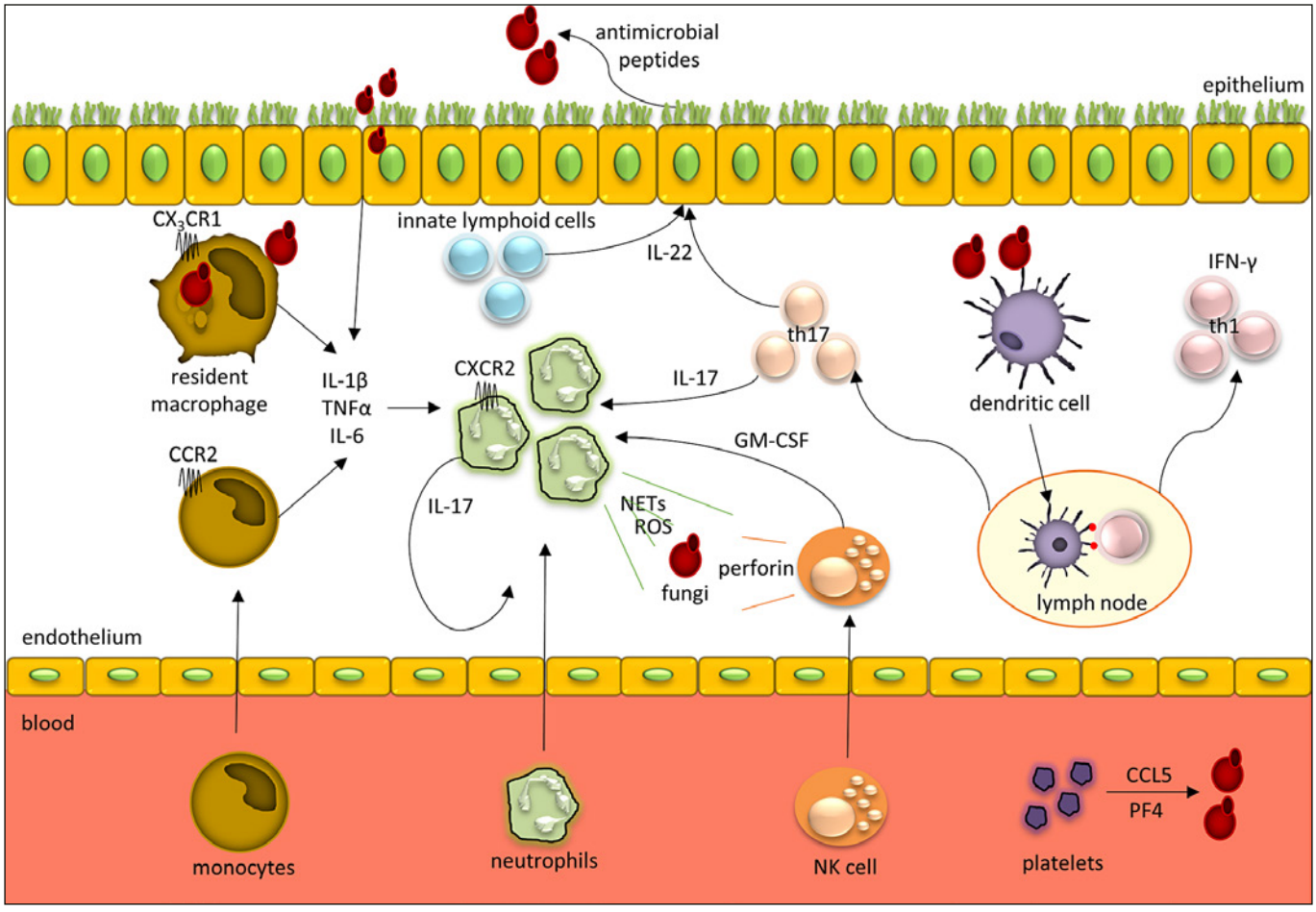

Fig. 3. Effector mechanisms against fungal pathogens. Fungi can invade tissue by inducing endocytosis or actively penetrating the epithelium. Epithelial cells can produce antimicrobial peptides with antifungal activities and proinflammatory cytokines that can recruit other immune cells, such as monocytes, which will also contribute to fungal clearance. Tissue resident macrophages can phagocyte and kill fungal pathogens; in addition, neutrophils can also produce ROS and release neutrophil extracellular traps (NETs) that capture fungi and contain antimicrobial proteins that inhibit their growth. Dendritic cells can migrate to lymph nodes and activate specific T-cell responses depending on the microbial morphology and site of infection. Innate lymphoid cells can also produce proinflammatory cytokines that contribute to mucosal antifungal responses. Finally, in the last steps of invasion, fungi breach the endothelium allowing them access to the bloodstream where they can activate platelets to produce cytokines and molecules with antifungal activity. Adapted from Netea et al. [84].

Despite their crucial role, excessive neutrophil activation and/or recruitment can also be harmful. For example, increased neutrophil recruitment into the kidney amplifies late renal immunopathology and increases mortality in a model of invasive candidiasis [99]. This demonstrates that excess inflammation can be detrimental to the host, causing tissue damage and contributing to the pathogenesis of the disease. In an attempt to better describe the disease origins and progress, this and other concepts were incorporated in the damage-response framework by Pirofski and Casadevall [100]. This idea states that the disease-causing potential of a microbe is determined by the immune state of the host, and that the outcome of the interaction between host and pathogen is dependent on the amount of damage to the host, which can be a result of microbial factors and/or the host response [100].

Other granulocytes such as mast cells, basophils, and eosinophils have been implicated in allergic fungal diseases. For instance, due to their strategic location in the lung, mast cells can readily interact with invading fungi,

including *A. fumigatus*, which induces their degranulation, the secretion of granular proteins and cytokines, and fungal killing [101]. In addition, eosinophil protease-activated receptor 2 (PAR2) is cleaved by aspartate proteases produced by *Alternaria alternata*, exposing neoligands that activate eosinophils causing their degranulation and release of cytotoxic granule proteins and chemokines in the lung [102]. IgE binding to *A. fumigatus*-derived allergens can crosslink FcεR on the surface of basophils inducing their degranulation and histamine release leading to asthma exacerbation [103]. However, more studies are needed to fully decipher how these cell types interact with fungi and their role in antifungal immunity outside the lung.

Mononuclear Phagocytes

Besides neutrophils, mononuclear phagocytes are now being increasingly recognized as critical mediators of host defense against fungi. Several studies have focused on understanding the mechanisms by which resident and recruited monocytes, macrophages, and DCs accumulate and become activated at the sites of fungal infection. Tissue resident macrophages as well as monocyte-derived macrophages have been revealed to be key effector cells in controlling fungal infections through the direct killing of fungi and the production of proinflammatory cytokines and chemokines that can recruit and activate other immune cells in peripheral organs (Fig. 3) [6, 17].

Macrophages

The importance of macrophages in antifungal immunity was first shown over 20 years ago, in which in vivo depletion of macrophages increased susceptibility to disseminated candidiasis [6, 17]. This has been further supported by recent studies showing that deficiency in the chemokine receptor CX_3CR1, which is associated with impaired recruitment of monocyte-derived macrophages into tissues, increased fungal growth and mortality after *Candida* challenge. In fact, patients with a polymorphism leading to decreased function of CX_3CR1 also exhibit increased susceptibility to systemic candidiasis [104]. Macrophage switching between M1/M2 phenotypes has also been shown to be crucial in the protection against diverse fungal pathogens, including *C. albicans*, *C. neoformans*, *H. capsulatum*, and *P. brasiliensis*. For instance, type II cytokines, such as IL-4, impair host defense against *H. capsulatum* by amplifying macrophage generation of IL-33 via the STAT6/IRF4/dectin-1 pathway [105]. Conversely, type I cytokines and STAT1-mediated classical macrophage activation were essential for inducing protective immunity against *C. neoformans* associated with the induction of the downstream molecules IRF1 and SOCS1 [106].

Monocytes

In addition to macrophages, studies in the last decade have also highlighted the importance of monocytes in antifungal immunity. Monocytes can orchestrate and facilitate innate and adaptive antifungal immunity by regulating neutrophils, NK cells, and T-cell responses during infection [98, 107]. In experimental models, depletion of CCR2+ Ly6C+ inflammatory monocytes as well as deficiency in the chemokine receptor CCR2, which is essential for monocyte recruitment into tissues, has been shown to increase susceptibility to disseminated candidiasis and invasive aspergillosis [108, 109]. In addition, monocytopenia in humans has also been suggested to be a risk factor for developing fungal infections such as histoplasmosis and in invasive mold infections [110]. Conversely, excessive monocyte recruitment and activation can also lead to excessive neutrophil accumulation and lethal kidney immunopathology in mice with systemic candidiasis, as described above. This suggests that monocyte recruitment and activation in tissues needs to be tightly regulated during fungal infection [111]. Monocytes are also thought to play a critical role in trained immunity, as detailed above [13].

Dendritic Cells

DCs exposed to fungal pathogens exhibit augmented expression of proinflammatory cytokines and activation markers, which results in their migration to local lymph nodes where they can stimulate naïve T cells toward distinct effector T-cell subsets or induce tolerance (Fig. 3). Studies in the last decade have been focused on further understanding the role of diverse DC subtypes and DC-derived molecules in antifungal immunity. For instance, lymphoid-derived plasmacytoid DCs (pDCs) have been suggested to have a role in antifungal immunity in a tissue-dependent manner. Whereas depletion of pDCs was shown to render mice more susceptible to invasive aspergillosis in one study [112], others have suggested that pDCs can mediate tolerance in vaginal candidiasis and in

a model of lung infection with *P. brasiliensis* [113]. *P. brasiliensis* infection, for example, increased the number of pDCs expressing indoleamine 2,3-dioxygenase (IDO), an enzyme with immunoregulatory properties that drives regulatory T cell (T_{reg}) expansion [113]. Remarkably, dectin-1-mediated activation of pDCs has been suggested to promote Th2 responses, while dectin-1 activation on myeloid DCs decrease Th2 responses upon β-glucan challenge. This cell-specific effect was associated with their distinct abilities to control OX40L surface expression [114]. It is also interesting to mention that dectin-2-mediated *A. fumigatus* recognition by pDCs induces proinflammatory cytokine production and the formation of pDC extracellular traps [115].

Specific DC subsets have also been shown to act in a complementary fashion during fungal infections to induce appropriate T-cell responses. For instance, tissue-resident Flt3L-dependent DCs and CCR2-dependent monocyte-derived DCs can collaborate in antigen presentation and T-cell priming during mucosal candidiasis, while Langerhans cells appear not to be required for this response [116]. Monocyte-derived DCs also have a pivotal role in inducing CD4+ T-cell responses against *Aspergillus* infection in the lung. TNF-α from monocyte-derived DCs induces neutrophilia versus eosinophilia during persistent fungal infection in the airways by modulating the balance between IL-17 and IL-5 production [117].

The ability of DC to shape the type of effector T-cell responses depends on several factors, including the nature of fungal organisms, the site of infection, and host susceptibility. For instance, skin-resident DC subsets promote distinct and opposing antigen-specific T-helper responses. Using a *C. albicans* infection model, Kaplan et al. [118] have shown that Langerhans cells are necessary and sufficient for the generation of Th17 cells, while Langerin+ dermal DCs are required for the generation of antigen-specific cytotoxic lymphocytes and Th1 cells, and also inhibited the ability of Langerhans cells to promote Th17 responses. Fungal morphology can also determine T-helper cell differentiation. Yeast forms of *C. albicans* can induce Th17 responses through dectin-1 interaction on Langerhans cells and subsequent IL-6 production. Conversely, filamentous forms induced Th1 responses due to the absence of dectin-1 ligation [119]. Furthermore, the Kaplan group has shown that nociceptive sensory fibers drive IL-23 production in dermal DC, leading to the induction of IL-17 by dermal γδ T cells and subsequent activation of neutrophil antimicrobial activity, and conferring protection against *C. albicans* cutaneous infections [120].

Innate Lymphocytes

Innate lymphoid cells (ILCs) are the most recently identified population of immune cells that have been implicated in antifungal immunity. Three types of ILCs have been defined and characterized by their cytokine profile and transcription factor expression, ILC1 or Th1-like, ILC2 or Th2-like, and ILC3 or Th17-like cells. ILC3 or group 3 ILCs are characterized by their production of Th17 cytokines, including IL-17 and IL-22. IL-17-producing ILC3 cells were demonstrated to play an essential role in mucosal candidiasis [121, 122]. Additionally, it has been shown that *Candida*-mediated protection against *P. aeruginosa*-induced lung injury was dependent on pulmonary ILCs expressing IL-22 (Fig. 3) [123]. ILC2 or group 2 ILCs produce Th2 cytokines and have shown to exert a negative antifungal effect in mouse models and humans. For instance, IL-33-producing ILC2 cells were shown to have a detrimental role in pulmonary immunity against *C. neoformans* [124] and in patients with severe asthma associated with fungal sensitization [125]. Similar detrimental roles of IL-13-producing ILC2s were demonstrated in a mouse model of *C. neoformans*-induced airway inflammation [126] and in patients with *Aspergillus*-mediated chronic sinusitis [127]. Interestingly, prostaglandin I2 can reduce the number of Th2-expressing ILC2 in the lung, such as IL-13 and IL-5, and could potentially be exploited as a therapeutic strategy in this context [128].

NK cells represent the prototypical member of the ILC family. Together with ILC1, NK cells constitute group 1 ILCs, which are characterized by their capacity to produce IFN-γ. NK cell activation leads to direct killing of diverse fungal pathogens via the release of extracellular perforin (Fig. 3). Perforin-dependent microbicidal activity against *C. neoformans* requires PI3K-dependent ERK1/2 signaling on NK cells [129]. These cells can also produce GM-CSF necessary for the fungicidal activity of neutrophils, described above [97]. In the past, studies using NK cell-depleted mice have revealed their critical role in the control of infections with several fungal pathogens, including *C. neoformans*, *H. capsulatum*, *C. albicans*, and *A. fumigatus* amongst others [17, 24].

Recent studies have been focused on the mechanisms underlying the recognition of fungi by NK cells. The NKp30 receptor has been shown to be responsible for recognition of *C. albicans* and *C. neoformans*, and subsequent killing through perforin release [130], and the human NKp46 receptor and its mouse ortholog, NCR1, were reported to bind *C. glabrata* and mediate fungal

killing [131]. More recently, CD56 was suggested to play a role in *A. fumigatus*-mediated NK cell activation and proinflammatory cytokine production [132]. Clinical studies have suggested that adoptively transferred NK cells could be an attractive strategy in the prophylaxis or treatment of invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients, but we still know very little about the role of NK cells in human fungal diseases.

Additional innate-like lymphocytes including γδ T cells, characterized by the expression of distinct γ and δ TCR chains, and NK-T cells, having semi-invariable Vα and β TCR chains, have been found to contribute to immunity against diverse fungal pathogens, including *C. albicans*, *A. fumigatus*, and *C. neoformans*. Lastly, invariant NK-T cells, expressing conserved αβ chains, were also shown to be activated by the *Aspergillus* glycosphingolipid asperamide B and contribute to airway hyperreactivity in an IL-33-ST2-dependent fashion [133]. Interestingly, mice lacking invariable NK-T cells poorly control infections with *A. fumigatus* due to a decrease in IFN-γ production [134].

Platelets

Less well appreciated, platelets are also involved in immune responses. Originally appreciated as key players in coagulation, they have now been found to be involved in antifungal immunity by direct interaction with fungi and subsequent activation of antimicrobial effector mechanisms. For instance, *C. albicans* can bind and activate platelets in a systemic infection model. After activation, platelets can produce chemokines and peptides with antimicrobial activity against *Candida*, such as CCL5 and platelet factor 4, respectively (Fig. 3). *Aspergillus* can also activate platelets, and activated platelets enhance the production of IL-8 by human monocytes and inhibit fungal germination [24]. However, more studies are needed to better understand their interaction with other immune cells and their role in immunity against other fungal pathogens.

Epithelial Cells and Barrier Tissues

A decade ago, we were just beginning to appreciate the role of epithelial cells in homeostasis and immunity. We now know that epithelial cells not only act as a physical barrier against pathogens, allergens, and foreign substances, but that they also constitute the first line of defense through the expression of a wide range of PRRs, including CLRs, TLRs, and PARs. TLRs are widely expressed by epithelial cells, while the expression of CLRs is less well defined. Studies have suggested that MRs appear to be extensively expressed on epithelial cells in diverse tissues, and that dectin-1 can be induced on epithelial cells after microbial encounter. PARs are G-protein-coupled receptors expressed on airway epithelial cells characterized by a self-activation mechanism following cleavage by fungus-derived proteolytic allergens. Fungal-induced endocytosis by oral epithelial cells was shown to be mediated by E-cadherin and aryl-hydrocarbon receptor (AhR)/Src/EGFR/HER2 receptor tyrosine kinase signaling, inducing rearrangement of epithelial cell microfilaments, leading to the formation of pseudopods that engulf the fungus. Treatment with either a dual kinase inhibitor or an AhR inhibitor significantly reduced the severity of oropharyngeal candidiasis in mice [135, 136]. Furthermore, the receptor tyrosine kinase EphA2 was identified as a β-glucan receptor in oral epithelial cells involved in the control of fungal dissemination, as described above [78].

In addition to their ability to directly recognize fungi, epithelial cells can also participate in fungal phagocytosis and the production of inflammatory alarmins, chemokines, and cytokines [17, 24]. For instance, epithelial cells produce mucins and antimicrobial peptides, such as β-defensin and cathelicidin, which can repress tissue invasion and display direct fungicidal activities [137]. These proteins have also effects on bacterial components of the microflora [138]. Interestingly, the fungal germination process can be seen as a danger signal by epithelial cells since they can discriminate between commensal yeast and pathogenic hyphal forms of *C. albicans*, responding via an NF-κB and a biphasic MAPK signaling pathway, highlighting the importance of epithelial cells in maintaining commensal populations [139]. In addition, fungal-derived toxins, such as the recently described candidalysin, can damage epithelial membranes and trigger a danger response signaling pathway that activates epithelial immunity [140].

Along with epithelial cells, endothelial cells are also key responders during fungal invasion. During mucormycosis, an infection that primarily affects patients with diabetic ketoacidosis, the endothelial receptor glucose-regulated protein 78 (GRP78) binds *Rhizopus oryzae* promoting cell invasion via fungal coat protein homologue 3 (CotH3) [141]. Moreover, metabolic changes associated with hyperglycemia and diabetic ketoacidosis

increased the expression of GRP78 on endothelial cells promoting fungal invasion. Interestingly, antibodies directed against GRP78 or CotH3 protect mice from mucormycosis, which could be exploited as a therapeutic strategy [142]. *C. albicans* can also interact with endothelial cells and induce its endocytosis by an interaction between fungal-derived invasins and a complex containing N-cadherin, present on the endothelial cell surface, as well as septin 7. Septin 7 is a GTP-binding protein that can interact with endothelial cell microfilaments, thereby inducing microbial endocytosis, a mechanism that is likely to be relevant to host cell invasion by other microbial pathogens [143].

Mycobiome

In the last few years, interactions between the immune system and the mycobiome are being recognized as important for immune homeostasis and as a cause of pathology during disease. This is particularly evident at the mucosal surfaces, where many immune and nonimmune cells are not only important in surveillance, but also in maintaining commensal relationships and protection from invasion. The diversity of the microbiome on human skin is an area of intense investigation because changes in its composition are associated with the development of chronicity of many dermatological conditions and diseases. For instance, *Malassezia* species have been associated with exacerbating various skin conditions, such as psoriasis, eczema, and dermatitis, in which barrier functions are compromised [144]. In addition, skin sensitization to *C. albicans* is strongly correlated with the development of dermatitis, and *C. albicans* morphology and specific skin-resident DC subsets can determine T-helper-cell differentiation in the skin, as described above [118, 119]. Interestingly, a recent longitudinal metagenomic study revealed that despite the exposure of the skin to the external environment, its microbial communities, including fungi, were largely stable over time, suggesting that any changes in these interactions reflect disease states [145].

Little is known about the fungal microbiota of the respiratory tract. One of the most comprehensive studies analyzed the mycobiome of the mouth. In this study, it was found that the distribution of the fungal species in the mouth varied greatly between different individuals, including species of *Candida*, *Aspergillus*, *Fusarium*, and *Cryptococcus* amongst others. Of note, noncultivable fungi represent almost 40% of the fungi identified [146]. Another study shows that fungal communities in the lung of patients receiving lung transplants differ in structure and composition from healthy subjects, which could be a consequence of antibiotics and/or immunosuppressant treatment [147].

Inhalation of fungal spores results in sensitization and exacerbation of allergy and asthma, and specific fungal species have been associated with the development of airway conditions. *Pneumocystis*, for example, has been implicated in a number of chronic pulmonary inflammatory diseases, including pneumonia. Fungi can also directly interact with lung cells inducing antifungal and proinflammatory mechanisms. For instance, fungal-derived proteolytic allergens can activate PARs leading to an increase in lung epithelial permeability and the release of proinflammatory cytokines [148]. In addition, dectin-1 recognition of *A. fumigatus* in the lung was recently shown to enhance fungal allergy through IL-22 secretion [149].

The most common fungal pathogen colonizing the genital-urinary tract is *C. albicans*, which can become pathogenic in some individuals causing recurrent infections. Recent studies have shed some light on mechanisms conferring enhanced susceptibility to recurrent vulvovaginal candidiasis (VVC). For instance, S100 alarmin proteins have been shown to mediate immunopathogenic responses in susceptible patients, as epithelial cell-derived S100 alarmins induced by *C. albicans* are sufficient to induce acute neutrophil responses during experimental vaginal candidiasis [150]. Furthermore, protection against VVC was shown to be dependent on IL-22 and the enzyme IDO, as mice deficient in either IDO or IL-22 were more susceptible to VVC. Of note, replacement therapy with kynurenines restored immune protection to VVC, which suggests a potential therapy for these patients [151].

The mammalian gut contains a rich fungal community that accounts for around 0.1% of the genes in the fecal microbiota. Similar to the genitourinary tract, *C. albicans* is the most common commensal fungus [152]. Dysregulation in levels of colonization with this organism has been associated with enhanced severity in several conditions, including gastric ulcers, allergic sensitization to food allergens, ulcerative colitis, and Crohn disease, and has also been linked with susceptibility to systemic candidiasis. Interactions between commensal fungi and CLRs, such as dectin-1 and SIGNR3, have been shown to influence colitis, and the loss of these receptors has been suggested to affect fungal recognition as well as barrier integrity [22, 40]. It was shown, for example, that the absence of dectin-1 on DCs can significantly affect the de-

velopment of CD4+ T-cell responses to *Candida* infection in the GI tract [153]. Others have suggested that inhibition of dectin-1 signaling can ameliorate colitis, by decreasing antimicrobial peptide production, inducing *Lactobacillus* overgrowth and T_{reg} expansion [154]. SIGNR3 has been implicated in sensing fungi present in the microbiota, influencing inflammation in the colon; SIGNR3-deficient mice exhibited more severe colitis symptoms than wild-type controls [40]. In an experimental model of colitis, it was also shown that MBL1/2-deficient mice had higher levels of *C. albicans* colonization than wild-type littermates, which was associated with elevated expression of proinflammatory cytokines [51]. Finally, MCL-deficient mice have been shown to be more susceptible to dextran sodium sulfate-induced colitis and exhibited increased *Candida tropicalis* burden, which correlates with impaired phagocytic and fungicidal abilities of macrophages [155].

In the gut, several subsets of phagocytes can respond to fungal infection as well as to fluctuations in resident fungal communities. Among these, mononuclear phagocytes expressing CX_3CR1 and DCs expressing the integrins CD103 CD11b have been shown to be pivotal in inducing immune responses against microbes in the gut. However, there is some controversy regarding which cells are essential for initiating antifungal immune responses in the gut. IRF4-dependent CD103+ CD11b+ DCs, in particular, are central in intestinal Th17 differentiation and Th17-induced fungal clearance [156, 157]. Intestinal CD103+ DCs were shown to serve as classical DCs in antigen sampling and initiation of adaptive immune responses in gut lymph nodes, while CX_3CR1+ populations were suggested to modulate immune responses directly at the mucosal sites and serve as first-line barrier against invading pathogens [158]. In addition, CD103+ CD11b– DCs can restrain colitis by inducing an anti-inflammatory response by epithelial cells that is dependent on IDO [159]. In fact, CD103+ DCs can also express IDO themselves, influencing the balance between T_{reg}/T-effector cells and induction of tolerance that would protect mice from colitis [160]. Furthermore, CX_3CR1+ cells have been shown to directly transfer antigens to CD103+ DCs via gap junctions to induce tolerance [161]. A recent study has identified that CX_3CR1+ mononuclear phagocytes are essential for the initiation of innate and adaptive immune responses to intestinal fungi in the colon and mesenteric lymph nodes but not the small intestine, and genetic ablation of CX_3CR1+ cells in mice led to changes in gut fungal communities and the development of severe colitis [162].

Interaction between *Candida* and bacterial components of the microbiota has also been shown to shape immune responses in the GI tract. These bacterial communities can prevent high-level fungal colonization and disease, as germ-free mice, lacking natural microbiota, are highly susceptible to *Candida* colonization. In vitro studies have shown that bacterial components can block yeast adhesion to the epithelium and produce metabolites that reduce hyphal transformation and invasion. Alterations in the abundance of *Lactobacillus* strains, as observed in CARD9-deficient mice, make these animals more susceptible to colitis as their microbiota fail to metabolize tryptophan into the metabolites that act as AhR ligands [163]. CARD9 SNPs in humans have also been associated with increased susceptibility to colitis [164]. Furthermore, similar to studies using deficient mice, humans with an SNP in dectin-1 were associated with more severe forms of colitis [22].

Therapeutic Approaches

As eukaryotes, fungi are very similar to 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 focused on the use of recombinant cytokines. For instance, colony-stimulating factors, such as GM-CSF and G-CSF, designed to increase the number of myeloid cells and induce neutrophil activation, have been used with varied success. IFN-γ therapy, intended to activate phagocytes and restore defects in Th1 immunity, has proven to be beneficial as an adjunctive therapy in patients with chronic granulomatous disease and cryptococcal meningitis, and in the clearance of fungal disease in transplantation and sepsis patients [165, 166]. Monoclonal antibodies have also been used in immunotherapy. For instance, in murine models, monoclonal antibodies against cell wall β-glucan and *C. neoformans* capsule have proven to be beneficial by inducing opsonization and modulating fungal growth and metabolism [167, 168]. Furthermore, patients with AIDS and cryptococcal meningitis treated with the anticapsular monoclonal antibody show no severe side effects and transient reduction in serum fungal antigen titers [169]. However, more studies are needed to demonstrate their efficacy.

Cellular immunotherapy is a promising approach to treat fungal infections. Adoptive transfer of anti-*Aspergil-*

lus T cells has been shown to improve survival following hematopoietic transplantation [170]. In addition, re-engineered T cells expressing a chimeric antigen receptor that recapitulates the specificity of dectin-1 were effective against *A. fumigatus* in an experimental model [171]. Furthermore, innate cell therapy has steadily gathered pace as a promising alternative approach. For instance, DC pulsed with *Aspergillus* conidia or transfected with conidial RNA promote antigen-specific Th1-dependent antifungal resistance in mice, which are otherwise susceptible to invasive aspergillosis [172]. Most DC-based research for fungal immunotherapy is preclinical, but there are some exciting studies in patients with hematopoietic transplantation. After receiving adoptive therapy with *Aspergillus*-specific T-cell clones, for example, patients exhibited high-frequency T-cell responses to *Aspergillus* and high IFN-γ/IL-10 levels [170].

Vaccination of immunocompromised individuals, a group major risk for developing fungal infections, has also been a challenge regarding efficacy and safety, as they are unable to mount effective and strong immune responses. Therefore, in immunocompromised patients, vaccination should be targeted at the components of the immune system that are relatively intact [165]. Preclinical studies of vaccines containing attenuated fungi have shown promising results; however, they have the additional challenge of using fungi that are sufficiently attenuated so as not to cause disease. As an alternative, vaccines that employ killed whole organisms or purified antigens (subunit vaccines) are intrinsically safer, but they do not tend to elicit robust immune response. Thus, there is an increasing need to develop new adjuvants and delivery systems that can boost innate immune responses to subunit vaccines by targeting antigens to DCs, resulting in enhanced protection. In this context, chitosan, a polycationic homopolymer of glucosamine manufactured by the deacetylation of chitin, is being studied as an adjuvant in DNA- and protein-based vaccines. This polymer has been approved by the United States Food and Drug Administration and appears to be promising in mucosal vaccines.

Currently, there are no fungal vaccines available in clinical practice; however, there are some exciting studies in recent years using fungal components of the cell wall [173]. 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 [167]. In addition, subcutaneous vaccination with glucan particles containing *Cryptococcus* alkaline extracts can protect mice against cryptococcosis due to the induction of robust Th1 and Th17 immunity [174]. More recently, 2 subunit vaccines containing recombinant *C. albicans*-derived proteins were found to confer immunogenicity in phase I clinical trials, and they are currently the most promising candidates for a human vaccine [175, 176].

Concluding Remarks

In the last few years, we have seen significant advances in our understanding of antifungal immunity; however, there are still many questions to be answered. For example, we still have very limited knowledge about the interplay between microbial dysbiosis and immunity, and the impact of lifestyle and environmental factors such as diet, physical activity, hygiene, and exposure to xenobiotics on our ability to control infections or impact on the mycobiota. Our challenges in the forthcoming years will be to continue translating the advances we make into the development of novel strategies to combat fungal infections.

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References

1 Brown GD: Dectin-1: a signalling non-TLR pattern-recognition receptor. Nat Rev Immunol 2006;6:33–43.
2 van den Berg LM, Zijlstra-Willems EM, Richters CD, Ulrich MM, Geijtenbeek TB: Dectin-1 activation induces proliferation and migration of human keratinocytes enhancing wound re-epithelialization. Cell Immunol 2014;289:49–54.
3 Olynych TJ, Jakeman DL, Marshall JS: Fungal zymosan induces leukotriene production by human mast cells through a dectin-1-dependent mechanism. J Allergy Clin Immunol 2006;118:837–843.

4 Cohen-Kedar S, Baram L, Elad H, Brazowski E, Guzner-Gur H, Dotan I: Human intestinal epithelial cells respond to β-glucans via dectin-1 and Syk. Eur J Immunol 2014;44:3729–3740.
5 Gross O, Gewies A, Finger K, Schafer M, Sparwasser T, Peschel C, Forster I, Ruland J: Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. Nature 2006;442:651–656.
6 Dambuza IM, Levitz SM, Netea MG, Brown GD: Fungal recognition and host defense mechanisms. Microbiol Spectr 2017;5:FUNK-0050-2016.
7 Wirnsberger G, Zwolanek F, Asaoka T, Kozieradzki I, Tortola L, Wimmer RA, Kavirayani A, Fresser F, Baier G, Langdon WY, Ikeda F, Kuchler K, Penninger JM: Inhibition of CBLB protects from lethal *Candida albicans* sepsis. Nat Med 2016;22:915–923.
8 Xiao Y, Tang J, Guo H, Zhao Y, Tang R, Ouyang S, Zeng Q, Rappleye CA, Rajaram MV, Schlesinger LS, Tao L, Brown GD, Langdon WY, Li BT, Zhang J: Targeting CBLB as a potential therapeutic approach for disseminated candidiasis. Nat Med 2016;22:906–914.
9 Zhu LL, Luo TM, Xu X, Guo YH, Zhao XQ, Wang TT, Tang B, Jiang YY, Xu JF, Lin X, Jia XM: E3 ubiquitin ligase Cbl-b negatively regulates C-type lectin receptor-mediated antifungal innate immunity. J Exp Med 2016;213:1555–1570.
10 Roth S, Bergmann H, Jaeger M, Yeroslaviz A, Neumann K, Koenig PA, Prazeres da Costa C, Vanes L, Kumar V, Johnson M, Menacho-Marquez M, Habermann B, Tybulewicz VL, Netea M, Bustelo XR, Ruland J: Vav proteins are key regulators of Card9 signaling for innate antifungal immunity. Cell Rep 2016;17:2572–2583.
11 Cao Z, Conway KL, Heath RJ, Rush JS, Leshchiner ES, Ramirez-Ortiz ZG, Nedelsky NB, Huang H, Ng A, Gardet A, Cheng SC, Shamji AF, Rioux JD, Wijmenga C, Netea MG, Means TK, Daly MJ, Xavier RJ: Ubiquitin ligase TRIM62 regulates CARD9-mediated anti-fungal immunity and intestinal inflammation. Immunity 2015;43:715–726.
12 Zhao X, Guo Y, Jiang C, Chang Q, Zhang S, Luo T, Zhang B, Jia X, Hung MC, Dong C, Lin X: JNK1 negatively controls antifungal innate immunity by suppressing CD23 expression. Nat Med 2017;23:337–346.
13 Cheng SC, Quintin J, Cramer RA, Shepardson KM, Saeed S, Kumar V, Giamarellos-Bourboulis EJ, Martens JH, Rao NA, Aghajanirefah A, Manjeri GR, Li Y, Ifrim DC, Arts RJ, van der Veer BM, Deen PM, Logie C, O'Neill LA, Willems P, van de Veerdonk FL, van der Meer JW, Ng A, Joosten LA, Wijmenga C, Stunnenberg HG, Xavier RJ, Netea MG: mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. Science 2014;345:1250684.
14 Branzk N, Lubojemska A, Hardison SE, Wang Q, Gutierrez MG, Brown GD, Papayannopoulos V: Neutrophils sense microbe size and selectively release neutrophil extracellular traps in response to large pathogens. Nat Immunol 2014;15:1017–1025.
15 Tam JM, Mansour MK, Khan NS, Seward M, Puranam S, Tanne A, Sokolovska A, Becker CE, Acharya M, Baird MA, Choi AM, Davidson MW, Segal BH, Lacy-Hulbert A, Stuart LM, Xavier RJ, Vyas JM: Dectin-1-dependent LC3 recruitment to phagosomes enhances fungicidal activity in macrophages. J Infect Dis 2014;210:1844–1854.
16 Ma J, Becker C, Lowell CA, Underhill DM: Dectin-1-triggered recruitment of light chain 3 protein to phagosomes facilitates major histocompatibility complex class II presentation of fungal-derived antigens. J Biol Chem 2012;287:34149–34156.
17 Drummond RA, Gaffen SL, Hise AG, Brown GD: Innate defense against fungal pathogens. Cold Spring Harb Perspect Med 2014;5:a019620.
18 Chen SM, Hui S, Zhang T, Huang X, Liu XQ, Guo SY, Zhao JJ, Wang CF, Yan L, Xu GT, Jiang YY, An MM: Dectin-1 plays an important role in host defense against systemic *Candida glabrata* infection. Virulence 2017;8:1643–1656.
19 Yang AM, Inamine T, Hochrath K, Chen P, Wang L, Llorente C, Bluemel S, Hartmann P, Xu J, Koyama Y, Kisseleva T, Torralba MG, Moncera K, Beeri K, Chen CS, Freese K, Hellerbrand C, Lee SM, Hoffman HM, Mehal WZ, Garcia-Tsao G, Mutlu EA, Keshavarzian A, Brown GD, Ho SB, Bataller R, Starkel P, Fouts DE, Schnabl B: Intestinal fungi contribute to development of alcoholic liver disease. J Clin Invest 2017;127:2829–2841.
20 Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, Elbers CC, Johnson MD, Cambi A, Huysamen C, Jacobs L, Jansen T, Verheijen K, Masthoff L, Morre SA, Vriend G, Williams DL, Perfect JR, Joosten LA, Wijmenga C, van der Meer JW, Adema GJ, Kullberg BJ, Brown GD, Netea MG: Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med 2009;361:1760–1767.
21 Chai LY, de Boer MG, van der Velden WJ, Plantinga TS, van Spriel AB, Jacobs C, Halkes CJ, Vonk AG, Blijlevens NM, van Dissel JT, Donnelly PJ, Kullberg BJ, Maertens J, Netea MG: The Y238X stop codon polymorphism in the human beta-glucan receptor dectin-1 and susceptibility to invasive aspergillosis. J Infect Dis 2011;203:736–743.
22 Iliev ID, Funari VA, Taylor KD, Nguyen Q, Reyes CN, Strom SP, Brown J, Becker CA, Fleshner PR, Dubinsky M, Rotter JI, Wang HL, McGovern DP, Brown GD, Underhill DM: Interactions between commensal fungi and the C-type lectin receptor dectin-1 influence colitis. Science 2012;336:1314–1317.
23 Lionakis MS, Levitz SM: Host control of fungal infections: lessons from basic studies and human cohorts. Annu Rev Immunol 2017, Epub ahead of print.
24 Becker KL, Ifrim DC, Quintin J, Netea MG, van de Veerdonk FL: Antifungal innate immunity: recognition and inflammatory networks. Semin Immunopathol 2015;37:107–116.
25 Salazar F, Sewell HF, Shakib F, Ghaemmaghami AM: The role of lectins in allergic sensitization and allergic disease. J Allergy Clin Immunol 2013;132:27–36.
26 Nagata M, Izumi Y, Ishikawa E, Kiyotake R, Doi R, Iwai S, Omahdi Z, Yamaji T, Miyamoto T, Bamba T, Yamasaki S: Intracellular metabolite β-glucosylceramide is an endogenous Mincle ligand possessing immunostimulatory activity. Proc Natl Acad Sci USA 2017;114:E3285–E3294.
27 Ostrop J, Lang R: Contact, collaboration, and conflict: signal integration of Syk-coupled C-type lectin receptors. J Immunol 2017;198:1403–1414.
28 Wevers BA, Kaptein TM, Zijlstra-Willems EM, Theelen B, Boekhout T, Geijtenbeek TB, Gringhuis SI: Fungal engagement of the C-type lectin mincle suppresses dectin-1-induced antifungal immunity. Cell Host Microbe 2014;15:494–505.
29 Zhu LL, Zhao XQ, Jiang C, You Y, Chen XP, Jiang YY, Jia XM, Lin X: C-type lectin receptors dectin-3 and dectin-2 form a heterodimeric pattern-recognition receptor for host defense against fungal infection. Immunity 2013;39:324–334.
30 Miyake Y, Masatsugu OH, Yamasaki S: C-type lectin receptor MCL facilitates Mincle expression and signaling through complex formation. J Immunol 2015;194:5366–5374.
31 Saijo S, Ikeda S, Yamabe K, Kakuta S, Ishigame H, Akitsu A, Fujikado N, Kusaka T, Kubo S, Chung SH, Komatsu R, Miura N, Adachi Y, Ohno N, Shibuya K, Yamamoto N, Kawakami K, Yamasaki S, Saito T, Akira S, Iwakura Y: Dectin-2 recognition of α-mannans and induction of Th17 cell differentiation is essential for host defense against *Candida albicans*. Immunity 2010;32:681–691.
32 Wuthrich M, Wang H, Li M, Lerksuthirat T, Hardison SE, Brown GD, Klein B: *Fonsecaea pedrosoi*-induced Th17-cell differentiation in mice is fostered by dectin-2 and suppressed by Mincle recognition. Eur J Immunol 2015;45:2542–2552.
33 Wang H, Li M, Lerksuthirat T, Klein B, Wuthrich M: The C-type lectin receptor MCL mediates vaccine-induced immunity against infection with *Blastomyces dermatitidis*. Infect Immun 2016;84:635–642.

34 Wells CA, Salvage-Jones JA, Li X, Hitchens K, Butcher S, Murray RZ, Beckhouse AG, Lo YL, Manzanero S, Cobbold C, Schroder K, Ma B, Orr S, Stewart L, Lebus D, Sobieszczuk P, Hume DA, Stow J, Blanchard H, Ashman RB: The macrophage-inducible C-type lectin, Mincle, is an essential component of the innate immune response to *Candida albicans*. J Immunol 2008;180:7404–7413.
35 Yamasaki S, Matsumoto M, Takeuchi O, Matsuzawa T, Ishikawa E, Sakuma M, Tateno H, Uno J, Hirabayashi J, Mikami Y, Takeda K, Akira S, Saito T: C-type lectin Mincle is an activating receptor for pathogenic fungus, *Malassezia*. Proc Natl Acad Sci USA 2009; 106:1897–1902.
36 Kottom TJ, Hebrink DM, Jenson PE, Nandakumar V, Wuthrich M, Wang H, Klein B, Yamasaki S, Lepenies B, Limper AH: The interaction of *Pneumocystis* with the C-type lectin receptor Mincle exerts a significant role in host defense against infection. J Immunol 2017;198:3515–3525.
37 Hu XP, Wang RY, Wang X, Cao YH, Chen YQ, Zhao HZ, Wu JQ, Weng XH, Gao XH, Sun RH, Zhu LP: Dectin-2 polymorphism associated with pulmonary cryptococcosis in HIV-uninfected Chinese patients. Med Mycol 2015;53:810–816.
38 Geijtenbeek TB, Gringhuis SI: C-type lectin receptors in the control of T helper cell differentiation. Nat Rev Immunol 2016;16:433–448.
39 Peres da Silva R, Heiss C, Black I, Azadi P, Gerlach JQ, Travassos LR, Joshi L, Kilcoyne M, Puccia R: Extracellular vesicles from *Paracoccidioides* pathogenic species transport polysaccharide and expose ligands for DC-SIGN receptors. Sci Rep 2015;5:14213.
40 Eriksson M, Johannssen T, von Smolinski D, Gruber AD, Seeberger PH, Lepenies B: The C-type lectin receptor SIGNR3 binds to fungi present in commensal microbiota and influences immune regulation in experimental colitis. Front Immunol 2013;4:196.
41 Brown GD: Innate antifungal immunity: the key role of phagocytes. Annu Rev Immunol 2011;29:1–21.
42 van de Veerdonk FL, Marijnissen RJ, Kullberg BJ, Koenen HJ, Cheng SC, Joosten I, van den Berg WB, Williams DL, van der Meer JW, Joosten LA, Netea MG: The macrophage mannose receptor induces IL-17 in response to *Candida albicans*. Cell Host Microbe 2009; 5:329–340.
43 Wagener J, Malireddi RK, Lenardon MD, Koberle M, Vautier S, MacCallum DM, Biedermann T, Schaller M, Netea MG, Kanneganti TD, Brown GD, Brown AJ, Gow NA: Fungal chitin dampens inflammation through IL-10 induction mediated by NOD2 and TLR9 activation. PLoS Pathog 2014; 10:e1004050.
44 Schuette V, Embgenbroich M, Ulas T, Welz M, Schulte-Schrepping J, Draffehn AM, Quast T, Koch K, Nehring M, Konig J, Zweynert A, Harms FL, Steiner N, Limmer A, Forster I, Berberich-Siebelt F, Knolle PA, Wohlleber D, Kolanus W, Beyer M, Schultze JL, Burgdorf S: Mannose receptor induces T-cell tolerance via inhibition of CD45 and up-regulation of CTLA-4. Proc Natl Acad Sci USA 2016;113:10649–10654.
45 Rajaram MVS, Arnett E, Azad AK, Guirado E, Ni B, Gerberick AD, He LZ, Keler T, Thomas LJ, Lafuse WP, Schlesinger LS: *M. tuberculosis*-initiated human mannose receptor signaling regulates macrophage recognition and vesicle trafficking by FcRγ-chain, Grb2, and SHP-1. Cell Rep 2017;21:126–140.
46 Dan JM, Kelly RM, Lee CK, Levitz SM: Role of the mannose receptor in a murine model of *Cryptococcus neoformans* infection. Infect Immun 2008;76:2362–2367.
47 Wang H, LeBert V, Li M, Lerksuthirat T, Galles K, Klein B, Wuthrich M: Mannose receptor is required for optimal induction of vaccine-induced T-helper type 17 cells and resistance to *Blastomyces dermatitidis* infection. J Infect Dis 2016;213:1762–1766.
48 Wu SY, Huang JH, Chen WY, Chan YC, Lin CH, Chen YC, Liu FT, Wu-Hsieh BA: Cell intrinsic galectin-3 attenuates neutrophil ROS-dependent killing of *Candida* by modulating CR3 downstream Syk activation. Front Immunol 2017;8:48.
49 Almeida F, Wolf JM, da Silva TA, DeLeon-Rodriguez CM, Rezende CP, Pessoni AM, Fernandes FF, Silva-Rocha R, Martinez R, Rodrigues ML, Roque-Barreira MC, Casadevall A: Galectin-3 impacts *Cryptococcus neoformans* infection through direct antifungal effects. Nat Commun 2017;8:1968.
50 Bidula S, Schelenz S: A sweet response to a sour situation: the role of soluble pattern recognition receptors in the innate immune response to invasive *Aspergillus fumigatus* infections. PLoS Pathog 2016;12:e1005637.
51 Choteau L, Parny M, Francois N, Bertin B, Fumery M, Dubuquoy L, Takahashi K, Colombel JF, Jouault T, Poulain D, Sendid B, Jawhara S: Role of mannose-binding lectin in intestinal homeostasis and fungal elimination. Mucosal Immunol 2016;9:767–776.
52 Romani L: Immunity to fungal infections. Nat Rev Immunol 2011;11:275–288.
53 Brubaker SW, Bonham KS, Zanoni I, Kagan JC: Innate immune pattern recognition: a cell biological perspective. Annu Rev Immunol 2015;33:257–290.
54 Netea MG, Sutmuller R, Hermann C, Van der Graaf CA, Van der Meer JW, van Krieken JH, Hartung T, Adema G, Kullberg BJ: Toll-like receptor 2 suppresses immunity against *Candida albicans* through induction of IL-10 and regulatory T cells. J Immunol 2004;172:3712–3718.
55 Herbst S, Shah A, Mazon Moya M, Marzola V, Jensen B, Reed A, Birrell MA, Saijo S, Mostowy S, Shaunak S, Armstrong-James D: Phagocytosis-dependent activation of a TLR9-BTK-calcineurin-NFAT pathway coordinates innate immunity to *Aspergillus fumigatus*. EMBO Mol Med 2015;7:240–258.
56 Carvalho A, De Luca A, Bozza S, Cunha C, D'Angelo C, Moretti S, Perruccio K, Iannitti RG, Fallarino F, Pierini A, Latge JP, Velardi A, Aversa F, Romani L: TLR3 essentially promotes protective class I-restricted memory CD8$^+$ T-cell responses to *Aspergillus fumigatus* in hematopoietic transplanted patients. Blood 2012;119:967–977.
57 Bourgeois C, Majer O, Frohner IE, Lesiak-Markowicz I, Hildering KS, Glaser W, Stockinger S, Decker T, Akira S, Muller M, Kuchler K: Conventional dendritic cells mount a type I IFN response against *Candida* spp. requiring novel phagosomal TLR7-mediated IFN-β signaling. J Immunol 2011;186:3104–3112.
58 Biondo C, Malara A, Costa A, Signorino G, Cardile F, Midiri A, Galbo R, Papasergi S, Domina M, Pugliese M, Teti G, Mancuso G, Beninati C: Recognition of fungal RNA by TLR7 has a nonredundant role in host defense against experimental candidiasis. Eur J Immunol 2012;42:2632–2643.
59 von Bernuth H, Picard C, Jin Z, Pankla R, Xiao H, Ku CL, Chrabieh M, Mustapha IB, Ghandil P, Camcioglu Y, Vasconcelos J, Sirvent N, Guedes M, Vitor AB, Herrero-Mata MJ, Arostegui JI, Rodrigo C, Alsina L, Ruiz-Ortiz E, Juan M, Fortuny C, Yague J, Anton J, Pascal M, Chang HH, Janniere L, Rose Y, Garty BZ, Chapel H, Issekutz A, Marodi L, Rodriguez-Gallego C, Banchereau J, Abel L, Li X, Chaussabel D, Puel A, Casanova JL: Pyogenic bacterial infections in humans with MyD88 deficiency. Science 2008;321:691–696.
60 Pietrella D, Pandey N, Gabrielli E, Pericolini E, Perito S, Kasper L, Bistoni F, Cassone A, Hube B, Vecchiarelli A: Secreted aspartic proteases of *Candida albicans* activate the NLRP3 inflammasome. Eur J Immunol 2013;43:679–692.
61 Oikonomou V, Moretti S, Renga G, Galosi C, Borghi M, Pariano M, Puccetti M, Palmerini CA, Amico L, Carotti A, Prezioso L, Spolzino A, Finocchi A, Rossi P, Velardi A, Aversa F, Napolioni V, Romani L: Noncanonical fungal autophagy inhibits inflammation in response to IFN-γ via DAPK1. Cell Host Microbe 2016; 20:744–757.
62 Gringhuis SI, Kaptein TM, Wevers BA, Theelen B, van der Vlist M, Boekhout T, Geijtenbeek TB: Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1β via a noncanonical caspase-8 inflammasome. Nat Immunol 2012;13:246–254.
63 Tavares AH, Burgel PH, Bocca AL: Turning up the heat: inflammasome activation by fungal pathogens. PLoS Pathog 2015;11:e1004948.

64 Ketelut-Carneiro N, Silva GK, Rocha FA, Milanezi CM, Cavalcanti-Neto FF, Zamboni DS, Silva JS: IL-18 triggered by the Nlrp3 inflammasome induces host innate resistance in a pulmonary model of fungal infection. J Immunol 2015;194:4507–4517.
65 Tomalka J, Ganesan S, Azodi E, Patel K, Majmudar P, Hall BA, Fitzgerald KA, Hise AG: A novel role for the NLRC4 inflammasome in mucosal defenses against the fungal pathogen *Candida albicans*. PLoS Pathog 2011;7:e1002379.
66 del Fresno C, Soulat D, Roth S, Blazek K, Udalova I, Sancho D, Ruland J, Ardavin C: Interferon-β production via dectin-1-Syk-IRF5 signaling in dendritic cells is crucial for immunity to *C. albicans*. Immunity 2013;38:1176–1186.
67 Van Prooyen N, Henderson CA, Hocking Murray D, Sil A: CD103+ conventional dendritic cells are critical for TLR7/9-dependent host defense against *Histoplasma capsulatum*, an endemic fungal pathogen of humans. PLoS Pathog 2016;12:e1005749.
68 Espinosa V, Dutta O, McElrath C, Du P, Chang YJ, Cicciarelli B, Pitler A, Whitehead I, Obar JJ, Durbin JE, Kotenko SV, Rivera A: Type III interferon is a critical regulator of innate antifungal immunity. Sci Immunol 2017;2:eaan5357.
69 Jaeger M, van der Lee R, Cheng SC, Johnson MD, Kumar V, Ng A, Plantinga TS, Smeekens SP, Oosting M, Wang X, Barchet W, Fitzgerald K, Joosten LAB, Perfect JR, Wijmenga C, van de Veerdonk FL, Huynen MA, Xavier RJ, Kullberg BJ, Netea MG: The RIG-I-like helicase receptor MDA5 (IFIH1) is involved in the host defense against *Candida* infections. Eur J Clin Microbiol Infect Dis 2015;34:963–974.
70 Goodridge HS, Wolf AJ, Underhill DM: β-Glucan recognition by the innate immune system. Immunol Rev 2009;230:38–50.
71 Taborda CP, Casadevall A: CR3 (CD11b/CD18) and CR4 (CD11c/CD18) are involved in complement-independent antibody-mediated phagocytosis of *Cryptococcus neoformans*. Immunity 2002;16:791–802.
72 Johnson CM, O'Brien XM, Byrd AS, Parisi VE, Loosely AJ, Li W, Witt H, Faridi MH, LeFort CT, Gupta V, Kim M, Reichner JS: Integrin cross-talk regulates the human neutrophil response to fungal β-glucan in the context of the extracellular matrix: a prominent role for VLA3 in the antifungal response. J Immunol 2017;198:318–334.
73 Gresnigt MS, Becker KL, Smeekens SP, Jacobs CW, Joosten LA, van der Meer JW, Netea MG, van de Veerdonk FL: *Aspergillus fumigatus*-induced IL-22 is not restricted to a specific Th cell subset and is dependent on complement receptor 3. J Immunol 2013;190:5629–5639.
74 Tsoni SV, Kerrigan AM, Marakalala MJ, Srinivasan N, Duffield M, Taylor PR, Botto M, Steele C, Brown GD: Complement C3 plays an essential role in the control of opportunistic fungal infections. Infect Immun 2009;77:3679–3685.
75 Xu J, Flaczyk A, Neal LM, Fa Z, Eastman AJ, Malachowski AN, Cheng D, Moore BB, Curtis JL, Osterholzer JJ, Olszewski MA: Scavenger receptor MARCO orchestrates early defenses and contributes to fungal containment during cryptococcal infection. J Immunol 2017;198:3548–3557.
76 Vera J, Fenutria R, Canadas O, Figueras M, Mota R, Sarrias MR, Williams DL, Casals C, Yelamos J, Lozano F: The CD5 ectodomain interacts with conserved fungal cell wall components and protects from zymosan-induced septic shock-like syndrome. Proc Natl Acad Sci USA 2009;106:1506–1511.
77 Means TK, Mylonakis E, Tampakakis E, Colvin RA, Seung E, Puckett L, Tai MF, Stewart CR, Pukkila-Worley R, Hickman SE, Moore KJ, Calderwood SB, Hacohen N, Luster AD, El Khoury J: Evolutionarily conserved recognition and innate immunity to fungal pathogens by the scavenger receptors SCARF1 and CD36. J Exp Med 2009;206:637–653.
78 Swidergall M, Solis NV, Lionakis MS, Filler SG: EphA2 is an epithelial cell pattern recognition receptor for fungal β-glucans. Nat Microbiol 2018;3:53–61.
79 Huang JH, Lin CY, Wu SY, Chen WY, Chu CL, Brown GD, Chuu CP, Wu-Hsieh BA: CR3 and dectin-1 collaborate in macrophage cytokine response through association on lipid rafts and activation of Syk-JNK-AP-1 pathway. PLoS Pathog 2015;11:e1004985.
80 Chang TH, Huang JH, Lin HC, Chen WY, Lee YH, Hsu LC, Netea MG, Ting JP, Wu-Hsieh BA: Dectin-2 is a primary receptor for NLRP3 inflammasome activation in dendritic cell response to *Histoplasma capsulatum*. PLoS Pathog 2017;13:e1006485.
81 Sousa Mda G, Reid DM, Schweighoffer E, Tybulewicz V, Ruland J, Langhorne J, Yamasaki S, Taylor PR, Almeida SR, Brown GD: Restoration of pattern recognition receptor costimulation to treat chromoblastomycosis, a chronic fungal infection of the skin. Cell Host Microbe 2011;9:436–443.
82 Patin EC, Orr SJ, Schaible UE: Macrophage inducible C-type lectin as a multifunctional player in immunity. Front Immunol 2017;8:861.
83 Patin EC, Jones AV, Thompson A, Clement M, Liao CT, Griffiths JS, Wallace LE, Bryant CE, Lang R, Rosenstiel P, Humphreys IR, Taylor PR, Jones GW, Orr SJ: IL-27 induced by select *Candida* spp. via TLR7/NOD2 signaling and IFN-β production inhibits fungal clearance. J Immunol 2016;197:208–221.
84 Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL: Immune defence against *Candida* fungal infections. Nat Rev Immunol 2015;15:630–642.
85 Chen GH, Teitz-Tennenbaum S, Neal LM, Murdock BJ, Malachowski AN, Dils AJ, Olszewski MA, Osterholzer JJ: Local GM-CSF-dependent differentiation and activation of pulmonary dendritic cells and macrophages protect against progressive cryptococcal lung infection in mice. J Immunol 2016;196:1810–1821.
86 Xu J, Eastman AJ, Flaczyk A, Neal LM, Zhao G, Carolan J, Malachowski AN, Stolberg VR, Yosri M, Chensue SW, Curtis JL, Osterholzer JJ, Olszewski MA: Disruption of early tumor necrosis factor α signaling prevents classical activation of dendritic cells in lung-associated lymph nodes and development of protective immunity against cryptococcal infection. MBio 2016;7:e00510-16.
87 Wheeler ML, Limon JJ, Underhill DM: Immunity to commensal fungi: detente and disease. Annu Rev Pathol 2017;12:359–385.
88 Amulic B, Cazalet C, Hayes GL, Metzler KD, Zychlinsky A: Neutrophil function: from mechanisms to disease. Annu Rev Immunol 2012;30:459–489.
89 Wirnsberger G, Zwolanek F, Stadlmann J, Tortola L, Liu SW, Perlot T, Jarvinen P, Durnberger G, Kozieradzki I, Sarao R, De Martino A, Boztug K, Mechtler K, Kuchler K, Klein C, Elling U, Penninger JM: Jagunal homolog 1 is a critical regulator of neutrophil function in fungal host defense. Nat Genet 2014;46:1028–1033.
90 Hunniger K, Bieber K, Martin R, Lehnert T, Figge MT, Loffler J, Guo RF, Riedemann NC, Kurzai O: A second stimulus required for enhanced antifungal activity of human neutrophils in blood is provided by anaphylatoxin C5a. J Immunol 2015;194:1199–1210.
91 Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A: Neutrophil extracellular traps kill bacteria. Science 2004;303:1532–1535.
92 Urban CF, Ermert D, Schmid M, Abu-Abed U, Goosmann C, Nacken W, Brinkmann V, Jungblut PR, Zychlinsky A: Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against *Candida albicans*. PLoS Pathog 2009;5:e1000639.
93 Gazendam RP, van Hamme JL, Tool AT, van Houdt M, Verkuijlen PJ, Herbst M, Liese JG, van de Veerdonk FL, Roos D, van den Berg TK, Kuijpers TW: Two independent killing mechanisms of *Candida albicans* by human neutrophils: evidence from innate immunity defects. Blood 2014;124:590–597.
94 Shlezinger N, Irmer H, Dhingra S, Beattie SR, Cramer RA, Braus GH, Sharon A, Hohl TM: Sterilizing immunity in the lung relies on targeting fungal apoptosis-like programmed cell death. Science 2017;357:1037–1041.
95 Taylor PR, Roy S, Leal SM Jr, Sun Y, Howell SJ, Cobb BA, Li X, Pearlman E: Activation of neutrophils by autocrine IL-17A-IL-17RC interactions during fungal infection is regulated by IL-6, IL-23, RORγt and dectin-2. Nat Immunol 2014;15:143–151.
96 Huppler AR, Conti HR, Hernandez-Santos N, Darville T, Biswas PS, Gaffen SL: Role of neutrophils in IL-17-dependent immunity to mucosal candidiasis. J Immunol 2014;192:1745–1752.

97 Whitney PG, Bar E, Osorio F, Rogers NC, Schraml BU, Deddouche S, LeibundGut-Landmann S, Reis e Sousa C: Syk signaling in dendritic cells orchestrates innate resistance to systemic fungal infection. PLoS Pathog 2014;10:e1004276.
98 Dominguez-Andres J, Feo-Lucas L, Minguito de la Escalera M, Gonzalez L, Lopez-Bravo M, Ardavin C: Inflammatory Ly6C^{high} monocytes protect against candidiasis through IL-15-driven NK cell/neutrophil activation. Immunity 2017;46:1059–1072.e4.
99 Lionakis MS, Fischer BG, Lim JK, Swamydas M, Wan W, Richard Lee CC, Cohen JI, Scheinberg P, Gao JL, Murphy PM: Chemokine receptor Ccr1 drives neutrophil-mediated kidney immunopathology and mortality in invasive candidiasis. PLoS Pathog 2012;8:e1002865.
100 Pirofski LA, Casadevall A: The damage-response framework of microbial pathogenesis and infectious diseases. Adv Exp Med Biol 2008;635:135–146.
101 Urb M, Sheppard DC: The role of mast cells in the defence against pathogens. PLoS Pathog 2012;8:e1002619.
102 Matsuwaki Y, Wada K, White TA, Benson LM, Charlesworth MC, Checkel JL, Inoue Y, Hotta K, Ponikau JU, Lawrence CB, Kita H: Recognition of fungal protease activities induces cellular activation and eosinophil-derived neurotoxin release in human eosinophils. J Immunol 2009;183:6708–6716.
103 Madan T, Kishore U, Shah A, Eggleton P, Strong P, Wang JY, Aggrawal SS, Sarma PU, Reid KB: Lung surfactant proteins A and D can inhibit specific IgE binding to the allergens of *Aspergillus fumigatus* and block allergen-induced histamine release from human basophils. Clin Exp Immunol 1997;110:241–249.
104 Lionakis MS, Swamydas M, Fischer BG, Plantinga TS, Johnson MD, Jaeger M, Green NM, Masedunskas A, Weigert R, Mikelis C, Wan W, Lee CC, Lim JK, Rivollier A, Yang JC, Laird GM, Wheeler RT, Alexander BD, Perfect JR, Gao JL, Kullberg BJ, Netea MG, Murphy PM: CX3CR1-dependent renal macrophage survival promotes *Candida* control and host survival. J Clin Invest 2013;123:5035–5051.
105 Verma A, Kroetz DN, Tweedle JL, Deepe GS Jr: Type II cytokines impair host defense against an intracellular fungal pathogen by amplifying macrophage generation of IL-33. Mucosal Immunol 2015;8:380–389.
106 Hardison SE, Herrera G, Young ML, Hole CR, Wozniak KL, Wormley FL Jr: Protective immunity against pulmonary cryptococcosis is associated with STAT1-mediated classical macrophage activation. J Immunol 2012;189:4060–4068.
107 Hohl TM, Rivera A, Lipuma L, Gallegos A, Shi C, Mack M, Pamer EG: Inflammatory monocytes facilitate adaptive CD4 T cell responses during respiratory fungal infection. Cell Host Microbe 2009;6:470–481.
108 Ngo LY, Kasahara S, Kumasaka DK, Knoblaugh SE, Jhingran A, Hohl TM: Inflammatory monocytes mediate early and organ-specific innate defense during systemic candidiasis. J Infect Dis 2014;209:109–119.
109 Espinosa V, Jhingran A, Dutta O, Kasahara S, Donnelly R, Du P, Rosenfeld J, Leiner I, Chen CC, Ron Y, Hohl TM, Rivera A: Inflammatory monocytes orchestrate innate antifungal immunity in the lung. PLoS Pathog 2014;10:e1003940.
110 Vinh DC, Patel SY, Uzel G, Anderson VL, Freeman AF, Olivier KN, Spalding C, Hughes S, Pittaluga S, Raffeld M, Sorbara LR, Elloumi HZ, Kuhns DB, Turner ML, Cowen EW, Fink D, Long-Priel D, Hsu AP, Ding L, Paulson ML, Whitney AR, Sampaio EP, Frucht DM, DeLeo FR, Holland SM: Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. Blood 2010;115:1519–1529.
111 Majer O, Bourgeois C, Zwolanek F, Lassnig C, Kerjaschki D, Mack M, Muller M, Kuchler K: Type I interferons promote fatal immunopathology by regulating inflammatory monocytes and neutrophils during *Candida* infections. PLoS Pathog 2012;8:e1002811.
112 Ramirez-Ortiz ZG, Lee CK, Wang JP, Boon L, Specht CA, Levitz SM: A nonredundant role for plasmacytoid dendritic cells in host defense against the human fungal pathogen *Aspergillus fumigatus*. Cell Host Microbe 2011;9:415–424.
113 Araujo EF, Medeiros DH, Galdino NA, Condino-Neto A, Calich VL, Loures FV: Tolerogenic plasmacytoid dendritic cells control *Paracoccidioides brasiliensis* infection by inducting regulatory T cells in an IDO-dependent manner. PLoS Pathog 2016;12:e1006115.
114 Joo H, Upchurch K, Zhang W, Ni L, Li D, Xue Y, Li XH, Hori T, Zurawski S, Liu YJ, Zurawski G, Oh S: Opposing roles of dectin-1 expressed on human plasmacytoid dendritic cells and myeloid dendritic cells in Th2 polarization. J Immunol 2015;195:1723–1731.
115 Loures FV, Rohm M, Lee CK, Santos E, Wang JP, Specht CA, Calich VL, Urban CF, Levitz SM: Recognition of *Aspergillus fumigatus* hyphae by human plasmacytoid dendritic cells is mediated by dectin-2 and results in formation of extracellular traps. PLoS Pathog 2015;11:e1004643.
116 Trautwein-Weidner K, Gladiator A, Kirchner FR, Becattini S, Rulicke T, Sallusto F, LeibundGut-Landmann S: Antigen-specific Th17 cells are primed by distinct and complementary dendritic cell subsets in oropharyngeal candidiasis. PLoS Pathog 2015;11:e1005164.
117 Fei M, Bhatia S, Oriss TB, Yarlagadda M, Khare A, Akira S, Saijo S, Iwakura Y, Fallert Junecko BA, Reinhart TA, Foreman O, Ray P, Kolls J, Ray A: TNF-α from inflammatory dendritic cells (DCs) regulates lung IL-17A/IL-5 levels and neutrophilia versus eosinophilia during persistent fungal infection. Proc Natl Acad Sci USA 2011;108:5360–5365.
118 Igyarto BZ, Haley K, Ortner D, Bobr A, Gerami-Nejad M, Edelson BT, Zurawski SM, Malissen B, Zurawski G, Berman J, Kaplan DH: Skin-resident murine dendritic cell subsets promote distinct and opposing antigen-specific T helper cell responses. Immunity 2011;35:260–272.
119 Kashem SW, Igyarto BZ, Gerami-Nejad M, Kumamoto Y, Mohammed JA, Jarrett E, Drummond RA, Zurawski SM, Zurawski G, Berman J, Iwasaki A, Brown GD, Kaplan DH: *Candida albicans* morphology and dendritic cell subsets determine T helper cell differentiation. Immunity 2015;42:356–366.
120 Kashem SW, Riedl MS, Yao C, Honda CN, Vulchanova L, Kaplan DH: Nociceptive sensory fibers drive interleukin-23 production from CD301b+ dermal dendritic cells and drive protective cutaneous immunity. Immunity 2015;43:515–526.
121 Huang Y, Guo L, Qiu J, Chen X, Hu-Li J, Siebenlist U, Williamson PR, Urban JF Jr, Paul WE: IL-25-responsive, lineage-negative KLRG1^{hi} cells are multipotential "inflammatory" type 2 innate lymphoid cells. Nat Immunol 2015;16:161–169.
122 Gladiator A, Wangler N, Trautwein-Weidner K, LeibundGut-Landmann S: Cutting edge: IL-17-secreting innate lymphoid cells are essential for host defense against fungal infection. J Immunol 2013;190:521–525.
123 Mear JB, Gosset P, Kipnis E, Faure E, Dessein R, Jawhara S, Fradin C, Faure K, Poulain D, Sendid B, Guery B: *Candida albicans* airway exposure primes the lung innate immune response against *Pseudomonas aeruginosa* infection through innate lymphoid cell recruitment and interleukin-22-associated mucosal response. Infect Immun 2014;82:306–315.
124 Flaczyk A, Duerr CU, Shourian M, Lafferty EI, Fritz JH, Qureshi ST: IL-33 signaling regulates innate and adaptive immunity to *Cryptococcus neoformans*. J Immunol 2013;191:2503–2513.
125 Castanhinha S, Sherburn R, Walker S, Gupta A, Bossley CJ, Buckley J, Ullmann N, Grychtol R, Campbell G, Maglione M, Koo S, Fleming L, Gregory L, Snelgrove RJ, Bush A, Lloyd CM, Saglani S: Pediatric severe asthma with fungal sensitization is mediated by steroid-resistant IL-33. J Allergy Clin Immunol 2015;136:312–322.e7.
126 Piehler D, Eschke M, Schulze B, Protschka M, Muller U, Grahnert A, Richter T, Heyen L, Kohler G, Brombacher F, Alber G: The IL-33 receptor (ST2) regulates early IL-13 production in fungus-induced allergic airway inflammation. Mucosal Immunol 2016;9:937–949.

127 Shaw JL, Fakhri S, Citardi MJ, Porter PC, Corry DB, Kheradmand F, Liu YJ, Luong A: IL-33-responsive innate lymphoid cells are an important source of IL-13 in chronic rhinosinusitis with nasal polyps. Am J Respir Crit Care Med 2013;188:432–439.
128 Zhou W, Toki S, Zhang J, Goleniewksa K, Newcomb DC, Cephus JY, Dulek DE, Bloodworth MH, Stier MT, Polosuhkin V, Gangula RD, Mallal SA, Broide DH, Peebles RS, Jr.: Prostaglandin I2 signaling and inhibition of group 2 innate lymphoid cell responses. Am J Respir Crit Care Med 2016; 193:31–42.
129 Wiseman JC, Ma LL, Marr KJ, Jones GJ, Mody CH: Perforin-dependent cryptococcal microbicidal activity in NK cells requires PI3K-dependent ERK1/2 signaling. J Immunol 2007;178:6456–6464.
130 Li SS, Kyei SK, Timm-McCann M, Ogbomo H, Jones GJ, Shi M, Xiang RF, Oykhman P, Huston SM, Islam A, Gill MJ, Robbins SM, Mody CH: The NK receptor NKp30 mediates direct fungal recognition and killing and is diminished in NK cells from HIV-infected patients. Cell Host Microbe 2013;14:387–397.
131 Vitenshtein A, Charpak-Amikam Y, Yamin R, Bauman Y, Isaacson B, Stein N, Berhani O, Dassa L, Gamliel M, Gur C, Glasner A, Gomez C, Ben-Ami R, Osherov N, Cormack BP, Mandelboim O: NK cell recognition of *Candida glabrata* through binding of NKp46 and NCR1 to fungal ligands Epa1, Epa6, and Epa7. Cell Host Microbe 2016;20: 527–534.
132 Ziegler S, Weiss E, Schmitt AL, Schlegel J, Burgert A, Terpitz U, Sauer M, Moretta L, Sivori S, Leonhardt I, Kurzai O, Einsele H, Loeffler J: CD56 is a pathogen recognition receptor on human natural killer cells. Sci Rep 2017;7:6138.
133 Albacker LA, Chaudhary V, Chang YJ, Kim HY, Chuang YT, Pichavant M, DeKruyff RH, Savage PB, Umetsu DT: Invariant natural killer T cells recognize a fungal glycosphingolipid that can induce airway hyperreactivity. Nat Med 2013;19:1297–1304.
134 Cohen NR, Tatituri RV, Rivera A, Watts GF, Kim EY, Chiba A, Fuchs BB, Mylonakis E, Besra GS, Levitz SM, Brigl M, Brenner MB: Innate recognition of cell wall β-glucans drives invariant natural killer T cell responses against fungi. Cell Host Microbe 2011;10: 437–450.
135 Zhu W, Phan QT, Boontheung P, Solis NV, Loo JA, Filler SG: EGFR and HER2 receptor kinase signaling mediate epithelial cell invasion by *Candida albicans* during oropharyngeal infection. Proc Natl Acad Sci USA 2012; 109:14194–14199.
136 Solis NV, Swidergall M, Bruno VM, Gaffen SL, Filler SG: The aryl hydrocarbon receptor governs epithelial cell invasion during oropharyngeal candidiasis. MBio 2017; 8:e00025-17.
137 Tomalka J, Azodi E, Narra HP, Patel K, O'Neill S, Cardwell C, Hall BA, Wilson JM, Hise AG: β-Defensin 1 plays a role in acute mucosal defense against *Candida albicans*. J Immunol 2015;194:1788–1795.
138 Kamiya T, Tang C, Kadoki M, Oshima K, Hattori M, Saijo S, Adachi Y, Ohno N, Iwakura Y: β-Glucans in food modify colonic microflora by inducing antimicrobial protein, calprotectin, in a dectin-1-induced-IL-17F-dependent manner. Mucosal Immunol 2017.
139 Moyes DL, Runglall M, Murciano C, Shen C, Nayar D, Thavaraj S, Kohli A, Islam A, Mora-Montes H, Challacombe SJ, Naglik JR: A biphasic innate immune MAPK response discriminates between the yeast and hyphal forms of *Candida albicans* in epithelial cells. Cell Host Microbe 2010;8:225–235.
140 Moyes DL, Wilson D, Richardson JP, Mogavero S, Tang SX, Wernecke J, Hofs S, Gratacap RL, Robbins J, Runglall M, Murciano C, Blagojevic M, Thavaraj S, Forster TM, Hebecker B, Kasper L, Vizcay G, Iancu SI, Kichik N, Hader A, Kurzai O, Luo T, Kruger T, Kniemeyer O, Cota E, Bader O, Wheeler RT, Gutsmann T, Hube B, Naglik JR: Candidalysin is a fungal peptide toxin critical for mucosal infection. Nature 2016; 532:64–68.
141 Liu M, Spellberg B, Phan QT, Fu Y, Fu Y, Lee AS, Edwards JE Jr, Filler SG, Ibrahim AS: The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest 2010;120:1914–1924.
142 Gebremariam T, Liu M, Luo G, Bruno V, Phan QT, Waring AJ, Edwards JE Jr, Filler SG, Yeaman MR, Ibrahim AS: CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Invest 2014;124: 237–250.
143 Phan QT, Eng DK, Mostowy S, Park H, Cossart P, Filler SG: Role of endothelial cell septin 7 in the endocytosis of *Candida albicans*. MBio 2013;4:e00542-13.
144 Saunders CW, Scheynius A, Heitman J: *Malassezia* fungi are specialized to live on skin and associated with dandruff, eczema, and other skin diseases. PLoS Pathog 2012; 8:e1002701.
145 Oh J, Byrd AL, Park M, Program NCS, Kong HH, Segre JA: Temporal stability of the human skin microbiome. Cell 2016;165:854–866.
146 Ghannoum MA, Jurevic RJ, Mukherjee PK, Cui F, Sikaroodi M, Naqvi A, Gillevet PM: Characterization of the oral fungal microbiome (mycobiome) in healthy individuals. PLoS Pathog 2010;6:e1000713.
147 Charlson ES, Diamond JM, Bittinger K, Fitzgerald AS, Yadav A, Haas AR, Bushman FD, Collman RG: Lung-enriched organisms and aberrant bacterial and fungal respiratory microbiota after lung transplant. Am J Respir Crit Care Med 2012;186:536–545.
148 Salazar F, Ghaemmaghami AM: Allergen recognition by innate immune cells: critical role of dendritic and epithelial cells. Front Immunol 2013;4:356.
149 Lilly LM, Gessner MA, Dunaway CW, Metz AE, Schwiebert L, Weaver CT, Brown GD, Steele C: The β-glucan receptor dectin-1 promotes lung immunopathology during fungal allergy via IL-22. J Immunol 2012; 189:3653–3660.
150 Yano J, Kolls JK, Happel KI, Wormley F, Wozniak KL, Fidel PL Jr: The acute neutrophil response mediated by S100 alarmins during vaginal *Candida* infections is independent of the Th17-pathway. PLoS One 2012;7:e46311.
151 De Luca A, Carvalho A, Cunha C, Iannitti RG, Pitzurra L, Giovannini G, Mencacci A, Bartolommei L, Moretti S, Massi-Benedetti C, Fuchs D, De Bernardis F, Puccetti P, Romani L: IL-22 and IDO1 affect immunity and tolerance to murine and human vaginal candidiasis. PLoS Pathog 2013;9:e1003486.
152 Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Li S, Jian M, Zhou Y, Li Y, Zhang X, Li S, Qin N, Yang H, Wang J, Brunak S, Dore J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J, Meta HITC, Bork P, Ehrlich SD, Wang J: A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59–65.
153 Drummond RA, Dambuza IM, Vautier S, Taylor JA, Reid DM, Bain CC, Underhill DM, Masopust D, Kaplan DH, Brown GD: $CD4^+$ T-cell survival in the GI tract requires dectin-1 during fungal infection. Mucosal Immunol 2016;9:492–502.
154 Tang C, Kamiya T, Liu Y, Kadoki M, Kakuta S, Oshima K, Hattori M, Takeshita K, Kanai T, Saijo S, Ohno N, Iwakura Y: Inhibition of dectin-1 signaling ameliorates colitis by inducing lactobacillus-mediated regulatory T cell expansion in the intestine. Cell Host Microbe 2015;18:183–197.
155 Wang T, Pan D, Zhou Z, You Y, Jiang C, Zhao X, Lin X: Dectin-3 deficiency promotes colitis development due to impaired antifungal innate immune responses in the gut. PLoS Pathog 2016;12:e1005662.
156 Schlitzer A, McGovern N, Teo P, Zelante T, Atarashi K, Low D, Ho AW, See P, Shin A, Wasan PS, Hoeffel G, Malleret B, Heiseke A, Chew S, Jardine L, Purvis HA, Hilkens CM, Tam J, Poidinger M, Stanley ER, Krug AB, Renia L, Sivasankar B, Ng LG, Collin M, Ricciardi-Castagnoli P, Honda K, Haniffa M, Ginhoux F: IRF4 transcription factor-dependent CD11b+ dendritic cells in human and mouse control mucosal IL-17 cytokine responses. Immunity 2013;38:970–983.

157 Persson EK, Uronen-Hansson H, Semmrich M, Rivollier A, Hagerbrand K, Marsal J, Gudjonsson S, Hakansson U, Reizis B, Kotarsky K, Agace WW: IRF4 transcription-factor-dependent CD103^{+}CD11b^{+} dendritic cells drive mucosal T helper 17 cell differentiation. Immunity 2013;38:958–969.
158 Schulz O, Jaensson E, Persson EK, Liu X, Worbs T, Agace WW, Pabst O: Intestinal CD103+, but not CX3CR1+, antigen sampling cells migrate in lymph and serve classical dendritic cell functions. J Exp Med 2009;206:3101–3114.
159 Muzaki AR, Tetlak P, Sheng J, Loh SC, Setiagani YA, Poidinger M, Zolezzi F, Karjalainen K, Ruedl C: Intestinal CD103^{+}CD11b^{-} dendritic cells restrain colitis via IFN-γ-induced anti-inflammatory response in epithelial cells. Mucosal Immunol 2016;9:336–351.
160 Matteoli G, Mazzini E, Iliev ID, Mileti E, Fallarino F, Puccetti P, Chieppa M, Rescigno M: Gut CD103+ dendritic cells express indoleamine 2,3-dioxygenase which influences T regulatory/T effector cell balance and oral tolerance induction. Gut 2010;59:595–604.
161 Mazzini E, Massimiliano L, Penna G, Rescigno M: Oral tolerance can be established via gap junction transfer of fed antigens from CX3CR1^{+} macrophages to CD103^{+} dendritic cells. Immunity 2014;40:248–261.
162 Leonardi I, Li X, Semon A, Li D, Doron I, Putzel G, Bar A, Prieto D, Rescigno M, McGovern DPB, Pla J, Iliev ID: CX3CR1^{+} mononuclear phagocytes control immunity to intestinal fungi. Science 2018;359:232–236.
163 Lamas B, Richard ML, Leducq V, Pham HP, Michel ML, Da Costa G, Bridonneau C, Jegou S, Hoffmann TW, Natividad JM, Brot L, Taleb S, Couturier-Maillard A, Nion-Larmurier I, Merabtene F, Seksik P, Bourrier A, Cosnes J, Ryffel B, Beaugerie L, Launay JM, Langella P, Xavier RJ, Sokol H: CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. Nat Med 2016;22:598–605.
164 Drummond RA, Lionakis MS: Mechanistic insights into the role of C-type lectin receptor/CARD9 signaling in human antifungal immunity. Front Cell Infect Microbiol 2016;6:39.
165 Armstrong-James D, Brown GD, Netea MG, Zelante T, Gresnigt MS, van de Veerdonk FL, Levitz SM: Immunotherapeutic approaches to treatment of fungal diseases. Lancet Infect Dis 2017;17:e393–e402.
166 Armstrong-James D, Teo IA, Shrivastava S, Petrou MA, Taube D, Dorling A, Shaunak S: Exogenous interferon-γ immunotherapy for invasive fungal infections in kidney transplant patients. Am J Transplant 2010;10:1796–1803.
167 Torosantucci A, Bromuro C, Chiani P, De Bernardis F, Berti F, Galli C, Norelli F, Bellucci C, Polonelli L, Costantino P, Rappuoli R, Cassone A: A novel glyco-conjugate vaccine against fungal pathogens. J Exp Med 2005;202:597–606.
168 McClelland EE, Nicola AM, Prados-Rosales R, Casadevall A: Ab binding alters gene expression in *Cryptococcus neoformans* and directly modulates fungal metabolism. J Clin Invest 2010;120:1355–1361.
169 Larsen RA, Pappas PG, Perfect J, Aberg JA, Casadevall A, Cloud GA, James R, Filler S, Dismukes WE: Phase I evaluation of the safety and pharmacokinetics of murine-derived anticryptococcal antibody 18B7 in subjects with treated cryptococcal meningitis. Antimicrob Agents Chemother 2005;49:952–958.
170 Perruccio K, Tosti A, Burchielli E, Topini F, Ruggeri L, Carotti A, Capanni M, Urbani E, Mancusi A, Aversa F, Martelli MF, Romani L, Velardi A: Transferring functional immune responses to pathogens after haploidentical hematopoietic transplantation. Blood 2005;106:4397–4406.
171 Kumaresan PR, Manuri PR, Albert ND, Maiti S, Singh H, Mi T, Roszik J, Rabinovich B, Olivares S, Krishnamurthy J, Zhang L, Najjar AM, Huls MH, Lee DA, Champlin RE, Kontoyiannis DP, Cooper LJ: Bioengineering T cells to target carbohydrate to treat opportunistic fungal infection. Proc Natl Acad Sci USA 2014;111:10660–10665.
172 Bozza S, Perruccio K, Montagnoli C, Gaziano R, Bellocchio S, Burchielli E, Nkwanyuo G, Pitzurra L, Velardi A, Romani L: A dendritic cell vaccine against invasive aspergillosis in allogeneic hematopoietic transplantation. Blood 2003;102:3807–3814.
173 Levitz SM, Huang H, Ostroff GR, Specht CA: Exploiting fungal cell wall components in vaccines. Semin Immunopathol 2015;37:199–207.
174 Specht CA, Lee CK, Huang H, Tipper DJ, Shen ZT, Lodge JK, Leszyk J, Ostroff GR, Levitz SM: Protection against experimental cryptococcosis following vaccination with glucan particles containing cryptococcus alkaline extracts. MBio 2015;6:e01905–01915.
175 Schmidt CS, White CJ, Ibrahim AS, Filler SG, Fu Y, Yeaman MR, Edwards JE Jr, Hennessey JP Jr: NDV-3, a recombinant alum-adjuvanted vaccine for *Candida* and *Staphylococcus aureus*, is safe and immunogenic in healthy adults. Vaccine 2012;30:7594–7600.
176 De Bernardis F, Amacker M, Arancia S, Sandini S, Gremion C, Zurbriggen R, Moser C, Cassone A: A virosomal vaccine against candidal vaginitis: immunogenicity, efficacy and safety profile in animal models. Vaccine 2012;30:4490–4498.