frontiers in Immunology

REVIEW
published: 04 June 2018
doi: 10.3389/fimmu.2018.01261

The Interaction of Human Pathogenic Fungi With C-Type Lectin Receptors

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Fungi, usually present as commensals, are a major cause of opportunistic infections in immunocompromised patients. Such infections, if not diagnosed or treated properly, can prove fatal. However, in most cases healthy individuals are able to avert the fungal attacks by mounting proper antifungal immune responses. Among the pattern recognition receptors (PRRs), C-type lectin receptors (CLRs) are the major players in antifungal immunity. CLRs can recognize carbohydrate ligands, such as β-glucans and mannans, which are mainly found on fungal cell surfaces. They induce proinflammatory immune reactions, including phagocytosis, oxidative burst, cytokine, and chemokine production from innate effector cells, as well as activation of adaptive immunity *via* Th17 responses. CLRs such as Dectin-1, Dectin-2, Mincle, mannose receptor (MR), and DC-SIGN can recognize many disease-causing fungi and also collaborate with each other as well as other PRRs in mounting a fungi-specific immune response. Mutations in these receptors affect the host response and have been linked to a higher risk in contracting fungal infections. This review focuses on how CLRs on various immune cells orchestrate the antifungal response and on the contribution of single nucleotide polymorphisms in these receptors toward the risk of developing such infections.

Keywords: pattern recognition receptor, C-type lectin receptor, *Candida*, *Aspergillus*, pathogenic fungi, single nucleotide polymorphisms

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Molecular Innate Immunity, a section of the journal Frontiers in Immunology

Received: *09 March 2018*
Accepted: *18 May 2018*
Published: *04 June 2018*

Citation:
Goyal S, Castrillón-Betancur JC, Klaile E and Slevogt H (2018) The Interaction of Human Pathogenic Fungi With C-Type Lectin Receptors. Front. Immunol. 9:1261. doi: 10.3389/fimmu.2018.01261

INTRODUCTION

Fungi are ubiquitously present in the environment and as commensals in humans; therefore, innate immunity needs to continuously work against the constant exposure. Pattern recognition receptors (PRRs) found on cell surfaces and as soluble forms in body fluids can recognize microbe-specific molecules; the so-called pathogen-associated molecular patterns (PAMPs). PRRs are expressed on immune cells and also on epithelial cells. The interaction of PRRs with PAMPs induces cell- and receptor-specific cellular host responses involving both, the innate and the acquired immune system. There are mainly four different kinds of PRR families, including the toll-like receptors, Nod-like receptors, C-type lectin receptors (CLRs), and RIG-I-like receptors (1). CLRs can recognize carbohydrates by virtue of having a C-type lectin-like domain (2). The domain consists of a conserved double loop structure and a long, structurally, and evolutionarily flexible loop which is involved in Ca^{2+}-dependent carbohydrate binding (3). The characteristic fungal cell wall feature is its richness in carbohydrates and, therefore, they serve as the candidate targets for recognition by CLRs. It is widely accepted that CLRs play major role in antifungal immunity compared to other PRRs (1, 4).

C-type lectin receptors can be found as soluble forms in the serum and other body fluids or as transmembrane receptors on various immune cells, such as macrophages, dendritic cells (DCs), neutrophils, and various other cell types (**Table 1**) (5). Although CLRs have been divided based on their domain organization and phylogenetic features (3, 6), a broader classification of transmembrane receptors is possible based on the type of signaling mechanisms employed by them (7). One such mechanism is the signaling of CLRs *via* immunoreceptor tyrosine-based activation motifs (ITAMs). The ITAM motif (consensus sequence YxxL/I) recruits and phosphorylates Syk kinase on receptor ligation. Signaling *via* Syk typically leads to NF-κB activation *via* the complex consisting of caspase recruitment domain-containing protein 9 (CARD9) singalosome, a trimeric CARD9, B cell lymphoma/leukemia 10, and the mucosa-associated lymphoid tissue lymphoma translocation protein 1. Syk activation ultimately induces subsequent proinflammatory responses, as well as other responses, such as phagocytosis and reactive oxygen species (ROS) and reactive nitrogen species (RNS) production (8, 9). Some CLRs do not have their own cytoplasmic ITAMs. Such receptors couple with ITAM containing adaptor molecules like FcRγ to emanate signaling (10, 11). Dectin-1 is another non-classical CLR bearing a hemITAM motif (consensus sequence YxxL) and the ligand binding is Ca^{2+} independent (12). A second signaling mechanism with contrary effects to those elicited by ITAM signaling is employed by CLRs containing a cytoplasmic immunoreceptor tyrosine-based inhibitory motif (ITIM). Here, receptor ligation leads to the phosphorylation of tyrosine within the ITIM motif (consensus sequence I/V/L/SxYxxI/L/V) and the recruitment of SHP-1, SHP-2, and/or SHIP-1 phosphatases which exert an inhibitory effect by dampening the proinflammatory response (13, 14). Finally, some CLRs do not contain any known signaling motifs and, therefore, only little is known about their signaling mechanisms, such as LOX-1, MR, and langerin.

Fungal pathogens have a huge influence on human life, since they can infect the human body and cause various diseases from superficial infections to invasive and systemic infections. Infections of the skin and nails are the most common fungal diseases which affect ~25% of the general population worldwide (83). Invasive fungal infections have a lower incidence than superficial infections; however, they are of greater concern

TABLE 1 | C-type lectin receptors and their respective ligands involved in fungal recognition by different human cell types.

Receptor	Fungus	Ligand	Cell Type	Reference
Dectin-1	*Aspergillus fumigatus, Malassezia* spp., *Saccharomyces cerevisiae*, *Fonsecaea pedrosoi*, *Pneumocystis carinii*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Histoplasma capsulatum*, *Coccidioides posadasii*, *T. mentagrophytes*, *Candida albicans*, *Talaromyces marneffei*, *Fusarium solani*, *Exserohilum rostratum*, *Cladosporium cladosporioides*, *T. asahii*, and *Sporothrix schenckii*	β-1,3-glucan	hDC, macrophages, bronchial epithelial cells, monocytes, neutrophils, mast cells, dendritic cells (DCs), and pulmonary epithelium	(12, 15–32)
Dectin-2	*A. fumigatus*, *Malassezia* spp., *F. pedrosoi*, *H. capsulatum*, *T. rubrum*, *C. albicans*, *C. glabrata*, and *M. audouinii*	α-mannans	DCs, macrophages	(11, 33–37)
MR	*A. fumigatus*, *S. cerevisiae*, *P. carinii*, *C. neoformans*, *P. brasiliensis*, *C. albicans*, *C. parapsilosis*, *T. marneffei*, and *S. schenckii*	gp43 (*P. brasiliensis*), mannoproteins (*C. neoformans*), and α-mannans	Corneal epithelial cells, alveolar macrophages (AMs), DCs, monocytes, and keratinocytes	(38–47)
SP-A, SP-D	*A. fumigatus*, *S. cerevisiae*, *Pneumocystis* spp., *C. neoformans*, *Histoplasma* spp., and *Coccidioides* spp.	β(1→6)-glucan, gpA and gp120 (*P. carinii*), glucuronoxylomannan, and mannoprotein (*C. neoformans*)	Isolated from lung lavage fluids	(48–54)
MBL	*A. fumigatus*, *P. carinii*, *C. neoformans*, and *C. albicans*		Purified from plasma	(55–58)
DC-SIGN	*A. fumigatus*, *S. cerevisiae*, *C. neoformans*, *C.albicans*, *T. marneffei*, and *C. topicum*	Galactomannans (*A. fumigatus*), mannoprotein (*C. neoformans*), and N-linked mannans	DCs, AMs	(5, 39, 59–64)
Mincle	*A. fumigatus*, *Malassezia* spp., *F. pedrosoi*, *P. carinii*, and *C. albicans*	α-mannose, glyceroglycolipid and mannosyl fatty acids (*Malassezia* spp.), MSG/gpA (*P. carinii*)	Corneal epithelial cells, monocytes, macrophages, neutrophils, myeloid DCs, and some B-cell subsets	(36, 65–69)
MCL	*C. neoformans*, *C. albicans*	α-mannans	Plasmacytoid dendritic cells	(70, 71)
CR3	*A. fumigatus*, *M. furfur*, *S. cerevisiae*, *P. brasiliensis*, *H. capsulatum*, and *C. albicans*	pH-regulated Ag 1 (*C.albicans*)	Neutrophils, macrophages, natural killer cells, and monocytes	(5, 72–78)
Lox-1	*A. fumigatus*		Corneal epithelial cells	(79, 80)
Langerin	*M. furfur*, *S. cerevisia*, C. albicans, *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*	β-glucan	Langerhans cells	(81)
MelLec	*A. fumigatus*	1,8-dihydroxynaphthalene-melanin	Endothelial cells, macrophages	(82)

because they are associated with high morbidity and mortality. They are mostly caused by opportunistic fungal pathogens that take advantage of a debilitated immune system to proliferate in the human host and cause disease (84). Among the fungal species, only several 100 species are associated with human fungal diseases and just a minor number of species cause the most common invasive infections in immunocompromised individuals (85). The most notorious genera that are responsible for more than 90% of all reported fungal-related deaths are *Cryptococcus*, *Candida*, *Aspergillus*, and *Pneumocystis* (84). This increased prevalence of fungal infections has motivated the study of host–pathogen interactions in order to understand the protective and nonprotective mechanisms of antifungal immune responses in the human body. Investigation of the fungal recognition by the innate immune system led to the discovery of CLRs, the best-characterized PRRs for fungi. CLRs recognize carbohydrate polymers (mannan, glucans, and chitins) present in the fungal cell wall, resulting in the induction of innate and adaptive immunity to clear the pathogen (**Figure 1**; **Table 1**) (86).

In the following sections, we will summarize the current knowledge about the interaction of important human pathogenic fungi with CLRs. We further include information on CLR-associated single nucleotide polymorphisms (SNPs) and their effect on the susceptibility to fungal infections.

OPPORTUNISTIC INVASIVE MYCOSES

Aspergillus spp.

Aspergillus species (*Aspergillus* spp.) are ubiquitous molds commonly found in the soil. They produce a large number of conidia, which are released and dispersed into the air by wind leading to a deep penetration into the respiratory tract upon inhalation (87). These conidia are effectively cleared from the lungs of immunocompetent individuals. However, patients with a compromised immunity are at risk of developing an acute invasive aspergillosis (AIA). AIA is characterized by hyphal invasion of lung tissues and even dissemination to other organs (87). *Aspergillus fumigatus* (*A. fumigatus*) accounts for about 65% of all invasive infections

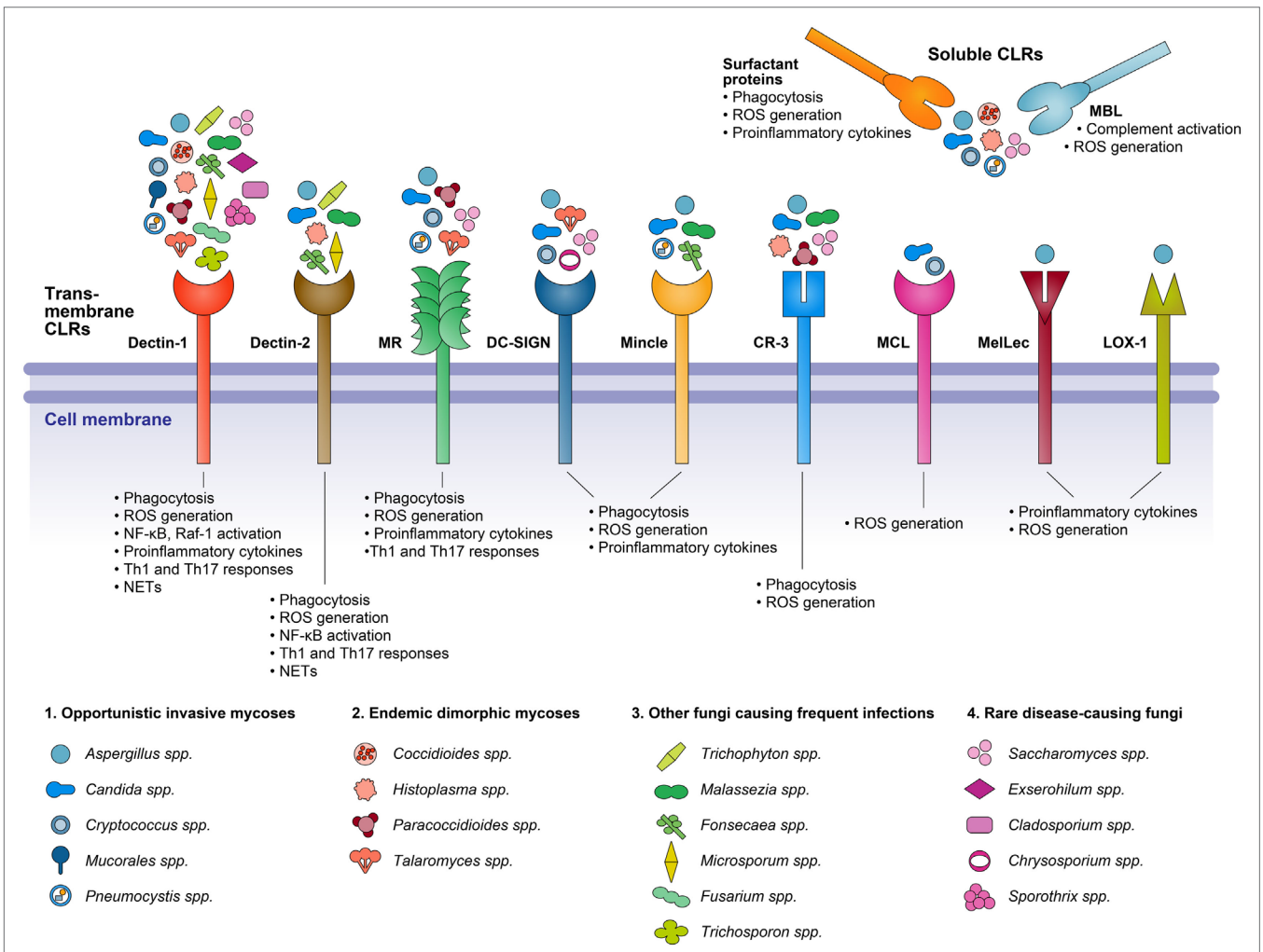

FIGURE 1 | A diagrammatic representation of C-type lectin receptors (CLRs) involved in the recognition of various fungal species, and the resepective cellular responses triggered on receptor–ligand binding.

in humans and is the most frequently encountered *Aspergillus* spp. in pulmonary infections. *A. flavus*, *A. niger*, *A. terreus*, and *A. nidulans* are less frequent causes of infections (87). The primary innate immune response is mediated mainly by macrophages, DCs, and neutrophils, taking place after *Aspergillus* spp. encounters these cells. Several of the *Aspergillus* cell wall components, such as β-glucans, chitins, and mannans act as ligands that are recognized by CLRs. Ligation results in the activation of cellular immune responses, such as phagocytosis, extracellular trap formation, conidial killing, and the production of proinflammatory and anti-inflammatory cytokines, such as TNF-α, IFN-α, IL-6, and IL-18 (88–91). Fungal recognition by specific CLRs can depend on morphological changes of *Aspergillus* spp., since different growth forms expose diverse PAMPs at variable amounts on their surface. For example, the surface of the *Aspergillus* dormant conidia does not present β-glucan, but is accessible for receptor recognition after the loss of hydrophobic cell wall components (outer layer of rodlets/hydrophobins and melanin) during the swelling of conidia and the development of germ tubes (89, 92, 93). Several CLRs are involved in the recognition of *Aspergillus* spp. such as the transmembrane receptors Dectin-1, Dectin-2, MR, DC-SIGN, and the soluble collectins MBL and the lung surfactant proteins (SP) SP-A and SP-D (94) (**Table 1**). The most studied *Aspergillus* receptor is Dectin-1. It is present on the surface of myeloid cells recognizing β-1,3-glucan, a common component of the cell wall of several fungi (15). However, another *Aspergillus* cell wall-associated polysaccharide, the galactosaminogalactan, has also been identified as a ligand and prevents host inflammatory responses *in vitro* and *in vivo*, in part by avoiding cell wall β-glucans recognition by Dectin-1 (95). Several observations suggest a significant role for Dectin-1 in protective immunity against *A. fumigatus* (96–98). *A. fumigatus* also induces the expression of cytokines (TNF-α and IL-12) and genes related to fungal recognition and phagocytosis in immature human DCs (99). The transcription of Dectin-1 in response to *A. fumigatus* likely occurs *via* granulocyte-macrophage colony stimulating factor (GM-CSF)/PU.1, where GM-CSF potentiates the expression of PU.1, which carries out transcription of Dectin-1 augmenting Dectin-1 protein expression and responsiveness in THP-1 cells (100, 101). In HEK293T cells, the activation of AP-1 by heat-killed swollen conidia was inhibited by treatment with Syk inhibitor, indicating that the Syk signaling pathway is required for AP-1 activation in a Dectin-1-dependent manner (102). Silencing of Dectin-1 in murine macrophages resulted in a reduced expression of proinflammatory cytokines, and an observed inhibition of phagocytosis (103). Likewise, *A. fumigatus* conidia and germ tubes stimulated NF-κB activation, mediated the secretion of proinflammatory cytokines involved in the recruitment of neutrophils, and led to ROS production by human monocyte-derived macrophages, murine macrophages, and alveolar macrophages (AMs) (89, 92, 93). Clinical studies showed that individuals who developed AIA during the course of chemotherapy often displayed a defective expression of Dectin-1. The frequency of Dectin-1-expressing monocytes was reduced in patients with AIA compared to controls (65.6 vs. 87.5%) (104). This important role of Dectin-1 was confirmed by transfecting murine AMs with a vector encoding full-length Dectin-1 (105). Results demonstrated that Dectin-1 overexpression enhanced the generation of proinflammatory cytokines TNF-α and IL-1β, and enhanced the killing ability of macrophages during *A. fumigatus* exposure (105). The epithelial lining of human airways is another important spot for host-pathogen interactions, and Dectin-1 is also expressed in lung tissues (12). One study found that *A. fumigatus* induces the expression of Dectin-1 *via* TLR-2 in human bronchial epithelial cells, resulting in the stimulation of proinflammatory responses and ROS generation in response to *A. fumigatus* indicating its important role in the innate immune response in non-phagocytic cells (106). Furthermore, some findings indicate that the pulmonary infection of mice with *A. fumigatus* induces concurrent Th1 and Th17 responses that depend on Dectin-1 (107). With regards to *Aspergillus*-induced fungal keratitis, recent findings demonstrated that Dectin-1 is expressed in the cornea of rat and mice, where it is involved in the detection of invading fungi (108–110). Also Dectin-2 triggers a response to *A. fumigatus* infection. Human plasmacytoid dendritic cells (pDCs) recognize *A. fumigatus* hyphae *via* Dectin-2, resulting in cytokine release and extracellular trap (pET) formation (88). The noticeable Dectin-2 expression of AMs in human lung during *A. fumigatus* invasion suggests a prominent contribution to antifungal defenses in pulmonary aspergillosis (90). Moreover, Dectin-2 ligation leads to NF-κB activation and ROS production in response to *A. fumigatus* infection in human macrophages (111). An *A. fumigatus*-specific ligand has not been described until now, but Dectin-2 binds to high-mannose structures distributed in several fungal species, including *Aspergillus* spp. (33). Collectins, such as SP-A, SP-D, and MBL also bind to *A. fumigatus* (55, 112). One study about the contribution of MBL in the antifungal defense in invasive pulmonary aspergillosis (IPA) showed that in murine models of IPA, rhMBL-treated (recombinant human MBL) mice showed 80% survival compared to untreated IPA mice. A clear increase of TNF-α and IL-1α in treated IPA mice and a significant decrease in pulmonary fungal hyphae and IL-10 could be observed (113). *In vitro*, there was an enhanced uptake of *A. fumigatus* conidia by polymorphonuclear neutrophil (PMNs) in the presence of rhMBL, indicating a protective role of this receptor during IPA, possibly through MBL-mediated lectin complement activation (113). SP-A and SP-D also enhanced agglutination and binding of conidia to AMs and neutrophils and increased the phagocytosis, oxidative burst, and killing of *A. fumigatus* conidia by human neutrophils and AMs (91). The SP-D-mediated protective mechanism is dependent on calcium-activated protein phosphatase calcineurin (114) and include enhanced phagocytosis by recruited macrophages and neutrophils and enhanced local production of the Th1 cytokines TNF-α and IFN-γ in the supernatant from mice lung cell suspension (115). Corneal epithelial cells also express SP-D and in the setting of fungal keratitis *A. fumigatus* may induce these cells to express inflammatory cytokines *via* the SP-D and NF-κB pathway (116, 117). Since β(1→6)-glucan is a ligand for SP-D and since many fungi, including *Aspergillus* spp., have this carbohydrate structure in their cell wall compositions, it is expected that SP-D recognizes all *Aspergillus* spp. (48).

Several other CLRs ligate *Aspergillus* spp., but for each only a few data are available. DC-SIGN, another transmembrane

receptor of the CLR family expressed on the surface of DCs, contributes to the binding of *A. fumigatus* conidia in human DC (59). However, DC-SIGN is also expressed in AMs and lung tissue, suggesting a contribution of DC-SIGN in the initial stages and in fungal spreading during AIA (60). Galactomannans appear to be the main DC-SIGN ligand on the cell wall of *A. fumigatus* conidia (60). Additionally, CR3 influences adaptive responses to *Aspergillus*. Blocking of CR3 significantly reduced *Aspergillus*-induced Th1 and Th17 responses independently from complement activation, demonstrating that CR3 might play a significant role in the adaptive host defense against *A. fumigatus* (72).

In fungal keratitis models, LOX-1 was increased in *A. fumigatus* infected corneas of C57BL/6 mice and human corneal epithelial cells, indicating a possible role of this receptor in controlling the infection (79, 80). In addition, Mincle and MR may play a role in the early innate immune response of the corneal resistance, since their expression increased significantly during the initial period of *A. fumigatus* infection, along with an increased expression of TNF-α and IL-1β in human and rat cornea (38, 65). *A. fumigatus*-specific ligands for these receptors have not been described up to now.

Recently, the CLR Clec1a, also called melanin-sensing C-type lectin receptor (MelLec), has been decribed to play an important role in the detection of *A. fumigatus* through recognition of the naphthalene-diol unit of 1,8-dihydroxynaphthalene-melanin in conidial spores of *A. fumigatus*. MelLec is ubiquitously expressed by CD31+ endothelial cells in mice and is required for protection against disseminated infection with *A. fumigatus*. MelLec is also expressed by myeloid cells in humans and a SNP within the coding region of this receptor (rs 2306894) was identified that significantly increased the susceptibility of stem-cell transplant recipients to AIA (82). AIA is of great interest for immunogenetic studies due to its high prevalence. A moderately large number of studies have investigated the association of SNPs and other genetic variations of different CLRs in order to get some benefit for preventive strategies. For Dectin-1, the *CLEC7A* rs3901533 (T/T) and rs7309123 (G/G) genotypes and the presence of Y238X (rs16910526) polymorphism resulted in a significantly increased risk of AIA in a Caucasian population (118–120). Two SNPs of *CD209* encoding DC-SIGN (rs735239 and rs735240) are associated with a higher susceptibility to fungal keratitis in the northern Han Chinese population (121). Association analysis revealed that carriers the *CD209* rs4804800 (G), rs11465384 (T), rs7248637 (A), and rs7252229 (C) alleles and the variant *CD209*-139A/G (rs2287886) in the Caucasian population had a significantly increased risk of contracting IPA (118, 122).

Several studies show that distinct alleles, genotypes, and genotype arrangements of *SFTPA2* and *MBL2* may contribute to a susceptibility of the host to aspergillosis. A significant association of *SFTPA2* 1649G and *SFTPA2* 1660G and *MBL2* 1011A alleles with allergic bronchopulmonary aspergillosis patients suggests that defects in these innate immune molecules may lead to an increased genetic susceptibility to allergic airway inflammation and asthma (123–126). Another study implies that the presence of the T allele and CT genotype at position 868 of *MBL2*, the CC genotype at position 1649 of *SFTPA2*, and its combination with the CC or CT genotype on position 868 of MBL gene increases susceptibility specifically to chronic cavitary pulmonary aspergillosis in the Caucasian population (127). It was demonstrated that the presence of the codon 52 mutation (W/M52) within the MBL gene was particularly common in patients with chronic necrotizing pulmonary aspergillosis. Since the mutation results in changes in the protein structure, it is likely that a reduced amount of active protein is available for pathogen clearance (128).

Overall, Dectin-1 plays an important role in the local immune response during aspergillosis by inducing the expression of proinflammatory cytokines. Dectin-1 is the best-characterized CLR for the recognition of *A. fumigatus*, since it recognizes β-1,3-glucan, which is a major component of the inner cell wall of this fungus. Even a single polymorphism results in a significantly increased risk of contracting AIA, indicating the importance of this receptor in the contribution to antifungal defenses. With regards to the other CLRs recognizing *Aspergillus* spp., more studies are required in order to establish a concrete role of them during an AIA.

Candida spp.

The most common species of *Candida* responsible for causing human diseases is *Candida albicans*. It is an opportunistic pathogen that commensally colonizes not only the skin but also the gastro-intestinal and urino-genital mucosal surfaces mostly in yeast form in healthy individuals. In cases of immunosuppression or weakening, the yeast forms can convert into virulent hyphae that can cause either muco-cutaneous infection or disseminate to internal organs causing candidaemia (129). In addition to phenotypic switching between yeast and hyphal forms, *C. albicans* virulence factors include adhesion properties, secreted lipases, and aspartyl proteases (130). Other clinically relevant *Candida* species include *C. krusei*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and others (131). Among the *Candida* species-recognizing CLRs are Dectin-1, Dectin-2, MCL, Mincle, MR, DC-SIGN, CR3, MBL, and Langerin.

Dectin-1 is a type II transmembrane receptor expressed on several antigen-presenting cells of myeloid origin, including macrophages, monocytes, neutrophils, mast cells, DCs, as well as pulmonary epithelium (12, 16). Like *A. fumigatus* and other fungi, Dectin-1 also recognizes *C. albicans* by binding to β-1,3-glucan (**Table 1**) (132).The binding of β-1,3-glucan to Dectin-1 is Ca^{2+}-independent (133). Notably, Dectin-1 recognition of the yeast form of *C. albicans* induces responses such as phagocytosis and oxidative burst in mouse phagocytes, ultimately resulting in the clearance of the yeast cells; in contrast, filamentous forms may mask the β-glucans by mannans and affect certain β-glucan-mediated responses (17, 134, 135). However, *C. albicans* germ tubes can be resognized by Dectin-1 in Syk-dependent mechanism and initiate Th-17 response (136).

Dectin-1 recognition of *C. albicans* or its ligand β-1,3-glucan initiates several distinct immune responses. β-1,3-glucan-Dectin-1 binding leads to NFκB-mediated ROS production and proinflammatory cytokine release, such as IL-12, TNFα, and IL-6, *via* the Syk-CARD9 pathway in mouse DCs and macrophages, as well as in human intestinal cells. The response is enhanced in co-operation with TLR-2 (137–141). Interestingly, *C. albicans* activation of Dectin-1 can also result in anti-inflammatory

responses, like IL-10 release by macrophages and peripheral blood mononuclear cells (PBMCs) or the production of IL-1 receptor antagonist (IL-1Ra) (142–144). Furthermore, ligation of Dectin-1 on APC by *C. albicans*, but also by other fungi and even the endogenous ligand galectin-9 drives T cell differentiation into a TH2/TH17 response (145–148). PKCδ is essential for CARD9-dependent NFκB activation (149). *C. albicans* also induces mast cell activation in rat and mice that leads to a differential cytokine production depending upon the fungal morphology, and induces phagocytosis and nitric oxide production in a TLR-2 and Dectin-1-dependent manner (150, 151). A similar co-operation of Dectin-1 with TLR-2 and TLR-4 can be observed in human mononuclear cells, PBMCs, and macrophages on stimulation with β-1,3-glucan (152, 153). The Dectin-1-Syk-CARD-9 pathway can also activate IRF5 to produce IFN-β (154) or ERK to generate proinflammatory responses against *C. albicans* (155). Moreover, Dectin-1 also mediates the β-1,3-glucan-medidated opsonization-independent phagocytosis by human neutrophils and retinal microglia (156, 157). The Syk-dependent pathway is also involved in β-1,3-glucan-containing phagosome maturation and recruitment of TLR-9 in RAW cells (158). Additionally, Dectin-1 involvement with *C. albicans* activates many other signaling pathways. Dectin-1 binding with *C. albicans* can activate NFAT transcription factors induce IL-2, IL-10, and IL-p70 release in collaboration with TLR-2 in mouse DCs (15, 159). β-1,3-glucan-induced human DCs activate NFκB *via* Syk as well as Raf-1 *in vitro*. In fact, Raf-1 activation represses Syk-induced RelB activity, although not completely, and increases p65 transactivation activity to induce IL-12p40 and IL-1β production (160). Several studies based on human and mouse cell lines have demonstrated that Dectin-1 is important in activating the inflammasomes such as the noncanonical caspase-8 inflammasome that promotes Th-17 responses which are essential for antifungal immunity (136, 161–166). Th17 responses are important against cutaneous infection, while Th1 responses are directed against systemic infection (134). Dectin-1 also co-operates with other CLRs such as SIGNR1 in mouse macrophages enhancing the oxidative burst against *C. albicans* (167). Some studies have also demonstrated a Dectin-1-dependent CR3 activation on mouse neutrophils and subsequent killing of *C. albicans* by these cells (168, 169). Human neutrophils release neutrophil extracellular traps in response to *C. albicans in vitro*, triggered by the ROS production on recognition of β-glucan by Dectin-1 and CR-3 (170, 171). Interestingly, Dectin-1 stimulation with *C. albicans* or β-1,3-glucan can also generate certain immunomodulatory responses, e.g., IL-10 production and reduction in ROS production *via* SHIP-1 activation in mouse GM-CSF-derived bone marrow cells (172). Additionally, *C. albicans*-Dectin-1 engagement induces human as well as mouse granulocytic myeloid-derived suppressor cells to dampen the pathogenic hyperinflammatory NK and Th17 responses (173). Moreover, a recent study has also demonstrated a role of Dectin-1 in adaptive immunity by controlling CD4+ T cell responses in the murine gut (174). All these results indicate how *C. albicans* can influence the immune responses by engaging the same receptor on different cell types.

Mouse knockout studies have shown contrasting results. Dectin-1 deficient mice display defective macrophage activation with impaired subsequent inflammatory responses and present enhanced fungal burden and dissemination after *C. albicans* infection (163, 175). However, further mouse studies implied that Dectin-1 deficiency probably plays a minor role in systemic *Candida* infection but may control the mucosal infections (176). The differences in the results may be attributed to different mouse and *C. albicans* strains used in experiments (177). Dectin-1-deficient mice also are more susceptible to *C. glabrata* infections and show impaired inflammatory responses (178).

Polymorphisms in Dectin-1 have been studied with respect to *Candida* infections. The first study to report an early-stop-codon mutation Y238X in a family with recurrent vulvovaginal candidiasis (RVVC) among four women demonstrated that the monocytes and neutrophils from homozygotes lack Dectin-1 expression and are defective in cytokine production such as IL-17 upon *C. albicans* stimulation *in vitro*. However, phagocytosis and killing of fungi is normal (179, 180). Another report demonstrated that heterozygotes for Y238X receiving hematopoietic stem cell transplantation display an increased incidence of gastrointestinal *Candida* colonization. The monocytes of homozygotes show less IL-1β production and lack of TLR-2-Dectin-1 synergism complementing the previous *in vivo* and *in vitro* studies describing the role of Dectin-1 in *Candida* infections (181). In an HIV-infected African population, a mutation I223S has been associated with a lower IFNγ response to *C. albicans* stimulation of whole blood and tends to provide protection against oropharyngeal candidiasis (182).

The hyphal form of *C. albicans* can be recognized by Dectin-2, which binds to high-mannose structures such as α-mannans in a cation-dependent manner and is expressed predominantly on macrophages and DCs (**Table 1**) (11, 33). Several studies in mouse DCs and macrophages have demonstrated that Dectin-2 mediates its signaling *via* the ITAM-bearing adapter FcRγ and the Syk-CARD9 pathway but the subsequent responses seem to differ depending upon the cell type, fungal morphology, and methodologies (11, 34, 183, 184). Nevertheless, *C. albicans* recognition by Dectin-2 can induce phagocytosis, proinflammatory cytokine production, such as IL-6, IL-23, TNFα, and IL-12 as well as protective Th-17 responses (34, 183). In addition, Dectin-2-deficient mice show decreased survival and high kidney fungal burden after 10 days of infection with *C. albicans* (34). Indeed, it was later shown in two independent studies that Dectin-2-deficient mice are also susceptible to *C. albicans* and *C. glabrata* systemic infections, showing high fungal burdens in kidneys and reduced neutrophilic phagocytosis (185, 186). Similar to Dectin-1, Dectin-2 can also induce type I IFN responses in mouse macrophages and DCs by activating IRF5 in response to *C. albicans* (154). PLCγ2 is essential for Dectin-2-mediated NF-κB, MAPK and ROS activation in mouse macrophages when infected with hyphal *C. albicans* (187). Zhu et al. showed that Dectin-2 and MCL (Dectin-3) heterodimers recognize *C. albicans* α-mannans more effectively than either receptor alone and that MCL-deficient mice are highly susceptible to systemic candidiasis (70). However, most of these studies have been performed in mouse models and provide a picture of Dectin-2 and MCL roles in murine *Candida* infections, and studies regarding

their role in the human host and the impact of mutations in the human receptors will be needed in order to complete the picture.

Mannose receptor is a mannan-binding lectin found on phagocytic cell surfaces and recognizes *C. albicans* α-mannans (**Table 1**) (39). Early studies have demonstrated the involvement of MR in cytokine release, non-opsonic phagocytosis, and killing of *Candida* spp. by phagocytic cells (**Figure 1**) (40, 188, 189). Human DCs phagocytose and kill *Candida via* MR leading to subsequent responses such as Th1 immunity and ROS production (39, 190–192). Dectin-1 engagement with *C. albicans* on mouse macrophages induces surface MR shedding which could be the reason for downregulation of MR surface expression observed on rat macrophages after *C. albicans* ingestion (193, 194). Dectin-1 was later shown to be the main phagocytic receptor, while MR is recruited to phagosomes in mouse macrophages in later stages and mediates the secretion of immunomodulators such as TNFα and MCP-1 (195). Indeed, MR-deficient mouse macrophages are able to take up and phagocytose *C. albicans* normally (195, 196). However, in human phagocytic cells, MR induces Th17 responses upon stimulation with *C. albicans in vitro* by inducing IL-1β and prostaglandin E2 production, which is enhanced by Dectin-1/TLR-2 synergism (162, 197–199). Neumann et al. reported the formation of unique MR-induced pseudopodial protrusions called fungipods in human monocyte-derived DCs in response to *C. albicans* yeast, which may have role in fungal phagocytosis. This response is species-specific with *C. parapsilosis* showing stronger fungipod formation compared to *C. albicans* and *C. tropicalis* (41). In fact, the innate immune recognition of *C. parapsilosis* complex and *C. albicans* by human PBMCs differ with respect to the receptors involved and the induced cytokine production; for example, MR is important for TNFα and IL-1β production upon *C. parapsilosis* stimulation (200). Interestingly, IFNγ stimulation of human monocyte-derived DCs and macrophages increases the candidacidal activity of these cells by increasing non-opsonic phagocytosis and ROS production which is related to a reduced expression of MR (201, 202). So far, no genetic studies have been performed to understand the significance of MR polymorphisms in *Candida* infections.

Candida albicans yeast and hyphae are also recognized by the collectin MBL (56, 203). Several studies have demonstrated the binding of *Candida* spp. to MBL followed by activation of the complement system and subsequent opsonophagocytosis of fungi by phagocytic cells *in vitro* (204–206). Li et al. demonstrated MBL-dependent opsonophagocytosis of *C. albicans* by human neutrophils but without complement activation. This response was coupled with intracellular Dectin-1-dependent ROS production (207). Parenteral administration of MBL increased the resistance of mice in a model of disseminated candidiasis (56). In fact, mice deficient in MBL-A and MBL-C (mice homologs to human MBL) are more susceptible to systemic *Candida* infection (208). MBL is expressed in the mouse gut and its blocking or elimination leads to increased *C. albicans* colonization (209). MBL can also modulate the *C. albicans*-triggered TLR-generated proinflammatory signals by THP-1 cells (210). MBL concentrations are greatly affected by promoter polymorphisms in the *MBL2* gene and the resulting lower MBL levels are linked to the risk to develop several infectious diseases (128, 211, 212). Reduced levels of MBL were observed in the cervicovaginal lavage of RVVC patients, while the levels were higher in VVC patients compared to healthy controls (213–215). Moreover, MBL deficiency is also associated with the development of abdominal yeast infection in peritonitis patients (216). However, MBL serum levels and genotypes were not associated with intra-abdominal candidiasis in a Swiss cohort (217). The RVVC patients also have a higher frequency of *MBL2* mutations compared to both VVC and healthy groups (214). Furthermore, the *MBL2* codon 54 allele B is associated with a higher susceptibility to RVVC as observed in Belgian, Latvian, and Brazilian women (215, 218, 219). A recent meta-analysis of five different studies also concluded the correlation of allele B of codon 54 to be associated with both RVVC and VVC (220). Only a couple of studies have addressed the polymorphisms in components of MBL complement pathway in development of invasive fungal infections (221, 222). The polymorphisms in MBL complement pathway components have been associated with other infectious diseases as well, such as tuberculosis and leprosy (223, 224) and further studies exploring the effects of mutations in complement proteins on the pathogenesis of fungal infections are still needed.

Another CLR, DC-SIGN, can recognize the N-linked mannans in the *C. albicans* cell wall (39, 225). It mediates the internalization of conidia by human DCs, which are abundantly present in mucosal tissue (**Table 1**) (61), although human DCs exhibit less-efficient phagocytic activity compared to monocytes and macrophages (226). Gringhuis et al. showed that *C. albicans* stimulation can modulate TLR-dependent pathways by Raf-1 activation in human DCs. There is also evidence for possible anti-inflammatory effects upon DC-SIGN ligation. However, data so far are derived from non-fungal ligands (227). The fungus-induced IL-10 production is mediated through coactivation of DC-SIGN and TLR signaling pathways (228). The mouse homolog of DC-SIGN, SIGNR1 works in co-operation with Dectin-1 and TLR-2 in mouse macrophages to induce responses such as oxidative burst and TNFα production *in vitro* (167, 229). Knockout mouse studies and genetic studies may enlighten us more regarding the importance of this CLR in these fungal infections.

Candida albicans is also recognized by Mincle, another CLR expressed on several immune cells (**Table 1**), although the related ligand has not yet been discovered (230). An *in vivo* study demonstrated a non-redundant role of Mincle against *Candida* infection as Mincle-deficient mice were highly susceptible to systemic candidiasis. Mincle induces TNFα production in mouse macrophages upon *C. albicans* hyphae stimulation *in vitro* but is not important for phagocytosis, indicating that Mincle has a role in initial macrophage binding and early responses to the fungus (66). A similar effect was observed in human monocytes where the stimulation with *C. albicans* yeast leads to TNFα production but is related to poor yeast uptake. However, human neutrophils expressing Mincle show a fungicidal activity correlated with phagocytosis of the yeast (231). Taken together, more studies are needed to discover the *C. albicans* ligand(s) for Mincle and the related pathways as well as *in vitro* and *in vivo* immune responses and further work is necessary to elucidate the role of Mincle polymorphisms in fungal infections.

CR3 is an important CLR expressed on neutrophils, macrophages, NK cells, and monocytes and is involved in adhesion and phagocytosis of *C. albicans* (5, 73, 232). CR3 has a role in *C. albicans* hyphae recognition as the human lymphocyte adhesion of *C. albicans* hyphae was abrogated upon blocking CR3 with monoclonal antibodies (233, 234). Soloviev et al. showed that *C. albicans* releases a soluble CR3-binding mannoprotein called pH-regulated Ag 1 (Pra1), which mediates CR3-dependent adhesion and migration of THP-1 cells and neutrophils toward *C. albicans* (74, 235). Pra1 is expressed highly and exclusively on *C. albicans* hyphae (236). Soluble Pra1 was found to be beneficial for fungal survival as it inhibits the human neutrophil activation upon stimulation with Pra1 overexpressing *C. albicans* hyphae (235). Additionally, a CR3 knockout mouse study demonstrated that these mice show an increased susceptibility toward *C. albicans* systemic infection (168, 237) and their neutrophils display impaired adhesion, migration, and oxidative burst when challenged with *C. albicans in vitro* (237). Several studies have shown β-glucan to be another potential ligand for CR3 (238–240). Dectin-1 and CR3 co-localize on yeast *C. albicans* phagocytic cups in mouse peritoneal macrophages (195). Further studies support the interaction of Dectin-1 and CR3 in *C. albicans* infection as mentioned earlier. Dectin-1 activates CR3 for recognition of *C. albicans* yeast components and together they induce neutrophil cytotoxic responses in mice (168, 169).

Langerhans cells (LCs), found in epidermis and mucosal linings, express Langerin, which can bind to β-glucans and recognizes Candida spp., including *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*, among others, *in vitro* (81, 241, 242). Some studies have shed light on the roles of LCs in *Candida* infections (243, 244), but specific studies regarding the role of Langerin are lacking.

Taken together, *Candida* is recognized by a number of CLRs, each of which is able to generate fungal-specific immune responses. While Dectin-2 and CR3 can recognize and respond to the fungal hyphae, Dectin-1, MR, and DC-SIGN mainly recognize the conidial forms. For Mincle, MCL and Langerin little is known and they need to be further investigated for their roles in *Candida* infections. Moreover, more studies need to focus on the genetic component of the effect of CLRs on *Candida* infections.

Cryptococcus spp.

Cryptococcosis is a worldwide distributed and invasive fungal infection that is caused by species of the genus *Cryptococcus*. Nearly 100 species have been described within this genus so far, but *Cryptococcus neoformans* and *C. gattii* species are considered to be the only disease-causing fungi (245). Although cryptococcosis is predominantly a disease of immunocompromised patients (AIDS-defining illness), a recent outbreak showed the capacity of some lineages of the fungus to act as primary pathogens in healthy individuals (246). Within the lung, *Cryptococcus* spp. can cause pneumonia in immunosuppressed patients, and the latent infection can then disseminate to other tissues, most particularly the central nervous system (CNS), where this fungus causes an infection of the meninges accompanied by elevated intracranial pressure and without a rapid treatment it becomes fatal (246).

The interaction of *Cryptococcus* with CLRs is poorly understood. Initial data demonstrated that *C. neoformans* binds to soluble collectin MBL and the ingestion of the acapsular form is inhibited by both soluble mannan and β-1,3-glucan, showing that ingestion of acapsular *C. neoformans* takes place *via* mannose and β-glucan receptors in murine macrophages (247).

The role of Dectin-1 is still controversial, since no significant differences were observed in the clinical course and cytokine production between Dectin-1-deficient and control mice in a cryptococcosis model (248), but another study found that *C. neoformans* spores are phagocytosed by murine AMs *via* Dectin-1 (18). The role of Dectin-2 is also poorly understood. Some results show that it may not be required for the production of Th1 and Th17 responses, proinflammatory cytokines or for the clearance of *C. neoformans* in Dectin-2 knockout mice (249). Dectin-3 seems to have a role as it was demonstrated that human and murine pDCs have a direct Dectin-3-dependent anti-cryptococcal activity by inhibiting the growth of *C. neoformans via* ROS production (71). A *Cryptococcus*-specific ligand for this receptor has not been described yet.

Mannose receptor also has a role in *Cryptococcus* infection. After a pulmonary infection with *C. neoformans*, MR knockout mice died significantly earlier than wild-type mice and had higher lung fungal burdens (250). This receptor was required for the presentation of *C. neoformans* antigens to T lymphocytes by primary DCs, since blocking this receptor reduced both uptake of *C. neoformans* and lymphocyte proliferation (251). Some data suggest that mannoproteins, secreted by *C. neoformans,* might be the ligands for MR, as T cell stimulation is inhibited either by competitive blockade of MR in APCs or by removal of carbohydrate residues from mannoproteins. These results imply a capacity of mannoproteins to bind MR and to be processed by APCs to stimulate primary T cells (42). However, multiple receptors on DC could recognize this ligand, since DC-SIGN was also determined to have an affinity for mannoproteins. Further, MR and DC-SIGN both colocalize with mannoproteins, supporting a role for each in mannoprotein capture (62).

The pulmonary surfactant proteins, SP-A and SP-D bind to both encapsulated and acapsular *C. neoformans* (49, 252) and SP-D binds to the high-molecular weight polysaccharide glucuronoxylomannan and mannoproteins on the fungal cell wall (50). However, some data suggest that these receptors actually increase the susceptibility to *C. neoformans* infection. SP-A inhibits the IgG-dependent phagocytosis of *C. neoformans* by AMs and SP-A$^{-/-}$ mice exhibit wild-type vulnerability to *C. neoformans*; SP-D$^{-/-}$ mice are even protected during *C. neoformans* infection and display decreased fungal burden compared to wild-type mice. SP-D$^{-/-}$ AMs also demonstrate an enhanced ability to kill *C. neoformans* cells (253, 254). Indeed, SP-D increases vulnerability to *C. neoformans* infection by stimulating *C. neoformans*-driven pulmonary IL-5 and eosinophil infiltration (255). SP-D may also play a role in protecting *C. neoformans* cells during the early stages of infection by opsonization. It was found that SP-D increases phagocytosis of hypocapsular *C. neoformans* by murine macrophages and enhances fungal survival allowing to gain access to specific intracellular compartments where it can grow (256). Another study reports that both, the presence of

capsules and a wild-type cell wall design, prevent MBL binding to *C. neoformans* (257).

Last but not the least, complement activation by *Cryptococcus* spp. was demonstrated in the presence of MBL *in vitro* (57). A *Cryptococcus*-specific ligand for this receptor has not been described up to now.

Given that Dectin-1, Dectin-2, SP-A, and SP-D studies showed controversial results and their interactions with *Cryptococcus* are poorly understood, further studies are necessary.

Mucorales spp.

Mucormycosis is the second most-common form of invasive mold infections. The disease is characterized by vessel thrombosis and tissue necrosis resulting from extensive angioinvasion and further dissemination (258). The members of the *Mucorales* order of Zygomycetes are among the leading causes of mucormycosis in immunocompromised individuals apart from more common fungal genera, such as *Candida* or *Aspergillus*, with mortality rates ranging from 50 to 100% (259). Among *Mucorales* spp., although rare, *Rhizopus oryzae* accounts for 70% of mucormycosis infections. Mainly phagocytotic cells play an important role in restricting the infection (260). The studies on mechanistic details of fungal recognition by CLRs and their role in pathogenesis are still lacking. One study reported that patients with mucormycosis showed reduced expression of Dectin-1 on monocytes compared to healthy controls (104). However, further investigations into the role of C-type lectins and their polymorphisms in this infection are needed.

Pneumocystis spp.

The genus *Pneumocystis* includes a variety of ubiquitous fungi that colonize and infect several mammalian host species. The species *P. jirovecii* particularly infects humans, whereas *Pneumocystis carinii* (*P. carinii*) and *P. murina* are associated with rats and mice, respectively. In the immunocompromised host, *Pneumocystis* pneumonia (PCP) is fatal if untreated. However, infection of an immunocompetent host can result in a self-limited mild or subclinical lower respiratory tract infection (261).

The first studies demonstrated an interaction of *Pneumocystis* cell wall isolates with macrophage β-glucan receptors, which induced a potent stimulation of TNF-α release in rat AMs in response to *P. carinii* (262, 263). During *P. carinii* infection, the expression of Dectin-1 is upregulated in macrophages of immunocompetent rat models (264). According to some studies, Dectin-1 is required for the protection against *P. carinii* infection, since Dectin-1-knockout mice are more sensitive to infection than infected wild-type mice, and production of ROS is completely abolished in Dectin-1-knockout macrophages incubated with *P. carinii* (176). Probably, the expression levels of Dectin-1 in AMs are under the control of the transcription factor PU.1 during a PCP infection, where the GM-CSF appears to play a major role in the regulation of PU.1 expression (265). Phagocytosis of *P. carinii* and generation of hydrogen peroxide by murine AMs is mediated by Dectin-1, since the blockage of Dectin-1 inhibits the binding and killing of *P. carinii* (266). The binding of Dectin-1 to *Pneumocystis* was tested by creating recombinant Dectin-Fc fusion proteins which bind *P. carinii* and enhance murine macrophage-dependent killing. These findings demonstrate that Dectin-1 binds β-glucan from *Pneumocystis,* enhancing host recognition and clearance of *P. carinii* (19). *P. carinii* β-glucan cell wall component challenge of rat alveolar epithelial cells resulted in a prominent nuclear translocation of p65 NF-κB with a subsequent increase in MIP-2 and TNF-α mRNA production. However, rat alveolar epithelial cells do not require Dectin-1 for MIP-2 production, which rather involves the participation of the alternative lactosylceramide β-glucan receptor (267, 268).

Pneumocystis carinii also enhances soluble MR production in human and murine macrophages (269). In human AMs, phagocytosis of *Pneumocystis* is mediated through MR and depends on Cdc42 and especially RhoB activation (270). *Pneumocystis* also stimulates NF-κB nuclear translocation in human AMs, which is mediated primarily through MR (43). A recombinant soluble MR-Fc fusion protein binds *P. carinii* and leads to an increased uptake by hPMNs (271). The role of MR was confirmed by the fact that binding and uptake of cultured *P. carinii* by human and rat AMs is reduced 90% by using competitive inhibitors of MR, emphasizing the role of the AMs in the first-line host defense (272). Other studies suggest that a reduced AM MR-mediated binding of *P. carinii* may contribute to the susceptibility of HIV-infected individuals to this pathogen (273). However, it was demonstrated that IL-8 release by human AMs following the stimulation with *Pneumocystis* requires the co-expression of MR and TLR-2, since the IL-8 release is reduced significantly upon blocking of TLR-2 and silencing of MR gene (274). These results support the idea that MR on human AMs may suppress the production of proinflammatory cytokines and may serve to regulate the innate inflammatory responses to *Pneumocystis* infection in the lungs (275). A *Pneumocystis*-specific ligand for MR has not been described up to now.

Some results indicate that SP-A and SP-D can modulate the virulence of *P. murina* and *P. carinii* during development of infection in SP-D- and SP-A-deficient and immunosuppressed mice. They attenuate the production of proinflammatory cytokines and ROS and RNS, indicating that both receptors are local effector molecules in the lung host defense against *Pneumocystis in vivo* (276–280). These results are supported by the fact that SP-A and SP-D can bind *P. carinii*, acting as opsonins and enhancing their phagocytosis by AMs (281–284). However, some data suggest that the increased SP-A and SP-D mediated aggregation of *P. carinii* fungal particles interferes with AM recognition and thus the SPs may contribute to the pathogenesis of *P. carinii* pneumonia (285–287). This view is supported by the fact that SP-A in immunosuppressed mice acts as a therapeutic agent in the beginning of *Pneumocystis* infection, but not in the middle or late stages of the infection (288). SP-D strongly interacts with gpA, the main glycoprotein antigen on the surface of *P. carinii*. The interaction of SP-D with *P. carinii* gpA is mediated by the carbohydrate recognition domain (CRD) of this collectin (51, 289). Similarly, the CRD of SP-A mediates binding to the main surface glycoprotein gp120 of *P. carinii* (52, 290).

Binding of MBL to *P. carinii* is followed by the activation of the respiratory burst, indicating that the MBL in serum has opsonizing properties and might contribute in controlling fungal spread

from the lungs (58). A *Pneumocystis*-specific ligand has not been described up to now for this receptor.

Mincle binds whole *P. carinii* and a surface glycoprotein called MSG/gpA, a *Pneumocystis* cell wall component, which is expressed at enhanced levels during infection (67). Moreover, Mincle$^{-/-}$ mice exhibit significantly higher *P. murina* burdens with elevated levels of TNF-α, IL-6, and IL-1Ra during infection, indicating that Mincle functions as an important signaling receptor in host defense against *Pneumocystis* infection (67).

Little is known about polymorphisms affecting *Pneumocystis* recognition, however, one study analyzed 53 HIV patients having CD4 counts <200 μL, in order to find a correlation between MBL and PCP. Of these 53 patients, 30 had PCP at admission, and 23 did not. Genotypes related with a low production of MBL were significantly more common in the PCP group than in the non-PCP group. Serum MBL levels were significantly higher in the non-PCP group. Genetic variations influencing MBL production also affect the susceptibility to PCP in HIV-advanced infection patients, and may be considered as a risk factor for PCP (291).

Overall, CLRs seem to be of importance for orchestrating the *Pneumocystis*-induced immune response. However, *Pneumocystis* cannot easily be propagated in culture, which has delayed the understanding of its pathobiology. Efforts to study *Pneumocystis* have been greatly limited by the inability to maintain *ex vivo* culture of the organism. Early attempts to isolate and propagate *P. jirovecii*, have been moderately successful, however, none of these models garnered sufficient recognition to become a standard method for the isolation of *Pneumocystis* (292). Nonetheless, studies of organisms isolated directly from the infected lung of patients or immunosuppressed research animals still allow for some insight into the pathobiology of *Pneumocystis* (293).

ENDEMIC DIMORPHIC MYCOSES

Coccidioides spp.

There are two species of *Coccidioides* (*C. immitis* and *Coccidioides posadasii*) that cause human disease. They have similar phenotypes and pathogenicities, but differ in genotype and geographic distribution. They are the etiologic agents of coccidioidomycosis, which ranges from asymptomatic infections to pneumonia and severe disseminated disease. These organisms are found in the soil, especially in low-moisture environments, so preventing exposure can be difficult due to the ubiquitous risk of dust inhalation by individuals living in endemic areas. The pathogenesis of coccidioidomycosis is complex and can be asymptomatic but also cause extrapulmonary dissemination (294).

The reasons of the complexity of the pathogenesis of coccidioidomycosis are not well understood; however, some data suggest the main involvement of Dectin-1. Some results suggest that an alternative splicing of the Dectin-1 gene enhances the susceptibility of C57BL/6 mice to coccidioidomycosis, regulating the cytokine responses of macrophages and mDCs to spherules, the pathognomonic structure of this fungus (295). RAW 264.7 macrophages overexpressing Dectin-1 produced more TNF-α than control macrophages in respond to *C. posadasii* spherules. Also, macrophages overexpressing Dectin-1 and activated with purified β-glucan from *C. posadasii* spherules produced a significantly higher level of TNF-α than control macrophages, indicating a role of β-glucan from *C. posadasii* as a ligand for Dectin-1 (20). Moreover, Dectin-1 activation is essential to leading the adaptive immune response toward Th1 and Th17 pathways, thus leading to the resolution of infections in mice (35, 296).

Other results suggest that there is an association between low serum MBL levels and symptomatic coccidioidomycosis, but in order to understand the role of MBL in the pathogenesis of this fungal disease, further studies are necessary (297). SP-A and SP-D also bind coccidioidal antigens (53). Deficiencies of MR and Dectin-2, either alone or in combination, affect cellular responses to formalin-killed spherules *in vitro* but do not make C57BL/6 mice more vulnerable to pulmonary coccidioidomycosis (298). A *Coccidioides*-specific ligand for these receptors has not been described up to now.

In conclusion, further studies are necessary to elucidate interactions of *Coccidioides* with CLTRs, since few receptors and no ligands have been studied. However, Dectin-1 seems to have an important role in this infection.

Histoplasma spp.

Fungi of the genus *Histoplasma* cause histoplasmosis and are found throughout the world, but are most common in North America and Central America. *Histoplasma capsulatum* is a member of this group of fungal pathogens that cause respiratory and disseminated disease in mammals. It grows as a saprobic conidia-producing mycelium in the environment, and when the aerosolized mycelium fragments and conidia are inhaled, they reach the lower respiratory tract causing disease even in immunocompetent hosts (299).

Little is known about the receptors recognizing *Histoplasma* and its signaling response. However some CLRs, such as Dectin-1, Dectin-2, and some collectins are involved in *Histoplasma* immunity (**Table 1**). Dectin-1 and Dectin-2 exert several contributions to the development of antifungal Th1 and Th17 cells and vaccine resistance in mice against *H. capsulatum* (35, 300). CR3 and Dectin-1 act together to induce murine macrophages to TNF and IL-6 responses through a Syk-JNK-AP-1-dependent mechanism (75). Some data show that CR3 participates in phagocytosis and cytokine responses, but Dectin-1 takes part in cytokine production only on murine macrophage (21). *Histoplasma* pathogenic yeast cells secrete Eng1, a β-glucanase that hydrolyzes β-(1,3)-glycosyl linkages, which reduces levels of surface-exposed β-glucans on yeast cells, thereby enabling *Histoplasma* yeasts to escape detection by Dectin-1. *Histoplasma* yeasts deficient for Eng1 show an enhanced binding to Dectin-1 and an increased TNF-α and IL-6 production in murine macrophages and DCs (301, 302). Also, SP-A and SP-D demonstrate potent antifungal properties, since they cause a dose-dependent decrement in yeast viability, which is associated with an increase in the permeability of the yeast cells. Mice lacking SP-A manifest a modestly higher fungal burden in lungs than wild-type littermates (54). A *Histoplasma*-specific ligand for these receptors has not been described up to now.

Together, these studies indicate minor roles for CLRs in the control of *Histoplasma* infections, but further studies are needed to understand the significance of CLRs in *Histoplasma* infections.

Paracoccidioides spp.

Paracoccidioides spp. is the causal agent of paracoccidioidomycosis (PCM), a systemic mycosis endemic to Latin America. It comprises two species: *Paracoccidioides brasiliensis* and the recently described *P. lutzii* (303). Manifestations of PCM include subclinical or asymptomatic infection. The symptomatic disease causes an acute/subacute or a chronic form, the latter involving the lungs as well as other organs. PCM is acquired after inhalation of infectious propagules in the environment, leading to a primary pulmonary infection (303).

Few studies have investigated the role of CLRs on *Paracoccidioides* infection. Human monocytes display a decrease in Dectin-1 expression as soon as 30 min after stimulation with *P. brasiliensis* (22). There is a trend toward an increased Dectin-1 mRNA expression in response to *P. brasiliensis* and this receptor is able to induce a balanced production of TNF-α, IFN-γ, IL-12, and IL-10 in human neutrophils and monocytes (22, 304, 305). By binding to Dectin-1, *P. brasiliensis* induces neutrophil extracellular trap (NET) release that is responsible for trapping yeast cells, promoting their immobilization, as well as contributing to their extracellular killing (306). Moreover, the fungal infection of Dectin-1$^{-/-}$ mice results in enhanced tissue pathology and mortality rates. The deficiency of Dectin-1 has also reduced the production of Th1, Th2, and Th17 cytokines and the activation and migration of T cells to the site of infection (307). Altogether, these results suggest the participation of Dectin-1 in *P. brasiliensis* recognition, internalization, and consequent activation of the immune response against the fungus. A *Paracoccidioides*-specific ligand for Dectin-1 has not been described up to now, however, it is known that Dectin-1 binds glucan structures that are distributed in a wide range of fungal species.

The gp43 glycoprotein is the main antigenic component secreted by *P. brasiliensis*. gp43 binds to TLR2, TLR4, and MR receptors and all three receptors influenced a high production of IL-10 and TNF-α in human monocytes (44). The specific blockade of MR and CR3 impaired fungal recognition and modified the production of cytokines (308). The CR3 receptor may participate in phagocytosis of *P. brasiliensis* conidia through both opsonic and non-opsonic mechanisms, since treatment of murine macrophages with anti-CR3 and α-methyl-d-mannoside, a competetive inhibitor of the binding of mannose, decreased phagocytosis of *P. brasiliensis* (76). In the same way, the mannose-binding lectin complement pathway was demonstrated to play a key role in complement activation by *P. brasiliensis* (309). A *Paracoccidioides*-specific ligand for this receptor has not been described until now.

Overall, interactions between host immune cells and *Paracoccidioides* spp. are mediated by the recognition of Dectin-1 which controls internalization by phagocytes as well as lymphocyte proliferation during *P. brasiliensis* infection. However, further studies are necessary, since few receptors and no ligands have been studied.

Penicillium spp.

Penicillium species are rarely considered as human pathogens except *Talaromyces (Penicillium) marneffei,* which can cause opportunistic infections, called penicilliosis, in immunocompromised patients, especially in HIV positive persons, but also in old and new born (310). The infection is most prevalent in South-east Asia and is characterized by symptoms, such as weight loss and fever, skin lesions, generalized lymphadenopathy and hepatomegaly, and respiratory signs such as hemoptysis (310, 311). The main virulence factor of *T. marneffei* is its temperature-dependent dimorphic growth, owing to which it grows as mycelium at 25°C while at 37°C it grows as yeast (311). *In vitro* experiments have shown that *T. marneffei* can be recognized by Dectin-1, DC-SIGN, and MR (**Figure 1**) (23, 45, 63). Koguchi and colleagues demonstrated that blocking MR with antagonists reduces the osteopontin production from PBMCs upon *T. marneffei* stimulation and suggested a mannoprotein as the possible ligand (45). Indeed, MR was later found to be involved in adhesion and phagocytosis of the fungus by human monocyte-derived DCs, while DC-SIGN only mediated adhesion (63). IL-12p40 production by bone marrow-derived dendritic cells (BMDCs) upon stimulation with *T. marneffei* is abrogated in Dectin-1 knockout mice (23). Together, these studies suggest that CLRs modulate the immune response to *T. marneffei*; however, further studies are needed to dissect the *in vivo* role of CLRs and their polymorphisms in *T. marneffei* infections.

OTHER FUNGI CAUSING FREQUENT INFECTIONS

Trichophyton spp.

Dermatophytosis is one of the most common mycoses worldwide. Compromising keratinized tissues and characterized by establishing chronic inflammatory processes, it is highly resistant to standard antifungal therapies. The main etiological agent in humans is *Trichophyton rubrum*. It establishes infection after being inoculated in the host tissue, where it survives through the degradation of dead cells, consuming keratin and other host components (312).

Only few studies analyzed the roles of CLRs in *Trichophyton* spp. infections. Dectin-1 is involved in mediating inflammation induced by trichophytin, a *T. mentagrophytes* antigen with β-glucans and zymosan as the main components (24). *T. rubrum* hyphae are recognized by Dectin-1 and Dectin-2 in murine DCs, triggering production of inflammatory cytokines, mainly IL-1β and TNF-α. This inflammatory process is able to promote the clearance of the pathogen *in vivo* without the involvement of lymphocytes. Even though IL-17 is induced, it is not essential for infection resolution (313). Moreover, trichophytin enhances the Dectin-1 expression in mice, and the blockage of Dectin-1 inhibits the increased IFN-γ production in cervical lymph node cells from mice *in vitro* (314). Dectin-2 preferentially binds to hyphae of various fungal species, including *T. rubrum* (11).

Malassezia spp.

The fungal genus *Malassezia* comprises yeast species that are part of the normal skin microbiota. However, *Malassezia* spp. can be

involved in skin disorders, such as pityriasis versicolor, seborrheic dermatitis, atopic eczema, and folliculitis (315). *Malassezia* spp. may also cause invasive infections in infants and in immunocompromised individuals. The clinical spectrum ranges from asymptomatic infections to life-threatening sepsis and disseminated diseases (316).

Various *Malassezia* spp. (*M. japonica*, *M. slooffiae*, *M. furfur*, and *M. sympodialis*) induce a Dectin-1-dependent NLRP3 inflammasome activation with a subsequent IL-1β secretion in human APCs. This activation is dependent on Dectin-1, since the blocking of Dectin-1 decreased the IL-1β secretion upon *M. furfur* exposure (25). A *Malassezia*-specific ligand has not been described until now, but β-1,3-glucan is most likely present on their surface.

Several *Malassezia* spp. (*M. pachydermatis* and *M. furfur*) are recognized by Mincle and Dectin-2 through different ligands. A glyceroglycolipid and mannosyl fatty acids linked to mannitol are two Mincle ligands, and an O-linked mannobiose-rich glycoprotein is a ligand for Dectin-2. Both receptors cooperatively contribute to the TNF and IL-10 production in BMDCs from mice in response to *Malassezia spp* (36). Other results indicate that Mincle also recognizes *Malassezia* spp. (*M. pachydermatis*, *M. dermatis*, *M. japonica*, *M. nana*, *M. slooffiae*, *M. sympodialis*, *M. furfur*, and *M. pachydermatis*) through α-mannose but not mannan. Mincle may recognize a particular distribution of α-mannosyl residues on *Malassezia* spp. and use this to discriminate them from other fungi, inducing inflammatory responses (TNFα and IL-10) in murine macrophages (317).

Langerin plays a role in pathogen recognition by facilitating pathogen uptake and processing for antigen presentation (318). Langerin on primary LCs isolated from human epidermis interact strongly with *M. furfur via* β-glucan structures and the interaction can lead to the phagocytosis of the fungus (81). *M. furfur* is also recognized through MR and CR3 on THP-1 cells (77).

Fonsecaea spp.

Fonsecaea spp. are found in soil and plants. Although they are considered a worldwide-distributed fungus, they are frequently found in tropical regions (319). *Fonsecaea pedrosoi* is a frequent causative agent of chromoblastomycosis (or chromomycosis), a chronic fungal disease limited to the skin and subcutaneous tissues. Initial lesions are habitually erythematous papules, which progressively enlarge to morphologies, such as verrucous nodules, cauliflower-like tumors, and psoriasis-like plaques (319).

Dectin-1, Dentin-2, and Mincle have a role in the recognition of this fungus (**Table 1**). Murine macrophages stimulated by co-culturing with muriform cells (the parasitic form of *F. pedrosoi*) show an elevated expression of the Dectin-1, and by blocking Dectin-1, the phagocytosis of muriform cells, was impaired, demonstrating that muriform cells are recognized by Dectin-1 *in vitro* (26). *F. pedrosoi* spores trigger Dectin-1 and Dectin-2 signaling and induce IL-6 production, but only the Dectin-2 signaling pathway promotes the differentiation of Th17 cells, indicating that the adaptive immune response to *F. pedrosoi* spores in this murine infection model is determined by Dectin-2 (37). A *Fonsecaea*-specific ligand has not been described until today.

Mincle acts as a major receptor involved in the innate immune response to *F. pedrosoi* through the Syk/CARD9 pathway in murine BMDCs (68). However, another study identified Mincle as a suppressor of antifungal defenses by suppressing IL-12. The absence of IL-12 leads to impaired Th1 responses. Dectin-1 binding of *F. monophora* activates the transcription factor IRF1, which is crucial for the *IL12A* transcription. However, simultaneous binding of *F. monophora* to Mincle induces a Mdm2 (E3 ubiquitin ligase)-dependent degradation pathway *via* Syk-CARD9-mediated PKB signaling, that leads to the loss of nuclear IRF1 activity, therefore, blocking *IL12A* transcription (320). A *Fonsecaea*-specific ligand has not been described up to now for this receptor.

Regarding Mincle, it is difficult to ascertain a particular role for this CLR in *Fonsecaea* infection, since it is not clear if this receptor is mainly involved in the recognition and subsequent clearance of this fungus or acts as a suppressor of antifungal defenses and is exploited for immuno evasive strategies.

Microsporum spp.

Microsporum causes skin infections or dermatophytosis characterized by severe scalp itching and patchy scaly scalp skin which is highly contagious. The pathogenic species include mainly *M. cani*, *M. gypseum*, and *M. hominis* (321). The fungi secrete a number of enzymes and immunomodulators such as keratinolytic subtilase and keratinolytic metalloprotease as well as other cell wall glyco-proteins, endoproteases, and exoproteases (322). *M. cani* activates the NLRP3 inflammasomes in THP-1 cells. The production of IL-1β and its precursor are decreased in Dectin-1, Syk, and CARD-9 knockdown cells (323). Soluble Dectin-2 can bind the filamentous *M. audouinii* (11). Further research on CLR ligands, their recognition, and corresponding immune response in *Microsporum* infection are lacking.

Fusarium spp.

Fusarium species can cause superficial, locally invasive infections in immunocompetent individuals, or disseminated infections in immunocompromised patients. The infection is called fusariosis and is characterized by keratitis, onychomycosis, fungimia with or without organ involvement, and other symptoms depending upon the fungal species, port of entry, and host immune status. In humans, *Fusarium solani* and *F. oxysporum* are responsible for most cases of infections by these species (324). *Fusarium* spp. secrete various mycotoxins as well as certain proteases and collagenases, which modulate the immune response and destroy tissue (324).

Dectin-1 expression is highly elevated in the corneal tissue from patients infected with *F. solani* when compared to healthy non-infected individuals (325). Human corneal epithelial cells secrete defensive antimicrobial peptides in response to heat-killed *F. solani* or zymosan and this effect was Dectin-1- and TLR-2-dependent (326). Another more recent study addressed the Dectin-1-dependent CXCL-8 release from the human bronchial epithelial cell line BEAS-2B in response to *F. proliferatum* and showed that the chemokine release is decreased to various degrees by inhibiting Dectin-1, Syk, MAPKs, PI3K, and NFκB, respectively (27). The expression of SP-D increased in rat corneal cells after *F. solani* infection but its further role in murine models as well in humans is still to be established (327).

Trichosporon spp.

Trichosporon are ubiquitous dimorphic fungi, which also exist as commenals on the skin and in the gastrointestinal tract in humans. They induce superficial infections such as white piedra characterized by the presence of irregular nodules on the affected hair, as well as invasive infections such as allergic pneumonitis and trichosporonosis (invasive mycoses) especially in immunocompromised patients and those with hematological malignancies (328, 329). *T. asahii*, *T. asteroids*, and *T. mucoides* are the major causes of trichosporonosis and opportunistic infections (330). Only a little is known about the interaction of these fungi with CLRs. Dectin-1 binds *T. asahii via* β-glucan recognition (28). Dectin-1-deficient mice with *T. asahii* induced hypersensitivity pneumonitis show decreased Th-17 cell populations and less monocytes/MDMs compared to wild-type mice (28).

RARE DISEASE CAUSING FUNGI

Saccharomyces spp.

Classically, *Saccharomyces* spp. are considered safe, non-pathogenic organisms. Within this genus, *Saccharomyces cerevisiae* is the most important species (331). However, due to its ubiquity and long association with humans, *S. cerevisiae* has been implicated as a causative agent of infections in immunocompromised individuals, those with underlying diseases or medical conditions (332). Several cases of life-threatening invasive infections with *S. cerevisiae* resulting in pneumonia, liver abscess, and sepsis have been reported (333).

Saccharomyces cerevisiae cells cause a subtle upregulation of Dectin-1 from the moment of initial recognition in human DCs (334). Most studies have been performed by evaluating pure soluble and particulate β-glucans such as β-1,6-branched and β-1,3-D-glucan found in the *S. cerevisiae* cell wall (335), which can be directly recognized by Dectin-1 (29, 336). β-glucan induces Dectin-1 signaling pathways for the activation of TNFα in both human and mouse macrophages. The signaling pathways involve RTKs, ROS production, and NF-κB activation (337, 338). The Dectin-1-dependent response is essential for immunomodulatory effects on DC activation and macrophage phagocytosis. It induces the expression of immuno-regulatory cytokines, such as IL-10, TGF-β1, and IL-2 and can promote both Treg and Th17 responses (339–341). Moreover, the Dectin-1 response was investigated by observing the direct phagocytosis of β-glucan-coated particles by RAW macrophages expressing a GFP-Dectin-1 fusion protein. As expected, the β-1,3-beads induced a higher TNF-α response and a GFP-Dectin-1 recruitment to the phagosome, indicating that Dectin-1 recruitment is specific to β-1,3-glucan (342). In general, binding of particulate β-glucans to Dectin-1 triggers phagocytosis (343, 344). However, phagocytosis of β-glucan-bearing particles by human neutrophils is CR3-dependent, with a very minor role for Dectin-1, if any (78). Like *C. albicans*, also *S. cerevisiae* components in form of Zymosan are able to induce anti-inflammatory responses such as IL-10 release in human and mouse DCs and macrophages (345, 346).

Also, Langerin and DC-SIGN interact strongly with *S. cerevisiae* (64, 81). SP-D but not SP-A binds *S. cerevisiae,* and β(1→6)-glucan is a ligand for SP-D (48). Moreover, phagocytosis of unopsonized heat-killed yeast by murine macrophages is also mediated by MR (46).

Several studies have concluded that genetically determined low MBL concentrations in patients could be, at least in part, responsible for the enhanced immune reactivity to *S. cerevisiae* antigens (347–349). The analysis of *MBL2* polymorphisms revealed an association between three variants rs930508, rs1800450, and rs5030737, with a reduction in MBL serum levels in Crohn's disease patients (350). However, these results are in contrast with other reports in which such an association was not found. Therefore, the relationship between enhanced immune reactivity to *S. cerevisiae* antigens and MBL is still controversial (351, 352).

Despite its low pathogenicity, *S. cerevisiae* constitutes one of the better studied microorganisms, since it was developed as a model organism for several traits. Zymosan is mostly prepared from *S. cerevisiae* cell walls and consists of a glucan with repeating glucose units linked by β-1,3-glycosidic linkages, which have served as a model for recognition of microbes by the innate immune system for over 50 years (353). Many studies have been conducted testing and evaluating the zymosan interaction with human receptors and Dectin-1 emerged as the most important receptor for detecting *Saccharomyces* spp. However, for the other CLRs more studies are required in order to stablish a concrete role for them.

Exserohilum spp.

Exserohilum species are environmental fungi and, although rare, can lead to a number of human diseases such as skin and corneal infection, invasive disease, as well as allergic fungal sinusitis especially during impaired immunity, trauma, and atopy (354). Members of this genus are among the causes of phaeohyphomycosis which is characterized by the presence of dark septate mycelial elements in tissues (355). Not much work has been done to elucidate the mechanism of infection and immune responses against these fungi. A very recent work demonstrates the role of Dectin-1 in the recognition of *Exserohilum rostratum* (30). Mouse macrophages generate a Dectin-1 dependent TNF-α, IL-1β, MIP-1, and MIP-2 secretion in response to *E. rostratum* hyphae *in vitro* and the response is diminished in Dectin-1-deficient macrophages. However, wild-type and Dectin-1-deficient mice show no difference with respect to the type of inflammatory response and fungal control (30).

Cladosporium spp.

The *Cladosporium* genus consists of ubiquitous fungi that are mainly plant pathogens but few species such as those belonging to *Cladosporium cladosporioides* and *C. herbarum* complexes may cause infections in humans (356). The clinical manifestations range from keratitis, opportunistic phaeohyphomycosis including superficial or deep infections such as those of the CNS, to acnes (356–359). *Cladosporium* conidia are widely present in the air and have also been associated with respiratory allergy (360). The *C. cladosporioides* cell wall is rich in β-glucans but unavailable for recognition on live spores. A mouse *in vivo* study demonstrated that *C. cladosporioides* induces airway hyperresponsiveness and eosinophilia in a Dectin-1-independent manner (361).

Furthermore, the heat-induced availability of surface β-glucans is important for a Dectin-1-dependent pulmonary IL-17 response and Dectin-1$^{-/-}$ mouse DCs show a decreased IL-17 response upon stimulation with heat-killed *C. cladosporioides* (31). The ligands on live *Cladosporium* cell surfaces and the corresponding CLRs, as well the subsequent immune responses are still to be investigated.

Chrysosporium spp.

The members of this genus are saprophytic soil fungi and many species are keratinolytic (362). Several case reports of superficial infections affecting nails and skin as well as opportunistic infections in immunocompromised patients have been reported (362–365). Superficial infections are mainly caused by species, such as *C. keratinophilum*, *C. tropicum*, and *C. queenlandicum* (362). Invasive infections are rare but have been reported (366–368). A single study demonstrated that DC-SIGN recognizes *C. topicum* conidia probably by recognition of fungal cell wall mannans *in vitro* (59).

Sporothrix spp.

These fungi are usually found living as a saprophytes thriving on decaying vegetation or soil. Sporotrichosis, caused by dimorphic *Sporothrix* spp., is one of the most prevalent forms of subcutaneous mycoses with a worldwide distribution particularly in tropical and subtropical regions (369, 370). While different species of clinical interest have been identified, including *S. globosa*, *S. brasiliensis*, *S. Mexicana*, and *S. luriei*, the most commonly reported species in human clinical isolates is *Sporothrix schenckii* (371, 372). Infection results in cutaneous or subcutaneous lesions usually with compromised adjacent lymphatic vessels. Rarely, disseminated disease can also ensue and several publications report infection of the lung, the CNS, bones, and other organs, mostly in immunocompromised individuals (372–375).

In a rat co-infection model of *Tenia taeniaeformis* and *S. schenckii*, a high expression of Dectin-1 only occurs in cutaneous lesions of co-infected rats, but is dispensable for the clearance of *S. schenckii* (376). However, a more recent study shows an increased Dectin-1 expression in peritoneal macrophages from *S. schenckii*-infected mice. Furthermore, the antibody-mediated blockade of Dectin-1 inhibits the cytokine production in response to different stimuli by peritoneal macrophages. A Dectin-1 blockade additionally results in a decreased phagocytic uptake of *S. schenckii* yeast cells (32). Martínez-Álvarez et al. proved that Dectin-1 is crucial for the secretion of cytokines by human PBMCs during *S. schenckii* infection, but dispensable for the recognition of *S. brasiliensis*. The authors also reported that while MR appears to have only a minor role in the recognition of *S. schenckii* yeast-like cells, it mediates the production of proinflammatory cytokines by human PBMCs in response to conidia from this fungus as well as yeasts from *S. brasiliensis* (47). An earlier study on the contribution of MR in the recognition of *S. schenckii* evidenced the presence of mannose residues in the cell wall of *S. schenckii* conidia and yeasts. Nevertheless, MR seemed to be involved only in the phagocytosis of opsonized conidia (377). Taken together, Dectin-1 seems to be important for the generation of cytokines while MR mainly plays a role in the phagocytosis of this fungus.

CHALLENGES AND FUTURE DIRECTIONS

C-type lectin receptors recognize carbohydrate ligands in fungal cell walls and years of research have provided a huge body of evidence on their importance in modulating immune responses against fungal infections. However, there are still a number of gaps to be filled and areas that need attention from the scientific community. Almost all of the fungal infecitons are opportunistic, mainly concerning people with a compromised immune system, including HIV-infected individuals. Although they are a major high-risk group, many studies exclude HIV-infected patients and, therefore, this area of research seems to be largely unexplored. More studies focusing on HIV co-infection and the genetic make-up of HIV-infected individuals which affects their susceptibility toward developing specific fungal infections would be fundamental in developing tailored therapies for such cases. Fungi such as *Aspergillus* and *Candida* species interact with a number of CLRs upon infection, opening up opportunities to study the interactions between these receptors on a functional level [for example, the formation of heteromers as precdicted in case of Mincle and MCL (378)] as well as on a genetic level, including epistatic effects that the concerned genes have on each other. Another complex aspect that still needs to be studied in detail is how different cell types interact in an *in vivo* environment in order to control the infection. On the other hand, there are many fungal species such as *Paracoccidiodes*, *Fusarium*, etc., with few identified immune receptors, ligands, and/or virulence factors. Discovering these ligands and their corresponding receptors or new virulence factors will not only improve our understanding of fungal interactions with immune cells but also aid in developing vaccines and diagnostic or even therapeutic strategies against these fungi. Moreover, we now also know that CLRs not only recognize carbohydrate ligands but also lipids, proteins, and nucleic acids (3). We need to widen our views and explore this aspect more fully, since the fungal cell walls in addition to their manyfold carbohydrate structures also contain a number of lipids and proteins that may as well serve as potential ligands for CLRs (379). Moreover, some recent studies have demonstrated how differential immune responses are generated by different fungal isolates or strains depending on their individual pahogenic potential and virulence (380–383). Such studies suggest that a strain-specific comparison of immune response might be essential to fully understand the host–pathogen interactions. This knowledge would be helpful in generating data for individual case-specific therapies and, therefore, such studies need to be encouraged. Furthermore, it is often noted that many studies, such as *in vivo* mouse studies, provide contrasting results that lead to contradictions and questions. Therefore, the scientific studies need to be designed more carefully taking into account the strains of mice and the fungal species being studied, cell type or cell lines being used, and the type of *in vitro* or *in vivo* environment provided. Also, population structures and stratification in genetic studies should be addressed. The effects of each of these factors on the outcome of the results should be appropriately discussed in order to have a comprehensive view. In summary, there is a need to further enhance the understanding of how CLRs recognize pathogenic fungi in order to promote approaches to take advantage of this

knowledge for future therapeutic interventions. The ability of these receptors to bind a wide variety of pathogens which share the same ligand as fungi, makes them important molecules in the innate immune response. While there are many functional aspects of CLRs yet to be discovered, there is an increasing amount of information published over the past decade that already allows us to benefit from our knowledge on regulatory functions and new translational opportunities.

CONCLUSION

It is widely excepted that CLRs play a major role in modulating immune responses with respect to fungal infections, being able to recognize the carbohydrate moieties in the fungal cell walls. Fungal infections, though mainly opportunistic, can prove fatal in case of faulty diagnosis or treatment. The fungal recognition by CLRs mainly leads to proinflammatory responses and a subsequent activation of adaptive immunity *via* Th17 responses. However, negative or anti-inflammatory effects have also been noted and both types of responses are necessary to mount a specific immune response. A considerable body of work has been done with regards to frequent pathogens, such as *Candida*, *Aspergillus*, and *Cryptococcus*, etc., and genetic susceptibilities pertaining to fungal infections have been attributed to various mutations in CLRs. While some fungal infections are frequent, others are emerging into a major health problem with the continous increase in immuno-compromised patients. A thorough knowledge of the molecular mechanisms of fungal infections and the interaction of these fungi with their major receptors, the CLRs, can provide a basis to a better and more specific diagnosis and treatment regime. Also, knowledge about the host-related genetic factors, which can greatly affect the course and outcome of these infections, may advance a timely diagnosis and care for the patient.

AUTHOR CONTRIBUTIONS

HS conceived the review framework. SG and JC-B wrote the manuscript. EK and HS revised the manuscript. JC-B and SG created the figure. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

We thank Peder Iblher (Kreativdirektion Konzept und Design, Berlin) for the graphical improvement of the figure.

FUNDING

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) under the framework of the Collaborative Research Center/Transregio 124 "Pathogenic fungi and their human host: Networks of Interaction," Project A5, to HS and EK, and the International Leibniz Research School for Microbial and Biomolecular Interactions under the framework of the DAAD Graduate School Scholarship Programme to JC-B.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.