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Fungal Immunology: Mechanisms of Host Innate Immune Recognition and Evasion by Pathogenic Fungi

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Abstract

For a fungal pathogen to successfully infect, colonize and spread inside a susceptible host, it must have overcome the host immune responses. The early recognition of the fungal pathogen-associated molecular patterns (PAMPS) by the host's pattern recognition receptors (PRRs) results in the establishment of anti-fungal immunity. Although, our immune system has evolved several processes to combat these pathogens both at the innate and adaptive immune levels. These organisms have developed various escape strategies to evade the recognition by the host's innate immune components and thus interfering with host immune mechanisms. In this chapter, we will summarize the major PRRs involved in sensing fungal PAMPS and most importantly the fungal tactics to escape the host's innate immune surveillance and protective mechanisms.

Keywords: PAMPs, PRRs, innate immunity, escape mechanisms, pathogenic fungi

1. Introduction

Pathogenic fungi are an important cause of morbidity and mortality in humans particularly in immune-compromised individuals [1, 2]. The most common risk factors for the increased incidence of fungal infections in immunocompromised individuals are cancer therapy, use of corticosteroids and neutropenia [3–5]. Sporadic occurrence of fungal infections has also been described in immunocompetent individuals that have undergone any traumatic inoculation such as the use of catheters or surgeries [6, 7]. Fungal pathogens show a considerable variation in their biology and disease pathogenesis and may include opportunistic fungi, i.e., *Aspergillus fumigatus* (*A. fumigatus*), and *Fusarium spp.* as well as some commensals such as *Candida albicans* (*C. albicans*).

The human innate immune system is the first line of defense and plays a pivotal role in the body's defense on confrontation to the invading pathogens. One of the fundamental responses towards the infectious agents including fungi is the

inflammatory response that is launched immediately by the host body following an immunological insult. This inflammatory response drives the antigen specific adaptive immune response such as activation of antigen-specific lymphocytes against the invading pathogens. The innate immune system recognizes a particular set of conserved surface molecules exhibited by the pathogens called pathogens-associated molecular patterns (PAMPs). Host cell pattern recognition receptors (PRRs) detect microbial PAMPs and trigger the intracellular signaling pathways that lead to the production of cytokines, reactive oxygen species (ROS), reactive nitrogen species (RNS), and lipid mediators [8, 9]. Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) are the most common PRRs characterized for the detection of fungal PAMPs. Microbial detection by these PRRs results in a cascade of signaling events that eventually result in the production of inflammatory mediators, phagocytosis and induction of adaptive immune response [10]. However, fungal pathogens have adapted simple yet innovative strategies to evade and/or counteract the host innate immune responses thus resulting in the establishment of a successful infection inside the host. In the current chapter, we have made a comprehensive understanding of the major innate immune receptors involved in the detection of the fungal pathogens as well as the strategies employed by the pathogenic fungi to evade and therefore enhance their viability inside the host during infection.

2. Innate immune recognition of fungal PAMPs by host PRRs

2.1 Role of TLRs in recognition of pathogenic fungi

TLRs are a family of receptors that share structural homology with the Toll receptor (first described in the *Drosophila*). To date, 13 types of human and 10 types of murine TLRs have been discovered [11–13]. Generally, TLRs are comprised of extracellular and intracellular domains. The extracellular domain is rich in leucine repeats whereas the intracellular domain shares homology with the Toll/IL-1 receptor (TIR) domain. The TIR domain recruits the adapter proteins such as MyD88, TRIF, TRAM, and TIRAP followed by the initiation of intracellular signaling pathways which eventually result in the activation of different transcription factors, i.e., NF- κ B, AP-1, IRFs (IRF3/7), and MAP kinases. These transcription factors lead to the expression of cytokines and co-stimulatory molecules [11].

Both TLR2 and TLR4 are involved in the innate immune recognition of fungal PAMPs (**Table 1**) (**Figure 1**) [10]. TLR4 has been described to recognize the fungal-derived mannans. Recognition of *Saccharomyces cerevisiae* (*S. cerevisiae*) and *C. albicans* derived mannans by human monocytes have been attributed to a mechanism dependent on TLR4 and CD14 with Lipopolysaccharide Binding Protein (LBP) amplifying this mechanism [14]. Further investigation in this regard reveals that recognition of mannans is brought by the cooperation of TLR4 with Mannose Receptor (MR) with TLR4 recognizing the O-linked mannans and MR recognizing the N-linked mannans [15]. TLR4 is required for the innate immune recognition of rhamnomannans isolated from *P. boydii*. Rhamnomannans trigger cytokine production from macrophages via TLR4 activation [16]. Similarly, TLR4 also detects glucuronoxylomannans (GXM) from *Cryptococcus neoformans* (*C. neoformans*) suggesting the vital role of TLR4 in innate immune recognition of mannose-containing polysaccharides [17].

Alike TLR4, TLR2 is also involved in the recognition of the fungal molecules. TLR2 triggers the activation of NF- κ B and subsequent release of cytokines from the macrophages in response to phospholipomannan (a cell wall lipoglycan isolated from *C. albicans*). On the other hand, both TLR4 and TLR6 respond partially to

PRRs	Fungal pathogen	Fungal PAMPs
1. TLRs		
TLR4	O-linked mannans	<i>C. albicans</i>
	Mannans	<i>Sacchromyces spp.</i>
	Rhamnomannans	<i>P. boydii</i>
	Phospholipomannans	<i>C. albicans</i>
	Glucuronuxylomannans	<i>C. neoformans</i>
	Unknown/ α -, β -glucan, galactomannan	<i>A. fumigatus</i>
	Unknown	<i>P. brasiliensis</i>
TLR2/TLR6	Phospholipomannans	<i>C. albicans</i>
	Glucuronuxylomannans	<i>C. neoformans</i>
TLR2/TLR1	Glucuronuxylomannans	<i>C. neoformans</i>
TLR2	A 1,4 glucans	<i>P. boydii</i>
	Unknown	<i>A. fumigatus</i> (conidia and hyphae form)
2. CLRs		
MR	N-linked mannans	<i>C. albicans</i>
	Mannans	<i>P. Carinii</i>
	Mannoproteins	<i>C. neoformans</i> <i>A. fumigatus</i>
	gp43	<i>P. brasiliensis</i>
Dectin-2	α -mannans	<i>C. albicans</i> <i>A. fumigatus</i>
Dectin-1	B (1, 3)- glucans	<i>C. albicans</i> <i>A. fumigatus</i> <i>Sacchromyces spp.</i>
DG-SIGN	Galactomannans	<i>A. fumigatus</i>
	Mannans	<i>C. albicans</i>
	Unknown/surface carbohydrates in extracellular vesicles	<i>P. brasiliensis</i>
Mincle	Polysaccharides containing α -mannosyl residues	<i>Malassezia spp.</i> <i>C. albican</i>
CD14	Mannans	<i>Sacchromyces spp.</i>
	Unknown	<i>A. fumigatus</i>
	A (1,4) glucans	<i>P. boydii</i>
3. NLRs		
NLRP3	Unknown/ β (1,3)-glucans	<i>C. albicans</i> <i>A. fumigatus</i> <i>C. neoformans</i> <i>P. brasiliensis</i>

Table 1.
List of major PRRs involved in recognition of various fungal-derived PAMPs.

phospholipomannan [18]. Moreover, TLR2 is responsible for the detection of glucogen (i.e., α -1,6-branched α -1,4-glucans) [19]. TLR2/TLR1 and TLR2/TLR6 heterodimers are described to be important receptors in the detection of GXM isolated from the capsules of *C. gatii* and *C. neoformans* [20].

Figure 1.

Major receptors involved in the innate immune recognition of fungal polysaccharides and glycoconjugates (Barreto-Bergter and Figueiredo, 2014).

It has been observed that cytokine production from macrophages and dendritic cells is mediated by TLR2 and CD14 in response to *P. boydii*-derived α -glucans [21]. Polysaccharides extracted from medicinal fungi (*Ganoderma lucidum* and *Cordyceps sinensis*) possess immune-modulatory and anticancer activities. These polysaccharides also trigger cytokine production and B cells activation through TLR2 and TLR4. Although, direct binding of fungal polysaccharides with the TLR2 and TLRs has been described [22]. The exact underlying mechanisms by which TLR2 and TLR4 interact and recognize fungal polysaccharides and other glycoconjugates containing mannose are still poorly defined. Fungal polysaccharides such as α -glucans and mannans are structurally different from the TLR2- and TLR4-prototypical agonists. There could be a possibility that complex fungal polysaccharides or cell wall components may present some uncharacterized glycolipids anchored to their structures that could serve as true TLR2- and/or TLR4- agonists. However, to find these answers, sensitive analytical techniques such as mass spectrometry and nuclear magnetic resonance are required in combination with other complementary approaches, i.e., selective inhibition of investigating molecules, use of chemically defined ligands, availability of genetic models deficient in synthesizing the specific fungal molecules. Both TLR4 and TLR2 interact directly with bacterial lipid A and lipopeptides, respectively. Moreover, crystallographic studies of lipid A-TLR4 complex and lipopeptide-TLR1/TLR2 or lipopeptide-TLR6/TLR2 complex have demonstrated a physical interaction between these ligands and their respective receptors [23–25]. It was observed that fatty acid chains present in the bacterial ligands interact and bind with the hydrophobic pockets in the extracellular domains of the receptors complex. This suggests that TLR4 and TLR2 interact with hydrophilic ligands such as fungal polysaccharides in a way that is distinct from that of classical bacterial ligands. Thus, knowing the structural basis for interactions between fungal polysaccharides and TLR2 or TLR4 will be very helpful in understanding how distinct structures, i.e., LPS (lipopolysaccharide), lipopeptides and

mammalian endogenous molecules (hyaluronic acid, carboxy alkyl pyrroles, heme) are recognized by these receptors [26].

2.2 Role of CLRs in recognition of pathogenic fungi

CLRs are a group of proteins receptors involved in the detection of fungal glycoconjugates and are characterized by the presence of two motifs; the EPN motif and QPD motifs both of which drive the specificity of CTLRs towards carbohydrate moieties. The EPN motif helps in the recognition of mannose, N-acetylglucosamine, glucose and L-fucose whereas the QPD motif is involved in the recognition of N-acetylgalactosamine and galactose [27–31]. The major CTLRs implicated in the recognition of fungal molecules are Dectin-1, Dectin-2, Mannose receptors (MR), Mincle, DC-SIGN, CD-12, and CD-11b/CD18 (**Table 1**) (**Figure 1**).

2.2.1 Mannose receptor (MR)

The mannose receptor is a type I transmembrane receptor that contains an N-terminal cysteine-rich domain and a type II fibronectin domain. The extra-cellular component of MR comprises of eight CTLDs (C-type lectin domains) whereas the intracellular component possesses a motif required for endocytic signaling [32]. MR is capable of recognizing fungal PAMPs that contain either mannose, glucose, N-acetylglucosamine [32–34], or sulfated galactose and sulfated N-acetylglucosamine (**Table 1**) (**Figure 1**). Recognition of sulfated glycoconjugates is mediated by the cysteine-rich domain of MR and is independent of CTLDs [35, 36]. On the other hand, recognition of mannose-based fungal PAMPs is dependent on the activity of CTLDs (mostly 4–8) [34]. Several fungal pathogens can be detected by MR including *C. albicans* and *Pneumocystis carinii* [15, 37, 38]. MR is considered a phagocytic receptor due to its involvement in the phagocytosis of pathogenic fungi (**Table 1**) [37, 38]. However, the expression of MR on non-phagocytic cells questions its designation as a professional phagocytic receptor [39]. The role of MR in the recognition and phagocytosis of pathogenic fungi containing mannose ligands is well established [37, 38]. There is a possibility that role of MR as a phagocytic receptor might be cell type-specific.

Besides its role in endocytosis, MR also contributes to the production of cytokines in response to glycoconjugates comprising mannans [15, 40, 41]. On recognizing the *C. albicans* derived mannans, MR induces the release of TNF- α from macrophages [15]. MR is also considered to be involved in sensing of mannosylated glycoconjugates such as those derived from mycobacteria and *Pichia pastoris* indicating that in addition to *C. albicans* derived mannans, MR can also recognize mannosylated glycoconjugates presented from other pathogenic fungi [42, 43]. The mechanism of cytokine induction by MR in response to fungal glycoconjugates is still undefined. MR also contains a short cytoplasmic tail that lacks motifs involved in intracellular signaling and eventually cytokine production. There could be a possibility that MR confers cytokine production in association with other CLRs or TLRs.

2.2.2 Dectin-2

A transmembrane protein that was first characterized in a cell line derived from Langerhans cells. Dectin-2 is comprised of a short cytoplasmic domain and an extracellular domain with CLTD present in the COOH-terminal region. Activation of Dectin-2 by the fungal ligands leads to the production of eicosanoids and cytokines [44–46]. Usually, macrophages, some dendritic cells and IL-6/IL-23-stimulated neutrophils express Dectin-2 receptors [45, 47, 48]. The EPN motif

present in the extracellular domain of Dectin-2 recognizes fungal glycoconjugates containing mannose and fucose (**Table 1**) (**Figure 1**) [47]. The binding of Dectin-2 to zymosan requires Ca^{2+} , however, higher concentrations of mannose, fucose, glucose, galactose and N-acetylglucosamine can inhibit this binding. Dectin-2 shows a higher binding affinity towards synthetic carbohydrates that are extensively mannosylated. However, the binding affinity decreases with the decrease in mannosylated residues [49]. Dectin-2 receptor recognizes *C. albicans* by binding to its α -mannans [46, 50]. In case of *Malassezia spp.*, this recognition is mediated through the binding of Dectin-2 with a glycoprotein containing O-linked α -1,2-mannobiose [51]. Besides this, in cooperation with MCL, Dectin-2 also has been described to promote recognition of *C. albicans* hyphae through binding to α -mannans followed by the formation of heterodimer complex. This cooperation between Dectin-2 and MCL results in higher sensitivity in recognizing the *C. albicans* and eventually leads to amplified leukocyte responses towards the fungal pathogens [50].

2.2.3 Dectin-1

Dectin-1 is a type II transmembrane receptor that recognizes and binds to the molecules containing β (1,3)-glucans. It is expressed by many cell types including macrophages, dendritic cells, eosinophils and neutrophils [52–54]. Dectin-1 mediated signaling results in the production of cytokines [55], maturation of dendritic cells [56] and production of ROS [57]. This suggests that Dectin-1 is an important PRR in recognizing β (1,3)-glucans followed by leukocytes activation and induction of adaptive immunity. However, in contrast to many other CTLRs, Dectin-1 binding to β -glucans is not dependent on Ca^{2+} [58, 59]. Dectin-1 possesses higher specificity towards β (1,3)-glucans having β (1,6)-branches. On the other hand, Dectin-1 is unable to bind with mannans, pullulans, β 1,6-glucans or β (1,3)/(β 1,4)-glucans [58]. In contrast to TLRs which recognize soluble ligands, activation of Dectin-1 is dependent upon its clustering by the β -glucans molecules followed by exclusion of tyrosine phosphatases (CD45 and CD48) and phosphorylation of hemi-ITAM motif present in the cytoplasmic tail of Dectin-1 [60, 61]. The hemi-ITAM recruits Syk kinases and initiates the upstream signaling pathway leading to the activation of NF- κ B and NFAT [60, 62]. Usually, alveolar macrophages (AMs), resident peritoneal macrophages and dendritic cells present Dectin-1 dependent responses towards β -glucans while bone marrow-derived macrophages do not. However, Dectin-1 dependent responses can be promoted in non-responding cells such as bone marrow-derived macrophages in the presence of IFN- γ and GM-CSF thus suggesting that responses mediated by Dectin-1 are flexible [63, 64].

2.2.4 Mincle

Also known as CLEC4E is a type II transmembrane protein that was first identified as a macrophage-expressed gene dependent on the activity of the NF-IL6 transcription factor [65]. It is composed of a short cytoplasmic tail with an extracellular domain containing a CLTD. Mincle triggers cell signaling by recruiting the FcR γ chain which leads to the activation of NFAT and NF- κ B and eventually induces transcription of cytokines [66]. Like other CTLRs, Mincle also plays an important role in the recognition of fungal molecules (**Table 1**) (**Figure 1**) [67, 68]. Soluble Mincle has been described to interact with *C. albicans* [68]. Moreover, in response to *C. albicans* infection, Mincle is required for TNF- α production from the macrophages [67]. Mincle also detects *Malassezia spp.* (human commensal fungi) and activates NFAT mediated cytokine transcription in cell lines. However, an impaired cytokine production and leukocyte recruitment was observed in Clec4e $^{-/-}$ macrophages in

response to *Malassezia spp.* [69]. Currently, two glycolipids ligands have been identified from *C. albicans* that bind with Mincle. One is a polar glycolipid (comprising one dimannosyl-10-hydroxy-octadecanoic acid and two mannosyl-10-hydroxy-octadecanoic acids). The second ligand is a glyceroglycolipid containing the disaccharide gentiobiose joined to a glycerol backbone acylated with C14 and C18 fatty acids [51]. Although, Mincle ligands for other species of fungi have not been identified yet. However, it seems that Mincle must be specific in binding and recognizing glycolipid molecules among other pathogenic fungi [67, 68].

2.2.5 DC-sign

A type II transmembrane receptor with extracellular domain containing one CRD in its COOH- terminal and an and extracellular stalk. The stalk is comprised of seven residues that aid in DC-SIGN oligomerization [70, 71]. The CRD of DC-SIGN contains an EPF motif. DC-SIGN binds to glycoconjugates containing mannans and fucosylated carbohydrates in the presence of Ca^{2+} [72]. Both macrophages and dendritic cells express DC-SIGN. It is an endocytic receptor that can recognize and internalize several fungal pathogens followed by their release in the endosomal vesicles [73, 74]. In response to mannose-containing ligands, DC-SIGN has been described to enhance the cytokine production induced by the TLRs whereas fucosylated ligands amplify the IL-10 while inhibiting the production of proinflammatory cytokines. Mannosylated lipoarabinomannans (ManLAM) mediated activation of DC-SIGN results in inhibition of dendritic cells maturation by the LPS [75]. Thus, some pathogens infecting the dendritic cells can escape the immune activity by activating and inhibiting the DC-SIGN mediated maturation of dendritic cells. Thus, activation of DC-SIGN seems to exhibit complex effects such as internalizing the pathogens, triggering cytokine production and restricting the maturation of dendritic cells [76].

DC-SIGN has been involved in the recognition of many fungal pathogens including *C. albicans* (**Table 1**) (**Figure 1**). DC-SIGN is involved in the internalization and delivery of *C. albicans* to the phagolysosome of dendritic cells [77]. The binding and internalization of *C. albicans* is associated with the presence of N-linked mannans as a decreased binding was observed in *C. albicans* strains deficient in N-linked mannansylation [38]. However, dendritic cells do not exhibit any decreased binding affinity to the *C. albicans* strains lacking N-linked mannansylation. It appears that the binding of *C. albicans* through DC-SIGN in dendritic cells requires N-linked mannans whereas other glycoconjugates such as phosphomannans, O-linked mannans, or terminal β (1,2) mannosides are dispensable. There is no doubt regarding the role of DC-SIGN in recognition of *C. albicans* but it's the MR that in cooperation with DC-SIGN, contributes majorly to *C. albicans* internalization by the dendritic cells [38]. DC-SIGN is also an important PRR for recognition of *A. fumigatus* conidia by macrophages and dendritic cells. Unlike the *C. albicans*, MR is not required for the recognition of *A. fumigatus* by the human dendritic cells, however, this recognition by DC-SIGN has been described to be inhibited by the purified mannans and galacto-mannans [78]. Soluble DC-SIGN detects the glycoconjugates such as mannans, monosaccharides comprising mannans and Lewis antigen structures in a Ca^{2+} dependent manner [72, 74, 79]. Although, DC-SIGN is involved in the recognition of fungal pathogens, the underlying phenomena of modulation of macrophage and dendritic cell-mediated immune responses by DC-SIGN in response to fungi are still undefined.

2.3 CD11b/CD18 (MAC-1, CR3)

CD11b/CD18 also recognized as CD18 is a heterodimer receptor comprising of type I protein chains; α M chain (CD11b) and the common chain CD18 both of

which are attached non-covalently. CD11b/CD18 is expressed by many of the leukocytes such as neutrophils, eosinophils, monocytes, macrophages and NK cells [80]. CD11b/CD18 helps in the adhesion of leukocytes to the activated endothelium and phagocytic receptors for antigens opsonized with iC3b [81]. In addition, CD11b/CD18 is also involved in the detection of β (1,3)-glucans. The α M chain of CD11b/CD18 possesses two distinct domains; the I-domain and a lectin domain. The I-domain binds ICAM-1, iC3b and fibrinogen whereas the lectin domain recognizes the fungal glycoconjugates such as β (1,3)-glucans, glucose, mannose and N-acetyl-D-glucosamine [82]. CD11b/CD18 triggers ROS production from neutrophils and macrophages in response to *S. cerevisiae* and zymosans [83]. Although, CD11b/CD18 is actively involved in the recognition of β (1,3)-glucans, however, some controversy exists in some experimental settings regarding its role in the identification of β (1,3)-glucans along with Dectin-1 mediated responses. The differences in experimental settings could be attributed to the observed disparities in results and can be attributed to many factors such as the use of distinct ligands (i.e., soluble vs. particulate β -glucan structures) [63, 84, 85], heterogeneity of β -glucan structures (both zymosan and fungi are heterogeneous and also contains carbohydrates and lipids in addition to mannans) [83], presence of the serum [85] and variability in the cell populations (neutrophils vs. macrophages) [84] used in the experiments. In conclusion, we can say that both CD11b/CD18 and Dectin-1 are involved in the recognition of β -glucan structures and their activation must lead to the induction of immune responses towards the fungal pathogens. Besides recognizing β -glucans, CD11b/CD18 also acts as an internalization receptor for mycobacterial PIM2 (a mycobacterial glycoconjugate-coated beads) [86] suggesting that CD11b/CD18 also work as a receptor for other fungal molecules other than β -glucan.

2.4 CD14

A glycosylphosphatidylinositol-anchored protein receptor was initially considered as an LPS binder. The Cd14 receptor is comprised of an extracellular domain containing cysteine-rich residues that form a horseshoe-like conformation [87–89]. Although, the CD14 receptor does not contain intracellular regions, however in cooperation with TLR2/MD receptors, it confers a high degree of sensitivity towards LPS [89]. CD14 has also been recognized as a co-receptor involved in TLR2- [90], TLR3- [91], TLR7- and TLR9-mediated detection of ligands [92]. Similar to the LPS, detection of mannans derived from *C. albicans* and *S. cerevisiae* also depends on CD14, LBP and TLR4 [14]. CD14 can also detect other fungal glycoconjugates, i.e., β (1,3)-glucans [21] and carbohydrate and therefore, act as an important receptor for innate immune recognition of *P. boydii* [93] and *A. fumigatus* [93]. However, the structural basis for the recognition of carbohydrate ligands by CD14 is still undefined. Also, the direct binding of CD14 with mannans and α -glucans has not been elucidated. There is a possibility that CD14 must be binding to these ligands *via* hydrophilic cleft. As CD14 also acts as a receptor for TLR ligands, we can speculate that CD14 must be promoting intracellular signaling first by binding to these carbohydrate ligands followed by their loading onto TLR2 or TLR4.

3. Fungal strategies of host innate immune evasion

3.1 Shielding of stimulatory PAMPs

Protecting the pathogen's inflammatory PAMPs from recognition by the host's PRRs is one of the most significant escape mechanisms employed by the microbes

[94, 95]. PRRs, which are found in various cellular components of primitive immune cells, are capable to identify recurrent pathogenic structures called PAMPs [96]. The host usually responds *via* phagocytic processes to establish the immediate antifungal mechanisms in response to fungal PAMPs. It is also accompanied by antimicrobial and pro-inflammatory responses launched through the activation of various intracellular signaling pathways that lead to the cytokine's and chemokine's gene transcription [97]. The prime objective of this response is to limit the disease while capturing as well as presenting the antigen to activate the adaptive immunity [98, 99]. NOD-like receptors (NLRs), TLRs, CLR and RIG-I-like, are the four groups of PRRs that vary in regards to ligand identification, signal transduction, as well as subcellular localization. Dendritic cells (DCs) and other myeloid cells exhibit the majority of PRRs, which are known for activating innate immune responses. PRR signaling, on the other hand, may regulate the progression of innate immune responses by the secretion of cytokines that helps in the polarization of CD4⁺ cells [100]. CLRs are the main class of receptors that identify fungus, according to multiple investigations, whereas NLRs and TLRs play leading functions. Microbes may hide such that they are often overlooked by the immune system [101]. Polysaccharides as well as many other components of the cell wall are often layered and serve physiological and architectural roles in the cell wall. The structure of the cell wall layers of fungus is critical in serological identification [102]. Cell wall elements (i.e., chitin, mannan, and glucans) are also included among the fungal PAMPs. Most fungi contain chitin and also α (1,3)-glucan-based internal skeletal layer of the cell wall, which is linked to certain cell wall glycoproteins and polysaccharides [102]. Many fungal species may alter glucans and chitin to decrease host recognition, thus avoiding immune activation. Antagonism or synergism of receptor activation may result in a variety of diverse pathways of inflammatory processes. *In vivo*, a variety of fungal ligands have been exhibited in varying proportions, resulting in the activation of various PRRs [103]. Dectin-1 has a specific key for detecting hyphal infections *via* the identification of β -glucans, a fundamental component of the hyphal cell wall [94, 95]. *C. albicans* (a polymorphic fungus) may exhibit a transition between yeast and filamentous types, depending on environmental conditions. The bud scars on the *Candida* wall, which are exposed during budding, reveal the usually hidden β -glucan, and are predisposed to Dectin-1 identification. Usually, β -glucans of *C. albicans* are hidden from identification *via* Dectin-1 and outer wall elements during hyphal development [104, 105]. Dectin-1 also enhances the fungicidal activities of human neutrophils, which seem to be key effector cells throughout the fight against hyphal morphology [106]. The failure of Dectin-1 to identify the fungi as a result of β -glucan protection in hyphal development shields these bigger morphologies by avoiding internalization. In addition, hyphal types elicit protective T-helper cell type 2 (Th2) immunological responses in DCs rather than a Th1 immune response [107, 108]. Consequently, immune cells respond differentially to hyphae and yeast.

Similar to Dectin-1, Dectin-2 and Dectin-3 are also integral membrane proteins that belong to the CLRs family. Dectin-1 detects glucans, while Dectin-2/3 identifies mannans [109]. These may produce heterodimer complexes that provide greater sensitivity to host tissues as well as a high potential for binding to mannans [50]. While investigating the functions of Dectin-2 in *C. albicans* related-diseases, it was observed that the mice lacking Dectin-2 were more vulnerable to infection. In addition, phagocytosis and cytokine production was also decreased in these mice [110].

The α (1,3)-glucans present in the outermost layer of the cell wall helps in the pathogenicity of *Histoplasma capsulatum* (*H. capsulatum*) by hiding its immune-stimulatory β -glucans. This is analogous to how external mannans protect β -glucan from Dectin-1 recognition in *Candida*. Further evidence was observed

in *H. Capsulatum* variants without α (1,3)-glucans which resulted in an increased TNF- α production. On the other hand, a reduction in Dectin-1 (necessary for β -glucans) expression, suppresses TNF- α levels. On switching into its infectious yeast stage, *Paracoccidioides brasiliensis* (*P. brasiliensis*) changes its β (1, 3)-glucans to α (1, 3)-glucans [111]. This is due to the reason that α (1, 3)-glucans are less likely to be identified by the host PRRs and therefore essential in fungal evasion of the immune system. *C. neoformans* masks the surface of PAMPs by producing GXM, which inhibits the production of IL-1 β and pro-inflammatory TNF- α [112]. Both the pigment DHN-melanin and the RodA protein create a hydrophobic coating on *A. fumigatus* conidia and cover the glucans in order to avoid TLR activation. Although, quiescent conidia do not cause macrophages to secrete cytokines during germination, and the surface of RodA is destroyed. Furthermore, proteins that are recognized by PRRs are exposed to dendritic cells and macrophages, promoting the expression of the co-stimulatory molecule and cytokine production [113]. Dectin-1 redundant function may be explained by the lack of numerous glucans on the surface of resting *Aspergillus* conidia. Dectin-1 suppression on alveolar macrophages has little effect on the phagocytosis of *Aspergillus* that may be influenced by conidia germination [114, 115]. The spherule external wall glycoprotein (SOWgp) of *Coccidioides posadasii* (a respiratory fungal pathogen) is involved in its escape from innate immune recognition. The fungal cells secrete a metalloproteinase (Mep1) during endospore development, which metabolizes SOWgp [116]. Because SOWgp is downregulated during endospore production, fungal cells are therefore capable of avoiding phagocytosis and death during the susceptible spore-forming stage [117]. The capacity of the fungi to live in various morphotypes and to transiently shift from one form to another during infection is one strategy of shielding the host's immune system [118, 119]. These polymorphic phases are linked to phenotypic switching and result in evasion from cellular PRRs. This ability has most likely developed to help fungi survive in a variety of environments.

The *C. neoformans* capsule obscures the α (1,3)-glucans and mannan of the basal cell wall. Macrophages can easily recognize and phagocytose the acapsular mutant strains of *C. neoformans* and both glucans and mannose receptors are involved in this identification [120]. However, the capsule acts as a shield and masks the recognition of fungal PAMPs from the phagocytic receptor. Generally, TLRs detect the capsule and initiate an inflammatory response that is essential for limiting fungal infections. Further evidence in this regard has been provided by TLR2-deficient mice that have shown increased susceptibility to *C. neoformans* infections [121]. Contrary to yeast-form, blastoconidia of *C. albicans*, as well as hyphal form, are capable of evading the innate immune recognition by the Dectin-1 [104]. These blastoconidia activate the TLR2 and TLR4 in the ancillary monocytes and peritoneal macrophages. Such hyphal forms are not detected by the TLR4 and cause tissue-invasive infection [122]. Phenotypic change during germination could be a crucial survival strategy for several fungal pathogens. TLR4-mediated responses are diminished after the germination of *A. fumigatus* while its conidia elicit TLR2- as well as TLR4-mediated responses, in the tissue invasion. Mostly conidia germinate specifically into hyphae when TLR4 production is reduced, resulting in less intense proinflammatory cytokine production [123]. Proinflammatory responses mediated by TLR4 are essential in the prevention of invasive infections (aspergillosis) [124]. The stealth mode is not always successful and a fungal pathogen will usually be detected by the host in a certain way. Therefore, microorganisms frequently discover new strategies to exploit the host recognition networks and manipulate them for establishing a successful infection. These organisms may have chemicals

on their surfaces or release compounds that trigger regulatory systems specifically. Throughout this way, the pathogen may either directly suppress or develop kinds of immune responses that aren't typically efficient against the pathogen [101].

3.2 Modulation of inflammatory signals

In respect of anti-inflammatory cytokine impact, TLR2 stimulation differentiates from TLR4 activation, with proinflammatory cytokine production being lower following TLR2 stimulation than the TLR4 stimulation [125]. TLR4 agonists selectively produced Th1-inducing cytokine signals in DCs, whereas TLR2 activation generate a more strong anti-inflammatory Th2 reaction [126]. Because each effector's arm elicits a different immune reaction, the equilibrium between Th1/Th2 reactions is thought to be important in deciding the severity of infection [127, 128]. The Th1 pathway generates pro-inflammatory cytokines such as IFN- γ , which stimulate cell-mediated immune mechanisms such as cytotoxicity and phagocyte activation. Th1 pathway is essential in the fight against intracellular and fungal infections. The Th2 pathway is characterized by cytokines such as IL-4, IL-5, as well as IL-10 and promotes a humoral response while suppressing the Th1-dependent effector functions [129]. Th2 cytokines may decrease monocyte anti-hyphal activity as well as lead to oxidative burst amid antifungal reactions [128]. TLR2-deficient macrophages have improved anti-candidal abilities [130], and TLR2 macrophages in mice are significantly more tolerant to widespread *C. albicans* related diseases [124, 130, 131]. As a result, the hyphal forms of *C. albicans* (tissue-invasive) and *A. fumigatus* are likely to shift the equilibrium towards that Th2 pathway by avoiding TLR4 stimulation in favor of TLR2 activation. *C. neoformans* has also been found to possess immunosuppressive properties. The primary virulence component of *C. neoformans* is indeed the GXM, which is a strong activator of the IL-10 (anti-inflammatory cytokine) and a pro-Th2 cytokine mediator in human monocytes [132, 133]. The melanin pigment produced frequently by pathogenic filamentous fungi has been associated with fungal pathogenicity and its immunomodulatory impact in *C. neoformans* has been investigated. Melanized *C. neoformans* variants result in increased pulmonary IL-4 levels thus driving the host cells to switch towards Th2 response [134]. *Blastomyces dermatitidis* (*B. dermatitidis*) that causes systemic and pulmonary mycosis, may result in comparative immunosuppression by reducing the synthesis of the TNF- α (a pro-inflammatory cytokine) [135]. The binding of *Blastomyces* surface adhesins to the complement receptor III on macrophages results in suppression of TNF- α synthesis which otherwise could be harmful to *B. dermatitidis*' existence [136].

3.3 Shedding of decoy components

Several innate immune evasion strategies have been identified for *Pneumocystis jiroveci* (*P. jiroveci*), an opportunistic fungi that usually infects AIDS patients. Glycoprotein A (gpA) complex is the main protein antigen present on the membrane of *Pneumocystis*. It is highly glycosylated with glucose, mannose, as well as galactose-containing carbohydrate moieties [137]. Mannose receptors present on the alveolar monocytes recognize these structures. However, *Pneumocystis* escapes this recognition by MR on alveolar macrophages and impedes its phagocytic activity by premature release of its gpA glycoprotein as a decoy [138]. Furthermore, *Pneumocystis* has also been described to deplete MR from the membrane of AMs, preventing non-opsonic absorption by MR (surface-expressed) [139].

3.4 Persistence in the intracellular environments

Several fungal pathogens have developed the potential to avoid the phagocytic activity of macrophages. For example, *C. neoformans* can phenotypically shift to a mucilaginous colony type generating a significantly bigger capsulated polysaccharide GXM with modified biochemical and biophysical characteristics thus limiting AM phagocytic effectiveness [140]. When certain variants fail to escape host identification, phagocytosis by macrophages does not necessarily result in death and the ending of the life cycle as some fungi may survive the harsh environment inside the phagolysosome. Some *C. albicans* spp. can withstand intracellular death and produce hyphal structures and thus escape the macrophages [141]. *C. albicans* have an extremely specialized anti-nitric oxide (NO) defense mechanism including the NO-scavenging flavohemoglobin genetic traits that convert NO to less toxic substances when comes into contact with reactive nitrogen molecules like NO and oxygen free radicals generated by monocytes/macrophages [142]. Comprehensive morphologic investigations have shown that *Candida* could produce germ tubes, proliferate, and ultimately escape the host cell despite phagocytosis by macrophages [143]. Phagocytosis provokes *C. albicans* within macrophages to switch into self-preservation mode, which includes a delayed growth rate, carbon utilization, as well as an oxidative stress reaction to thrive in the hostile environment inside macrophages [144, 145] suggesting that the phagocytic activity solely might not be sufficient to clear the infection from the host. During persistent infection, the fungi have been shown to survive and reproduce inside the phagocytic cells [146, 147]. To escape intracellular death, *C. neoformans* cause aberrant lysosomal transport and significant cytoplasmic vacuolation in the host cell, leading to host cell disintegration [148]. Similarly, *H. capsulatum*, is also capable of surviving inside macrophages for longer durations following primary infection and become activated as the immune responses are diminished [149, 150]. *Histoplasma* is supposed to prevent phagolysosome formation and proactively regulate the phagosomal pH following phagocytosis to maximize its survival inside phagosomes [151, 152]. Furthermore, *Histoplasma* can prevent the production of toxic superoxide radicals that are harmful to its survival inside macrophages [153].

3.5 Complement evasion

The complement system is a dynamic mechanism that plays a significant part in innate immunity and antibody-mediated protection against pathogenic microbes [154]. Several foreign antigens including fungal PAMPs, cellular debris, as well as antigen–antibody complexes can activate a series of complement pathways [98, 155]. Excessive tissue damage and inflammation by the complement system are avoided by the regulatory molecules of the complement system [156]. The complement system is split into three pathways; classical, alternative and lectin pathway. The activation of all these pathways varies in regards to associated components but all pathways submerge by producing the same group of effector molecules, i.e., opsonization and formation of membrane attack complex (MAC) [96]. All complement mechanisms contribute to the production of C3 convertase as well as the C3b fraction, which in turn promotes the synthesis of C5 convertase. C5 convertase cleaves the C5 factor into C5a and C5b. The distal complement components are formed as a result of a succession of accumulation and polymerization processes, as well as the mobilization of terminal complement elements such as C6, C7, C8, and C9. The terminal complement components form MAC causing cell lysis by inserting C9 into the lipid membrane layer [157–159]. Pathogenic organisms, on the other hand, have adopted different approaches to evade complement attacks, such as binding

to regulatory complement proteins by secreting proteases or evading opsonization. For example, *Aspergillus spp.* and *C. albicans* release proteins on their membranes that bind to complement proteins to prevent being eliminated by the complement system. These proteins, when linked to the hyphal surface, block the complement cascade, allowing the fungi to avoid the complement attack [156]. *Aspergillus* and *Candida* are recognized to activate complement by depositing C3 on the fungal membrane, which facilitates opsonization and the synthesis of the chemoattractant (C5a), which recruits leukocytes to the infected area [160–162]. Pigmentation on the conidial surface of *A. fumigatus* has been demonstrated to influence pathogenicity by reducing C3 protein accumulation and neutrophil activity [163]. Transcription factors such as Factor H-like protein 1 (FHL1), Factor H, as well as C4 binding protein (C4BP) for the signaling pathway, keep the complement system in balance against abnormal activation. *A. fumigatus* and *C. albicans* both have been described to bind FHL-1, C4BP, and Factor H, on their membrane to evade the complement cascade [164–166]. Furthermore, the dense yeast cell wall is impervious to immediate lysis by the MAC [161]. Complement is far more than a “defensive” mechanism against infections. It has a role in inflammatory responses, cellular response regulation, and cell–cell interactions, all of which are important for cell differentiation and initial growth [167]. Currently, two complement-targeted drugs for non-fungal illnesses have been approved in the health center: eculizumab (an anti-C5 antibody) and different formulations of C1 esterase inhibitor (C1-INH). Several other drugs that target distinct elements of the complement cascade are all in different phases of trials [167–170].

4. Conclusion

Our understanding regarding the innate immune recognition of pathogenic fungi by the corresponding fungal PAMPs is still poor. Moreover, the fungal ligands involved in the activation of host PRRs remain largely unknown for several pathogenic fungi. Characterization of fungal PAMPs and their recognition by the host PRRs can provide a comprehensive understanding of pathogenesis and immunity to the pathogenic fungi. In addition, characterization of these fungal ligands and their activation of respective PRRs is essential not only to discover new therapeutic approaches against fungal infections particularly in immune-compromised patients but also to develop novel adjuvants for enhancing the prophylactic immune responses against pathogenic fungi.

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