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The role of dendritic cells in the innate recognition of pathogenic fungi (*A. fumigatus*, *C. neoformans* and *C. albicans*)

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Dendritic cells (DCs) are the bridge between the innate and adaptive immune system. DCs are responsible for sensing and patrolling the environment, initiating a host response and instructing the proper adaptive immune response against pathogens. Recent advances in medical treatments have led to increased use of immunosuppressive drugs, leading to the emergence of fungal species that cause life-threatening infections in humans. Three of these opportunistic fungal pathogens: *Aspergillus fumigatus*, *Candida albicans* and *Cryptococcus neoformans* pose the biggest concern for the immune-compromised host. Here we will review the interactions between DCs and these fungal pathogens, the receptors expressed on DCs that mediate these responses and the signaling mechanisms that shape the adaptive host response.

Introduction

Mycoses have emerged over the last three decades as life-threatening infectious diseases; establishing a pressing need for the development of new anti-fungal drugs to combat the increasing incidence of fungal infections and drug-resistant fungal species. Fungal infections are of great importance to immune-compromised hosts; particularly those infected with HIV or patients receiving immunosuppressive drugs to combat cancer or prevent organ rejection following transplantation.[1,2] Fungi are among the most common microbes encountered by mammalian hosts, with the natural route of infection being the respiratory tract. To date, more than 100,000 fungal species ubiquitous to the environment have been described; however, only a handful cause disease in humans. Opportunistic fungal pathogens such as *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans* pose the biggest concern in immune-compromised hosts. Here we will review the interactions of these three pathogenic fungi with different subsets of dendritic cells (DCs).

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The Big Three: *Aspergillus fumigatus*, *Candida albicans* and *Cryptococcus neoformans*

Increase in the incidence of fungal infections correlates with advances in medical treatment resulting in increased numbers of immune-compromised patients, particularly those suffering from AIDS, cancer patients receiving chemotherapy and those taking immunosuppressive drugs following solid organ transplantation.[3]

Aspergillus fumigatus is the primary causative species of human aspergillosis. On a daily basis, humans inhale hundreds of microscopic conidia or non-motile spores of this mold. These 2–3 μm conidia are small enough to bypass the mucosal barriers and enter the lung alveoli. In immune-competent hosts the conidia are readily eliminated by the host innate immune system and, in most cases, the host remains asymptomatic. For many years *A. fumigatus* was viewed as a weak pathogen, causing mainly allergic forms of disease.[4] However, the prevalence of *A. fumigatus* infection and severity of disease has risen dramatically and correlates directly with the increased number of immunosuppressed patients. In these patients, the conidia are capable of bypassing mucocilliary clearance and establish infection in the lung. Once in the alveolar cavities, the conidia undergo a series of morphological changes, such as shedding of the hydrophobic protective layer, conidial swelling and the growth of branching filamentous structures or hyphae. Once *A. fumigatus* germinates into hyphae, it becomes the invasive form of the disease resulting in destruction of lung tissue. Therefore, it is not surprising that immune cells play a key role in regulating *A. fumigatus* infection.[5] For example, alveolar macrophages and DCs are responsible for phagocytosing conidia while neutrophils play a role in killing hyphae.

Cryptococcus neoformans is one of the etiological agents causing cryptococcosis. Similar to *A. fumigatus*, the incidence of *C. neoformans* infections has increased dramatically over the last three decades. This fungal pathogen is known to cause life-threatening disease in individuals with impaired T cell function, particularly AIDS patients and solid organ transplant patients.[6] It is estimated that *C. neoformans* causes approximately 1 million infections and over 600,000 deaths per year worldwide. Infection with *C. neoformans* occurs via inhalation of the yeast or spores into the lungs. In healthy individuals, once the organisms reaches the

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lungs, professional phagocytes such as macrophages, DCs and neutrophils are responsible for clearing the infection and inducing an adaptive immune response. However, in individuals with a compromised immune system, *C. neoformans* can disseminate from the lungs into the brain leading to meningoencephilitis.

The most common fungal pathogen, *Candida albicans*, is a commensal organism capable of colonizing mucosal surfaces and skin in healthy individuals. In contrast to *C. neoformans* and *A. fumigatus*, there is no environmental form of this yeast. This dimorphic fungus colonizes the skin, genital mucosa and/or gastrointestinal mucosa of approximately 50% of healthy individuals without causing severe disease. However, severe disease is observed in the absence of proper host-pathogen recognition.[7] In addition, perturbations in the distribution of competitive commensal bacteria may contribute to *C. albicans* infection. Similar to other fungal pathogens, the actions of phagocytes are required for controlling *C. albicans* infection and dissemination. One example is the prevalence of oropharyngeal candidiasis in AIDS patients, which results from the decreased numbers of CD4 T cells circulating in these patients.[8,9]

The role of phagocytes and antigen-presenting cells (APCs) are essential in host defense against pathogenic fungi. Advances in understanding the interactions between DCs and pathogenic fungi, by virtue of receptor-ligand interactions, have provided insights into the mechanisms employed by the immune system to provide protection against these pathogens. These advances could provide the key for developing vaccines against *A. fumigatus*, *C. albicans* and/or *C. neoformans*. Here we will review the role of DCs in the host response to these three major pathogenic fungi. In addition to "the big three," there are other important fungal pathogens to be considered. Additional information on the role of DCs in response to other endemic fungal infections such as Blastomyces, Histoplasma and Coccidioides has been reviewed elsewhere and will not be covered in this review.[10-14]

Overview of Dendritic Cells

The activation of the innate immune system via pattern recognition receptors (PRRs) shapes the development of the adaptive immune response. DCs express a myriad of PRRs and provide the link between these two arms of the immune system. DCs are responsible for sampling antigenic material in the environment, shaping T cell responses through secretion of cytokines and priming T cell responses via antigen presentation.[15] Priming of T cells by DCs is mediated by pathogen-associated antigen on major histocompatibility complex (MHC) class I (MHC-I) or MHC class II (MHC-II) molecules for the priming of $CD4^+$ or $CD8^+$ T cells, respectively. In their immature state, DCs are highly phagocytic and are constantly patrolling the environment for the presence of pathogenic antigen. In order to perform these tasks, DCs express PRRs on their cell surface or in endosomal compartments, which serve to recognize an array of pathogen-associated molecular patterns (PAMPs) (**Fig. 1**). DC interactions with pathogens and the specific signals obtained from the PRRs, leads to the activation of a pathogen-specific T cell response. Moreover, cytokines secreted by DCs following engagement of PRRs lead to the activation and polarization of CD4 T cells into specific subsets characterized as T helper (Th)1, Th2, Th17 or T regulatory (Tregs). Therefore, DCs are essential players in balancing immune responses to fungal pathogens and prime candidates for vaccine development.

DC subsets are characterized by their expression of specific surface markers and functions. Although multiple subsets of DCs have been characterized, two main groups have been established: conventional DCs (cDCs) and plasmacytoid DCs (pDCs). pDCs express the surface markers CD123 (IL3R), PDCA-1, BDCA2, BDCA4, SiglecH and Bst2. In addition, pDCs are low (mouse) or negative (human) for CD11c, while expressing the B cell marker B220/CD45RA. Furthermore, human pDCs express endosomal TLR7 and TLR9, but lack expression of TLR4.[16] pDCs are characterized as IFNα (type I interferon)-producing cells, and have been primarily associated with antiviral responses.[16] Recently, pDCs were shown to play a non-redundant role in the antifungal response against *A. fumigatus*. The role of pDCs in the anti-Aspergillus response will be reviewed in a later section.

cDCs are typically characterized by their high-surface expression of CD11c and MHC-II (**Fig. 2**). cDCs, also known as resident DCs, exist in the lymphoid tissue as two distinct populations: $CD8^+$ DCs and $CD4^+$ DCs. These two populations are capable of cross-presenting antigen to T cells via MHC-I and MHC-II. In addition, both subsets of DCs express PRRs such as: the Toll-like receptors (TLRs), C-type Lectin receptors (CLRs) and Fc Receptors (FcR) that recognize PAMPs via opsonization-dependent and -independent mechanisms.[15,17] Initially, pathogen engagement of PRRs on DCs results in the activation of a PAMP-specific signaling cascade and cytokine production. These secreted cytokines initiate an innate inflammatory response, which shapes the CD4 T cell response. Signaling via TLRs results in the activation of intracellular signaling cascades, which results in the nuclear translocation of the transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NFκB), or the interferon regulatory factor 3 (IRF3) (**Fig. 1**). Transmission of PAMP recognition by TLRs is mediated by TIR-mediated engagement of myeloid differentiation factor 88 (MyD88); however, TLR3 signals via a MyD88-independent TIR-domain containing adaptor-inducing IFN-β (TRIF)-dependent signaling cascade. In addition, signaling of TLR4 is capable of signaling via MyD88 and TRIF-dependent mechanisms. MyD88 plays an instrumental role in the development of Th1 responses; which are required for a protective response against fungal pathogens.[18] In addition, engagement of the CLRs by carbohydrate moieties in the fungal cell wall also leads to the production of cytokines; an event that can be dependent or independent on the collaboration between the CLRs and TLRs. For example, interaction of Dectin-1 with the TLRs results to the canonical activation of NFκB (**Fig. 1**). Therefore, outcome of fungal infections is tightly connected to the interplay between the fungal pathogen and the host immune system. The fact that fungal pathogens, such as the mold *A. fumigatus* and the yeasts *C. albicans* and *C. neoformans,* affect mainly immune-compromised hosts indicate that our immune system has evolved mechanisms to prevent infection.[19] The fine

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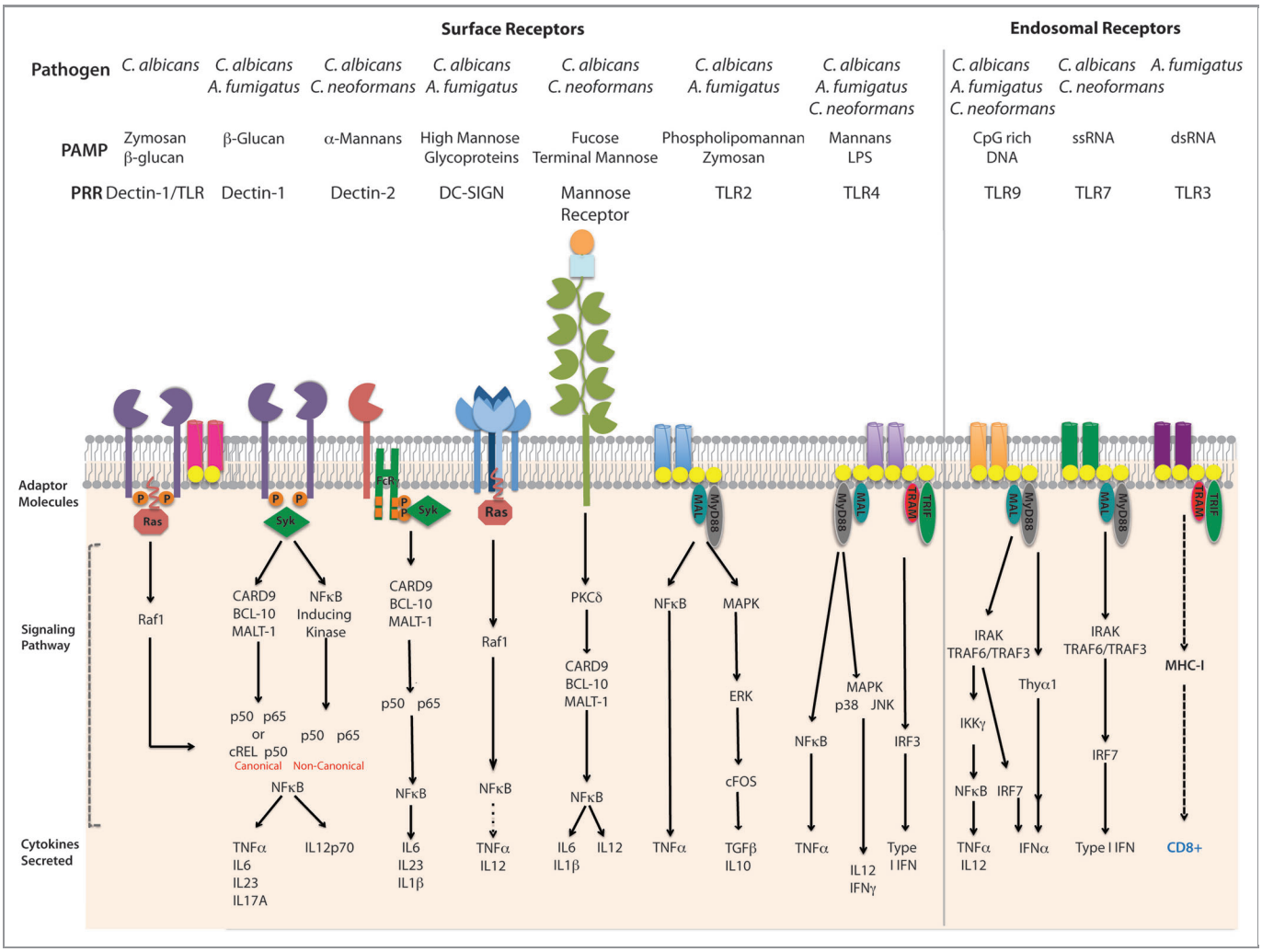

Figure 1. Pattern recognition receptors on DCs and signaling pathways that prime T cell differentiation. Recognition of *C. neoformans*, *C. albicans* and *A. fumigatus* mediates by detection of fungal pathogen-associated molecular patterns via Toll-like receptors (TLRs) in the cell surface or endosomes and C-type lectin receptors (CLRs). This graphic represents the TLRs and CLRs responsible for the detection of *C. albicans*, *C. neoformans* and *A. fumigatus* expressed on DCs and the signaling pathways involved in the antifungal response.

interplay between the innate and adaptive arms of the immune system dictates the outcome of the disease.

Conventional Dendritic Cells and PRR-Mediated Detection of Fungal Pathogens

Dendritic cells comprise a dense surveillance network in the lungs and periphery. In their immature or resting state, DCs are responsible for uptake, processing and presentation of antigen-following, cytokine-induced maturation signals. The complex process of antigen presentation is responsible for instructing the appropriate T cell response to the antigen. This process is of particular importance in the response to pathogenic fungi, as DCs are responsible for discriminating between different fungal morphotypes or growth stages. In order to discriminate between yeasts, conidia and hyphae, DCs express an array of cell surface receptors including TLRs, complement receptors (CRs), Fc Receptors (FcRs), Scavenger Receptors (SRs) and CLRs.[20] Depending on the receptor or combination of receptors engaged, DCs are responsible for priming and educating T cells toward the appropriate host response.

Host innate clearance of initial fungal infections is predominantly mediated by the complement system. Complement activation can take place via three pathways: the alternate pathway, the lectin pathway (MBL) and the classical pathway (CP). Even though target discrimination is different among these pathways, their activation leads to C3b binding to invading cells for opsonization and phagocyte killing. The MBL pathway is the most characterized in the antifungal response and has been reviewed elsewhere.[21] Recently, it was suggested that activation of the complment system by *C. albicans* is required for production of inflammatory cytokines via C5a-C5aR interactions; however, complement does not influence phagocytosis or killing of the yeast.[22] While fungal phagocytosis is most efficient following

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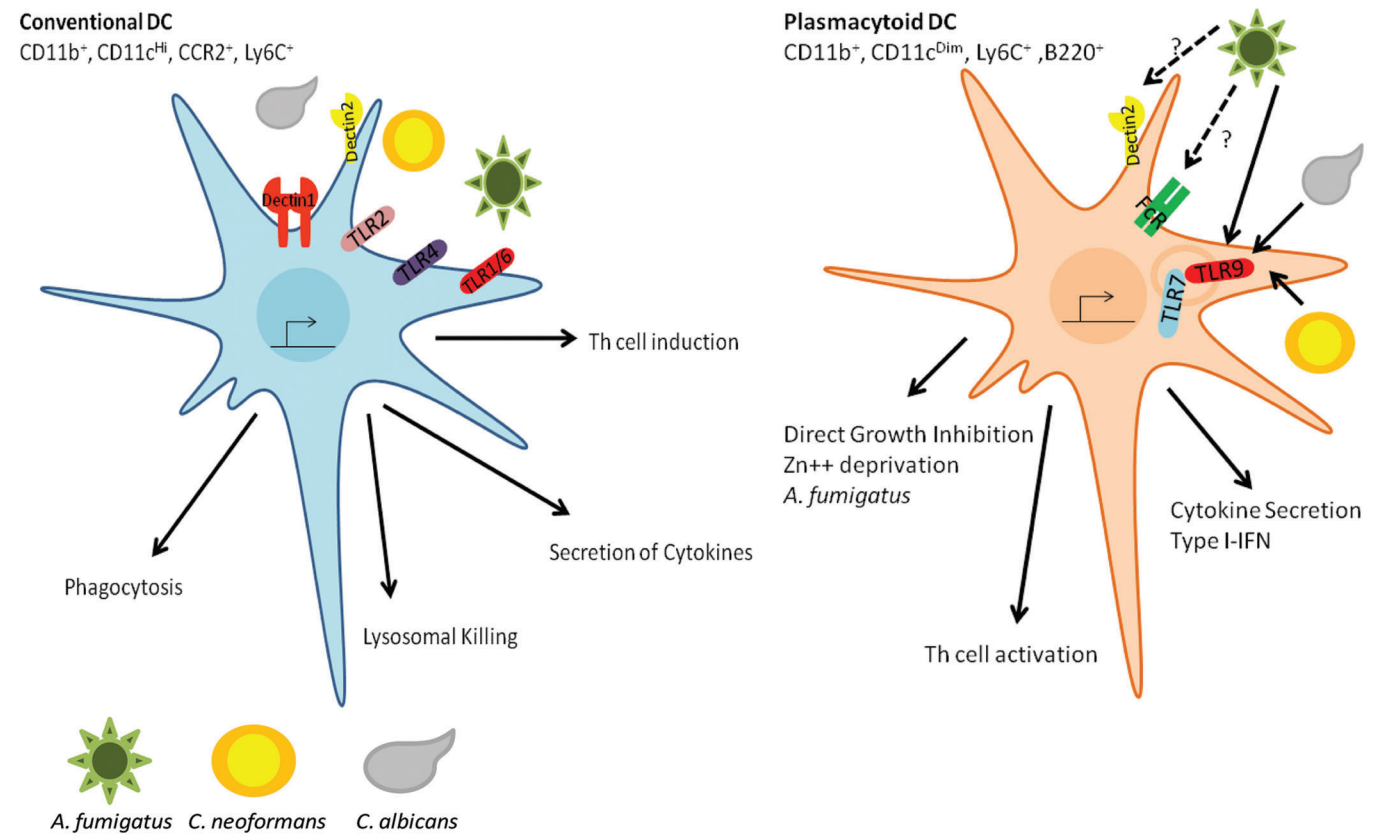

Figure 2. DC mediated responses to fungal pathogens. Conventional DCs are characterized by CD11b$^+$, CD11c^{HI}, Ly6C^{Hi} and CCR2$^+$. These cDCs express the surface TLRs (TLR1, TLR2, TLR4 and TLR6) and the CLRs (Dectin1, Dectin2 and DC-SIGN). Upon recognition of the fungal pathogen, cDCs activate a series signaling cascades that result in: (1) phagocytosis of the fungal pathogen, (2) uptake to lysosomal compartments where the pathogen is killed and antigens can be loaded into MHC for presentation to T cells, (3) Secretion of cytokines and chemokines responsible for communicating with other cells to induce a host response and (4) induce the proper Th response. pDCs express the endosomal TLRs (TLR7 and TLR9), FcRγ and possibly the CLR Dectin2. pDCs are responsible for: (1) detection of exogenous DNA and RNA resulting in the induction of an inflammatory response, (2) orchestrating Th cell responses and (3) direct killing of *A. fumigatus* hyphae.

opsonization by serum opsonins, several non-opsonic PRRs have been described to mediate fungal uptake.[12,19] Receptors such as Dectin-1, Dectin-2, dendritic cell-specific intracellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), macrophage mannose receptor (MMR) and Scavenger receptor class F member 1 (SCARF1) have been shown to mediate fungal uptake by recognition of cell wall components (i.e., β-glucans and mannans) (**Fig. 1**).

Dimorphic fungi, such as *C. albicans* and *A. fumigatus*, express different PAMPs during their morphological states. Therefore, it is not surprising that DCs have evolved to recognize and initiate a host response against these different morphotypes. Detection of fungal pathogens is highly dependent on detection of fungal cell wall components. The fungal cell wall is a complex and dynamic structure composed mainly of β-1,3 and β-1,6 glucans, chitin and mannoproteins.[19] The concentration and distribution of cell wall-associated glycoproteins differs greatly among the different fungal pathogens and their morphological state.[23,24]

For example, *A. fumigatus* conidia express a thick layer of a hydrophobic layer composed of small cysteine-rich proteins or hydrophobins, and a dense pigmented outer layer composed of the melanin. Following conidia swelling, the inner layer becomes translucent and exposes a network of carbohydrate polymers composed of the protein-associated glycoproteins: chitin, galactomannan, branched β-1,3/β-1,6 glucans and linear β-1,3/β-1,4 glucans also exposed in the germ tubes and hyphae. Thus, these PAMPs recognized by PRRs on DCs occur predominantly during *A. fumigatus* growth. In contrast, *C. neoformans* contains a hydrophobic capsule composed mainly of glucuronoxylomannan, galactoxylomannan and mannoproteins.[25] The *C. neoformans* capsule provides virulence to the yeast. The capsule functions as a physical barrier that interferes with normal phagocytosis, proinflammatory cytokine production and clearance by the immune system. Similarly, Candida yeast expresses a thick layer of N-linked and O-linked mannans in a network of glycoproteins associated with the fungal cell wall, including β-glucans and chitin.

It is well-established that the TLRs, mainly TLR2 and TLR4, and CLRs (such as Dectin-1) are responsible for the establishment and development of an effective host response against *C. albicans*,

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C. neoformans and *A. fumigatus*.[19] Both TLR2 and TLR4 have been shown to recognize cell wall components from pathogenic fungi; although these finding remain controversial and there exists contradictory findings between different TLR knockout mice. Perhaps some of this is due to the fact that TLR's interactions with pathogenic fungi depend on the route of infection, morphotype of the fungi and strain of mice. During *C. neoformans* infection, TLR2 and TLR4 appear to play a minor role in the detection of yeast. Shoham et al. showed that GXM from the Cryptococcal capsule induces the translocation of NFκB in human PBMCs and RAW264 macrophages.[26] In vivo, TLR2$^{-/-}$ and TLR4$^{-/-}$ mice infected with *C. neoformans* produce IL1β, IL6, IL12p40 and TNFα, and show increased survival over their WT counterparts.[27] During *C. albicans* infection, TLR2$^{-/-}$ mice appear to be more susceptible to candidiasis as a result of a decreased proinflammatory response and reduced neutrophil recruitment.[28] Pietrella et al. suggested that mannoprotein (MP65) from *C. albicans* was responsible for stimulating DCs partially via TLR2, TLR4 and MyD88. Stimulation of DCs with MP65 results in the induction of TNF, IL6 and IL12; as well as DC maturation and increased expression of CD14 and FcRγ.[29]

In addition to TLR2 and TLR4, other surface TLRs play a role in the development of fungal infections[30] (**Table 1**, adapted from Romani et al.[20]). Kesh et al. analyzed the role of single nucleotide polymorphisms in TLR1, TLR4 and TLR6 in the development of invasive aspergillosis in 127 allogenic stem cell transplant recipients. The presence of TLR1 293 G > C or the presence of both TLR6 745C > T and TLR1 743A > G were associated with invasive aspergillosis.[31] In 2012, Rubino et al. analyzed the role of TLR1 and TLR6 in the recognition of *A. fumigatus*. Although the work was done in macrophages rather than DCs, the group analyzed cytokine production in WT, TLR1$^{-/-}$ and TLR6$^{-/-}$ mice following incubation with WT or *A. fumigatus ΔrodA*. In TLR1- and TLR6-deficient mice, there were lower amounts of IL12p40, CXCL2, IL6 and TNFα when compared with WT bone marrow-derived DCs (BMDCs). Lungs from TLR1$^{-/-}$, TLR6$^{-/-}$ and WT mice infected intranasally (i.n.) with the mold revealed diminished CXCL1 and CXCL2 production in the TLR knockout mice. In addition, these mice showed higher fungal burden when compared with the WT counterparts. The observed response to the immunogenic *A. fumigatus* strain required the heterodimerization of murine TLR1/TLR2, TLR2/TLR6 and human TLR2/TLR1, but not human TLR2/TLR6.[32] These data suggest that TLR1 and TLR6 collaborate with TLR2, and possibly TLR4 in the host response against *A. fumigatus.* TLR1 and TLR6 also play a role in the host response against the yeast *C. albicans*.[33] In 2008, Netea et al. analyzed the role of these receptors in vivo. TLR1$^{-/-}$ and TLR6$^{-/-}$ mice were infected intravenously (i.v.) with *C. albicans* UC820 and followed for survival. In their model, TLR1 does not play a role in the recognition of *C. albicans* as mice showed comparable susceptibility to WT in the development of disseminated candidiasis.[34] However, TLR6 modulated the Th1/Th2 cytokine balance; as TLR6 mice displayed a defective production in IL10 and IFNγ. However, these mice displayed normal production of IL6, IL1β and TNF, as well as normal susceptibility to candidiasis; suggesting that TLR6 plays a minor role during Candida infection.[34] The extent of the role of TLR1 and TLR6 in host defense against fungal infections might be dependent on the species encountered, the morphology of the fungal pathogen and the association of TLR1 and/or TLR6 with other TLRs besides TLR2. Future studies should investigate the role of these receptors in association with other PRRs, such as other TLRs, CLRs and SRs.

The contribution of TLR3, an endosomal dsRNA sensor, was recently analyzed in an *A. fumigatus* infection model. TLR3$^{-/-}$ mice were highly susceptible to *A. fumigatus* conidia following intranasal challenge and these mice failed to develop MHC-I-restricted CD8^{+} T cell responses. Moreover, CCR7^{+} DCs from TLR3$^{-/-}$ mice failed to migrate from the lungs to the lymph nodes and prime a proper T cell response to *A. fumigatus*. These results were confirmed by predisposition to invasive aspergillosis (IA) in hematopoietic-cell transplant (HSCT) recipients with SNPs in *TLR3*. In a cohort of 223 HSCT recipients and their corresponding donors, one mutation in *TLR3* (95C/A) was found to significantly increase the risk of IA when present in the donors. Furthermore, functional analysis of this mutation demonstrated a defect in CD8^{+} T cell proliferation following incubation with DCs expressing this SNP.[35] To date, the role of TLR3 has been shown to be restricted to the recognition of viral RNA and synthetic poly I:C. However, Carvalho et al. recently showed for the first time that TLR3 in DCs mediates cross presentation of *A. fumigatus* RNA to CD8^{+} T cells.

The CLRs: Dectin-1

Dectin-1 was originally characterized on DCs, with high expression on the cell line on the DC cell line XS52, but not on the macrophage cell line J774.[36] In addition, Dectin-1 mRNA was predominantly expressed on spleen, thymus and skin-resident DCs.[36] In 2001, Brown et al. identified the ligand for Dectin-1.[37] The group screened RAW264 macrophages following treatment with zymosan, a β-glucan rich particle. They identified Dectin-1, a small type II membrane receptor on macrophages that binds β-1,3 glucans. In contrast to the original reports on Dectin-1, the receptor is expressed in all macrophage populations, with highest expression in the liver, lung and thymus.[37]

The role of Dectin-1 expression on immature human DCs (iDCs) was further analyzed by microarray following challenge with *A. fumigatus* germ tubes.[38] Using short interference RNA, *TLR2, TLR4, DC-SIGN, Pentraxin 3, Dectin 1* and *CARD9* were silenced then knockdown iDCs were treated with *A. fumigatus* germ tubes. By RT-PCR, *A. fumigatus* germ tubes induced expression of cytokines, chemokines, costimulatory molecules and genes involved in fungal recognition and phagocytosis in iDCs. Silencing of *Dectin-1* in these cells resulted in decreased expression of the proinflammatory cytokines TNFα and IL12. These data suggests that Dectin-1 might be the most important receptor in the detection of *A. fumigatus* germ tubes (**Fig. 1**). In contrast to previous reports, this group did not find alterations in the expression of TLR2 and/or TLR4 following treatment with *A. fumigatus*. This suggests that Dectin-1 plays an essential role in

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Table 1. Polymorphisms associated with susceptibility to fungal infections

Gene	SNP or haplotype	Effect	Disease outcome	References
TLR1	*TLR1* 293G > C *TLR1* 743A > G	Unknown	Susceptibility to invasive aspergillosis	31
TLR3	*TLR3* 95C > A	Defective CD8⁺ T cell proliferation	Susceptibility to IA	35
TLR4	*TLR4* 1063A > G *TLR4* 1363C > T	Impaired ligand-binding domain	Susceptibility to IA, *A. fumigatus* colonization, chronic cavitary pulmonary aspergillosis, systemic *C. albicans* infection	33, 83, 90 and 95
TLR6	*TLR6* 745C > T	Unknown	Susceptibility to IA	31
TLR9	TLR9 T1237C	Increased NFκB binding	Susceptibility to allergic bronchopulmonary asperillosis	33
Dectin1	Dectin1 Y223S	Decreased Zymosan Binding	Resistance to oropharyngeal candidiasis	95
	Dectin1 Y238X	Decreased surface expression, β-glucan binding and cytokine production	Susceptibility to chronic mucocutaneous candidiasis, *C. albicans* colonization, IA	30, 91 and 93
CARD9	CARD9 Q295X	Decreased Th17	Susceptibility to mucocutaneous candidiasis	92
CXCL10	+11101C/+1642G/-1101A	Decreased chemokines by DCs following *A. fumigatus* exposure	Susceptibility to IA	94

*This table has been adapted from Romani et al.[20]

the recognition and immune response against mold, while TLR2 and TLR4 involvement plays a minor role in the detection of *A. fumigatus*.

Dectin-2 Expression on DCs

Another member of the CLR family, Dectin-2, binds highly mannosylated structures. Similar to Dectin-1, Dectin-2 is a glycosylated type II transmembrane protein with a carbohydrate recognition domain (CRD). However, Dectin-2 expresses a shorter cytoplasmic region with an arginine-based activation motif.[39] Binding of Dectin-2 to high-mannose structures, found in a wide range of fungal species, was shown using a glycan array (**Fig. 1**).[40] Furthermore, Dectin-2 was found to preferentially bind hyphal components of *C. albicans* in a soluble binding assay and in macrophages expressing Dectin-2. The adaptor molecule FcRγ interacts with Dectin-2 and after phosphorylation of the FcRγ chain, this interaction results in the activation of NFκB, internalization of ligand and the expression of TNFα and IL-1R.[41] Dectin-2 contributes to the activation of DCs by fungal particles via Syk and CARD9 pathway; however, the interaction with Syk and CARD9 is indirect through the association of the FcRγ chain (**Fig. 1**). In an infection model of *C. albicans*, blocking Dectin-2 with antibody did not affect the innate immune responses to the fungal pathogen. Instead specific T cell production of IL-17 was abrogated and, when combined with Dectin-1 deletion, decreased Th1 host responses.[42] Elucidations of the signaling mechanisms employed by Dectin-2 were further analyzed with the generation of Dectin-2-deficient mice. Following challenge with *C. albicans* mannans, *Dectin-2*$^{-/-}$ DCs did not produce any cytokines in response to α-mannans. In agreement with previous work, Dectin-2 signaling was dependent on Syk-CARD9-NFκB mechanism and independent of MAP kinases. In contrast to initial findings, Saijo et al. reported that both morphologies of *C. albicans* (yeast and hyphae) induce Th17 differentiation via a Dectin-2-dependent mechanism.[43] Thus Dectin-2 appears to play an important role in the induction of a Th17 host response, and in collaboration with Dectin-1 orchestrates a balanced CD4⁺ T cell response in the host. While the role of Dectin-2 has not been analyzed in other fungal infection models, it is possible that this receptor plays a similar role in the detection of other dimorphic fungi.

Mannose Receptors: MMR and DC-SIGN

The mannose receptors (MRs) are a subgroup of CLR family of PRRs responsible for detecting manosylated proteins. One characteristic of fungal glycoproteins (in contrast to mammalian) is their high degree of mannosylation or richness of mannose groups, which was shown to be critical for their immunogenicity. In humans, two receptors expressed on DCs and macrophages have been shown to play a role in mannose-binding: MMR/CD206 and the DC-SIGN/CD209.[44,45] Furthermore, in the mouse, DC-SIGN has four isoforms (SIGN-R1, SIGN-R2, SIGN-R3 and SIGN-R4); but only SIGN-R1 and SIGN-R3 have been described to bind mannose moieties.[46]

Membrane-bound CLRs, such as MMR, are characterized by the presence of a cytoplasmic sorting motif responsible for directing internalization into early endosomes via clathrin-coated vesicles.[47] Upon internalization and delivery of mannosylated antigen to the early endosome, MMR is recycled to the cell surface; while the antigen is processed and presented via MHC-II. Similarly, DC-SIGN also contains an internalization motif responsible for targeting mannosylated antigen for T cell presentation. However, DC-SIGN targets the antigen to the late endosomes and lysosomes.[47]

The contribution of the membrane-bound CLRs was described by Mansour et al.[44] Initially, the group used stably transfected

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cells lines expressing human MMR or human DC-SIGN to determine whether these receptors bind and internalize *C. neoformans* mannoprotein (MP). Expression of human MMR and DC-SIGN in these genetically engineered cell lines results in avid binding and internalization of *C. neoformans* MP. However, parental cell lines (lacking MMR and DC-SIGN) were also capable of capturing small amounts of MP; which is not competitively inhibited by mannosylated ligands. Furthermore, DCs were capable of MHC-II presentation of MP and establish a T cell response. The uptake of MP by DCs was rapid and could be blocked by competitive inhibitors of MMR.[44] In 2005, Pietrella et al. demonstrated that MP activates and induces maturation of human DCs by a process that could be inhibited by blocking antibodies against MMR.[48] In 2008, Dan et al. further analyzed the importance of MMR in host response to *C. neoformans*.[49,50] The group observed that $MMR^{-/-}$ mice challenged i.n. with *C. neoformans* were more susceptible to infection than WT mice; in addition, $MMR^{-/-}$ mice had increased fungal burden when compared with WT. Similar results were observed ex-vivo, where DCs from $MMR^{-/-}$ mice challenged with *C. neoformans* exhibited decreased $CD4^+$ lymphoproliferation when compared with WT DCs.[50]

In addition to *C. neoformans*, MMR has also been shown to play a role in the recognition of *C. albicans*.[51] The commensal yeast was shown to be internalized via MMR instead of Dectin-1 or another CLR. Donini et al. suggested that entry via MMR results in inhibition of the NADPH oxidative pathway, which, if activated, kills *C. albicans*.[51]

DC-SIGN is another CLR responsible for the detection of fungal pathogens. While Mansour et al. demonstrated that cell lines stably transfected with human DC-SIGN could bind and internalize *C. neoformans*, there is no additional evidence of this receptor playing a role in host defense against the yeast.[47] However, DC-SIGN appears to play a role in the immune response to *C. albicans* and *A. fumigatus* conidia. In 2004, Serrano-Gomez et al. characterized the importance of DC-SIGN in the anti-Aspergillus response.[52] The group observed that DC-SIGN specifically interacts with clinical isolates of the mold.[52] Furthermore, the binding of *A. fumigatus* conidia was dependent on the expression of DC-SIGN; and uptake of the conidia directly correlated with the levels of expression of the receptor. In addition, analysis of hematological patients identified four SNPs in DC-SIGN allele that significantly increase the risk of IPA in these patients.[53] Similarly, Cambi et al. demonstrated that DC-SIGN binds *C. albicans* in a time and concentration-dependent manner.[54] In contrast to MMR, DC-SIGN expressed on immature DCs induces phagocytosis of the yeast. Uptake of *C. albicans* by DC-SIGN is mediated by exposure of N-linked mannans, rather than O-linked phosphomannans, in the cell wall of the yeast. Recognition of N-linked mannans on human DCs via DC-SIGN directly influences the production of the inflammatory cytokine IL-6.[55] Similarly, MMR also exhibits differential recognition of N-linked mannans vs O-linked mannans; however, there was no difference in the uptake of the different mannosylated glycoproteins.[56]

Conventional DCs and T Cell Responses

Initiation of the proper adaptive immune response against *A. fumigatus* is dependent on the actions of DCs (**Fig. 2**). Phagocytosis of conidia by DCs leads to a protective Th1 response; however, interactions with hyphae result in a non-protective Th2 response and IL10-producing CD4 T cells.[57] Interaction of conidia with DCs, and subsequent phagocytosis, requires the shedding of the protective hydrophobic layer (rodA) from resting conidia. Incubation of DCs with swollen conidia results in DC maturation, CXCL8 secretion and the recruitment of neutrophils. The role of DCs in neutrophil migration was further characterized by Park et al. where, neutropenic mice showed a marked accumulation of DCs in the lungs of mice challenged with *A. fumigatus*. Phenotypically, these DCs were more immature in the neutropenic mice and in in vitro experiments of coincubation of iDCs with neutrophils resulted in enhanced expression of co-stimulatory molecules after exposure to *A. fumigatus*; a process dependent on cell contact and DC expression of the receptor DC-SIGN.[58]

Activation of DCs, by engaging TLRs or non-opsonic receptors, leads to the activation of an adaptive immune response. Understanding the interactions between pathogenic fungi and DCs leads to the development of species/morphology-specific CD4-T cell responses, including Th1, Th2, Th17 and regulatory T cells (Tregs). Protection from fungal infections in human and mice are partially dependent on the development of fungal-specific $CD4^+$ T cell responses. Depending on the PRR or combination of receptors engaged defines whether host response against the fungal pathogen will be Th1 (IFNγ secretion, phagocyte activation) vs. Th2 (IL4, IL5 and IL10 anti-inflammatory cytokine secretion). Activation of certain PRRs and the deregulation of the host response against any of the fungal pathogens can lead to an unfavorable Th2 response.[12] PRR engagement influences several steps in DC activation and, consequently, T cell differentiation.

Pulmonary infections with *A. fumigatus* induce concurrent Th1 and Th17 responses dependent on TLR/MyD88 activation.[59] Deletion of Dectin-1 leads to decreased secretion of IFNγ and IL12p40 during *A. fumigatus* infection, resulting in a decrease in Th17 differentiation and a Th1 non-protective response.[60] Recent experiments suggest that production of TNFα produced by $Ly6C^+CD11b^+$ DCs promotes IL17A secretion from $CD4^+$ T cells.[61] In this infection model, C57Bl/6 mice and BalbC mice were sensitized with *A. fumigatus* via intratracheal (i.t.) infection and challenged eight additional times. When comparing these two mouse strains, BalbC mice exhibited a larger concentration of TNFα producing DCs in the lungs. Furthermore, CD11c-DTR, Dectin-$1^{-/-}$ and $MyD88^{-/-}$ BalbC mice exhibited decreased numbers of TNF-producing DCs and decreased IL17A production.[61] Production of TNFα by DCs, in this infection model, appears to play a role in orchestrating the events in DCs and CD4 T cells that lead to neutrophil airway inflammation.

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Lysosomal Killing of Fungal Pathogens by DCs

Dendritic cells phagocytose and kill *C. neoformans*. Wozniak et al. examined the in vivo interactions of DCs with *C. neoformans* in the lungs using a murine infection model.[62] C57Bl/6 mice were infected i.n. with fluorescently labeled *C. neoformans* serotype A strain 145 and heat-killed *C. neoformans*. Within 2 h of infection, DCs in the lungs internalize the yeast. Furthermore, expression of the DC maturation markers, CD80, CD86 and MHC-II, are observed 7 d post-infection. Incubation of DCs from *C. neoformans* infected mice with antigen specific T cells resulted in an increase of IL2 production when compared with naïve mice, showing that DCs play a role in both the innate and adaptive anticryptococcal response. In 2008, Wozniak et al. analyzed the early events following *C. neoformans* phagocytosis by DCs.[63] Human and murine DCs were incubated with encapsulated *C. neoformans* in the presence of opsonizing antibody and, subsequently, intracellularly stained with EEA1 (endosome) and LAMP-1 (lysosome). In the murine DC model, live *C. neoformans* traffics to the endosome within 10 min and to the lysosome within 30 min post-infection. Similar results were observed in human DCs, with the yeast trafficking to the endosome within 20 min and to the lysosome within 60 min. The mechanism of phagocytosis follows traditional zipper phagocytosis and appears to be independent of the opsonization method. Furthermore, lysosomal components kill *C. neoformans* in a dose-dependent manner. Together, these data suggest that DCs play a key role in host defense against *C. neoformans*. DCs are responsible for the detection, phagocytosis, killing and cryptococcal antigen presentation following infection with the yeast.

Plasmacytoid Dendritic Cells (pDCs) and Endosomal TLRs

Plasmacytoid dendritic cells (pDCS) are a rare subtype (0.3–0.5% of PBMCs) of cells that develop in the bone marrow. In humans, pDCs can be found circulating in the blood where they can easily migrate to the lymph nodes. In the mouse, pDCs mainly reside in lymphoid organs. While the core gene expression program in pDCs is conserved between humans and mice, some differences in surface markers between human and murine pDCs have been established.[64] Surface expression of CD11c is low (mouse) or negative (human) in pDCs, but these cells express the B cell marker B220/CD45RA (**Fig. 2**). In addition, pDCs express specific markers such as BDCA2 and ILT7 in human and SiglecH and Bst2 in mice.

pDCs were initially identified as a very small subset of human leukocytes responsible for high-level IFNα production. In 2001, it was reported that pDCs produced type I IFN in response to unmethylated CpG DNA from viruses and bacteria.[65] Furthermore, pDCs express the endosomal nucleic acidTLR7 and TLR9, and can sense single stranded RNA and unmethylated CpG DNA, respectively (**Fig. 2**). While plenty of work has been performed to dissect the role of pDCs during viral and bacterial infection, the role these cells play in the antifungal host response has received scarce attention.

In the last decade, several advances have been made in understanding the role of endosomal TLRs in the detection of fungal PAMPs.[3] Initial observations suggesting a role for TLR9 in host defense against pathogenic fungi were performed in vivo following infection with *C. albicans* and *A. fumigatus*. In 2004, Bellochio et al. showed that mice deficient in TLR9 were susceptible to infection with *C. albicans* hyphae and *A. fumigatus* conidia.[28] Infection of TLR9$^{-/-}$ mice resulted in lower CFU in the kidneys (Candida yeast and hyphae), stomach (Candida yeast) and lung (Aspergillus conidia). Furthermore, TLR9$^{-/-}$ mice exhibited decreased cytokine secretion. These initial studies suggested that the endosomal nucleic acid sensor TLR9 might be involved in the inflammatory response to *A. fumigatus* and *C. albicans*.

Fungal DNA acts as a PAMP for TLR9. In 2008, two groups independently showed, for the first time, that *A. fumigatus* DNA was capable of stimulating a TLR9-dependent response.[66,67] Ramirez-Ortiz et al. showed that *A. fumigatus* DNA contained unmethylated CpG motifs capable of inducing a TLR9-dependent response in mouse BMDCs and human pDCs. Stimulation with fungal DNA resulted in secretion of proinflammatory cytokines in a dose dependent manner. Furthermore, the stimulatory activity of *A. fumigatus* DNA could be abolished by enzymatic methylation. An *A. fumigatus* genome wide analysis identified 23 murine and 87 human putative immunostimulatory motifs, as human TLR9 detects CpG-A motifs and murine TLR9 detects CpG-B motifs.[66] A second model introduced by Ramaprakash et al. investigated the role of TLR9 in a murine model of IA and fungal asthma. For the IA model, neutrophil-depleted WT and TLR9$^{-/-}$ mice were challenged with swollen or resting *A. fumigatus* conidia and monitored for lung inflammation. Following challenge with resting conidia TLR9$^{-/-}$ mice had less airway hyper-responsiveness when compared with WT. However, *A. fumigatus*-sensitized mice deficient in TLR9 showed an increase in fungal growth at 14 and 28 d post-challenge, which correlated with a decrease in Dectin-1.[67] In summary, *A. fumigatus* DNA has the immunostimulatory capacity to engage a TLR9-dependent response. Future studies are needed to determine whether TLR9 can collaborate with Dectin-1 and/or other CLRs in the establishment of the host response against pathogenic molds.

The role of pDCs in host response against *A. fumigatus* was initially analyzed by Romani et al.[68] They pulsed mDCs and pDCs with thymosin 1α, a naturally occurring thymus peptide, and analyzed antifungal response to *A. fumigatus* conidia. DCs treated with thymosin 1α induce DC maturation and IL12 production by *A. fumigatus* conidia pulsed DCs.[68] Thymosin 1α also increased the secretion of IL10 by human pDCs; however, secretion of IFNα was not detected following treatment with thymosin 1α in the presence or absence of *A. fumigatus* conidia. Furthermore, BM-transplanted mice treated with thymosin 1α peptide showed increased Th1-dependent antifungal immunity, accelerated myeloid cell recovery and protection against IA.[68] These data provide insights into one of possibly multiple molecules that play a role in modulating the host response of DCs against *A. fumigatus*. Identifying such molecules could be useful in the development of antifungal treatment. In 2008,

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Montagnoli et al. studied the ability of GM-CSF/IL4-derrived (cDCs) or Flt3-derrived (pDCs) DC subsets to induce T reg/Th1 cell priming against *A. fumigatus*. In addition, they analyzed the contribution of each murine DC subset to antifungal responses following adoptive transfer in hematopoietic transplanted mice. Flt3-DCs were found to prime antifungal Th1/Treg responses, induce tolerization against antigens and divert T cell responses from alloantigen-specific to antigen-specific responses in the presence of donor T lymphocytes. Furthermore, Treg development and tolerization involved thymosin 1α modulation of pDCs via TLR9, resulting in the activation of indoleamine 2,3-dioxygenase-dependent pathway (**Fig. 1**).[69]

Recently, human pDCs were demonstrated to phagocytose *A. fumigatus* conidia and spread over these larger hyphae.[70] Human pDCs are capable of mounting an immune response to the fungal pathogen by release of proinflammatory cytokines, such as IFNα and TNFα. In addition, pDCs in close proximity to hyphae demonstrated high rates of cell death. The mechanism employed in the interaction between pDCs and *A. fumigatus* hyphae appears to be TLR9-independent, although *A. fumigatus* DNA can function as a PAMP for TLR9. In addition, pDCs showed increased cell death resulting in sequestering Zn^{2+} available in the environment and slowing down *A. fumigatus* growth. In a mouse infection model, pDCs migrated to the lungs following orotracheal (o.t.) challenge with *A. fumigtus* conidia. Furthermore, depletion of pDCs using the 120G8 antibody resulted in increased mortality.[70,71] These data suggest a new non-redundant role for pDCs in the detection of pathogenic fungi.

While a direct role for pDCs in the detection of *C. albicans* has not been directly established to date, this yeast can induce a TLR7, TLR9 and IFNβ-dependent host response. Initial studies by Bellochio et al. suggested a role for TLR9 during *C. albicans* infection. Following challenge with *C. albicans,* $TLR9^{-/-}$ mice infected with the yeast morphotype showed decreased survival than mice infected with hyphae or when compared with their WT counterparts. However, $TLR9^{-/-}$ mice showed decreased CFU in the kidneys and stomach following challenge with either *C. albicans* hyphae or yeast.[28] In 2008, van de Veerdonk et al. suggested that TLR9 played a redundant role in the detection of *C. albicans*.[72] This group concluded that TLR9 was involved in cytokine production against the opportunistic yeast; however, TLR9 played a redundant role in the host response against *C. albicans*. A year later, Miyazato et al. showed that *C. albicans* DNA was sufficient to induce a TLR9-dependent response in DCs; however, the mechanism of nucleic acid detection was independent of DNA methylation.[73] In their model, Miyazato et al. observed that *C. albicans* DNA induced a stronger IL12p40 response in WT vs $TLR9^{-/-}$ mice and this response was not eliminated following treatment with a DNA methylase, but could be eliminated following DNase treatment.[73] Furthermore, Biondo et al. observed that cDCs, rather than pDCs and macrophages, are responsible for mounting an IFNβ response against the pathogenic yeast. In this model, the host response requires the adaptor molecule MyD88; however, it is only partially dependent on TLR7 and TLR9. Following i.v. challenge with *C. albicans*, $IFN\alpha/\beta R^{-/-}$ mice showed decreased survival and increased CFU in the kidneys when compared with WT counterparts.[74]

DCs are usually associated with the induction of protective and non-protective adaptive immune responses.[75] In 2000, Bauman et al. used a murine immunization model to analyze which DC subsets were involved in cell-mediated immunity to *C. neoformans* antigens.[76] In their model, mice were immunized s.c. with cryptococcal culture filtrate Ag-CFA (protective) or with heat-killed cryptococci-CFA (non-protective) and the infiltrating cells were characterized by flow cytometry. The protective response resulted in increased numbers of mDCs and Langerhans cells in the draining lymph nodes. However, mice immunized with the non-protective antigen showed no significant increase in the total number of cells in the draining lymph node, nor was there a change in the LDC (now pDCs):mDC ratio. These data suggest that mDCs are the primary APC during cryptococcal infection. However, DC-mediated responses to *C. albicans* have revealed an opposing mechanism. Using a murine model of vaginal candidiasis whereby female mice were inoculated with blastoconidia from stationary phase culture into the vagina, LeBlanc et al. examined the role of DCs in the initiation of immunoregulatory events.[77] This group found that following vaginal inoculation, DCs reorganize and become more concentrated in the T cell zones of the lymph nodes. Analysis of the draining lymph nodes of mice infected with *Candida* vs. control mice demonstrated that pDCs were the predominant DC subset pre- and post-vaginal infection. Interestingly, pDCs retained their predominant state throughout the infection indicating a tolerizing condition suggesting that pDCs are involved in the induction of Th1 responses to *C. albicans* vaginal infection.[77]

Another fungal pathogen, *C. neoformans*, can induce a TLR9-dependent host response. Initial investigations suggested a role for TLR9 in mediating the Th1 vs. Th2-type response following during *C. neoformans* infection. Edwards et al. showed that immunization with CpG-DNA deviates the response from Th2 to Th1 type response following challenge with the yeast. This infection model resulted in increased IL12, TNF, MCP1 and macrophage nitric oxide production; as well as a decrease in pulmonary eosinophilia and fungal burden.[78] While initial studies engaged TLR9 activation prior to fungal infection, in 2008, Nakamura et al. analyzed the role of *C. neoformans* DNA as a PAMP.[79] Fungal DNA induced IL12p40 production and increased CD40 expression in BM-DCs, and *C. neoformans* DNA colocalized with CpG DNA to endosomal compartments. This response is abolished in $TLR9^{-/-}$ and $MyD88^{-/-}$ mice, and after treatment with DNase. In vivo, mice lacking TLR9 show increased susceptibility to *C. neoformans* infection, however TLR9 was required for the recruitment of effector cells such as macrophages and lymphocytes to the lungs during *C. neoformans* infection.[79,80] Finally, Zhang et al. found that TLR9 did not affect the fungal burden at the innate immune response stage, but increased clearance of the yeast during the adaptive phase.[81]

The role of the endosomal TLRs in the host defense against fungal pathogens has been well-characterized in the last decade. However, it is important to note that most of the work performed to dissect the role of TLR7 and TLR9 during infection utilizes

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mouse BM-DCs as their DC model. A basic difference between human and murine DCs is observed in the distribution of the PRRs among the different subsets of DCs. In humans, expression of the endosomal TLRs, TLR7 and TLR9 is restricted to pDCs while cDCs express all the surface TLRs. In mice, all DC subsets express all TLRs (with the exception of TLR3). Because of these differences in PRR, recognition of fungal PAMPs by human and murine DCs, it is important to be remindful that the results of fungal experiments performed in mice might not always be applicable to humans.

The importance of TLRs has also been shown during *A. fumigatus* disease. Polymorphisms in different TLRs, Dectin-1, CARD9 and chemokines have been shown to increase susceptibility to infection in an array of immunodeficiencies (**Table 1**).[10,30,31,35,82-95] Studies performed with a cohort of 336 HSCT patients showed that polymorphisms in TLR4 can increase the risk of invasive Aspergillus infection.[10,83] Furthermore, Bochud et al. showed that the haplotype was present in two single nucleotide polymorphisms (SNPs) that resulted in a strong linkage disequilibrium that affected TLR4 function. These results were confirmed by comparing 103 Aspergillus infected patients to control patients.[83] Another study examined the association between SNP in *TLR1*, *TLR4* and *TLR6* genes and development of IA from 22 patients with IA and 105 unaffected hematopoietic stem cell transplant patients. Kesh et al. found that the mutations in *TLR1* 239G > C (Arg80 > Thr) and *TLR6* 745C > T (Ser249 > Pro) were associated with IA.[31] The role of TLRs during infection was also assessed for susceptibility to non-invasive forms of pulmonary aspergillosis. Carvalho et al. found an association between the TLR4 mutation Asp299Gly and chronic cavitary pulmonary aspergillosis.[96] This group also found that pulmonary aspergillosis was associated with a mutation in TLR9 (T-1237C).[90]

Concluding Remarks

In this review, we highlighted the indispensable role of DCs in the antifungal response. DCs are responsible for sensing the fungal pathogen via their PRRs, secreting cytokines and chemokines into the environment, capturing fungal particles by phagocytosis and presenting antigens to T cells to induce an adaptive immune response. Great advances have been done over the last three decades in identifying the receptors involved in host responses to medically important fungi, which have great morphological diversity. However, there is a pressing need for the development of new antifungal treatments to combat the increasing number of fungal infections and the increase in drug-resistant fungal species. Identifying additional receptor and signaling pathways in DCs involved in initiating and regulating T cell responses against pathogenic fungi will provide valuable information about disease development. One group of PRRs that have received scarce attention, the SRs, might collaborate with TLRs and/or CLRs to detect fungal PAMPs. Indeed, the SRs CD36 and SCARF1 were shown to recognize *C. neoformans*.[20] However, the work on these SRs was performed on macrophages. Further understanding the mechanisms employed by DCs to recognize and kill fungal pathogens as well as dissecting the pathways involved in the antifungal response could lead to the development of antifungal vaccines and immune-boosting biological agents.

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