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## C-type Lectin Receptors Orchestrate Anti-Fungal Immunity

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### Abstract

Immunity to pathogens critically requires pattern recognition receptors (PRR) to trigger intracellular signaling cascades that initiate and direct innate and adaptive immune responses. For fungal infections, these responses are primarily mediated by members of the C-type lectin receptor family. In this review, we highlight recent advances in our understanding of the roles and mechanisms of these multifunctional receptors, explore how these PRR orchestrate anti-fungal immunity, and briefly discuss progress in the use of these receptors as targets for anti-fungal and other vaccines.

### Introduction

Fungi are ubiquitous; we inhale several hundreds of *Aspergillus* spores each day, most of us are colonized with *Candida* and other fungal species, and in our lifetimes we will be exposed to hundreds of potentially infective fungal species<sup>1</sup>. With the prevalence of these microorganisms and relatively low incidence of pathogenicity, it is easy to overlook their threat to public health. In reality, however, fungi are robust pathogens that when given the opportunity to cause infection, particularly in immune-compromised individuals, establish lifelong or life-threatening diseases for which current diagnostic techniques and treatment options are unacceptably limited<sup>1</sup>. Dermatological infections of the skin, nails, and mucosa occur in an estimated 25% of the worldwide population and although the incidence of invasive fungal infections is considerably less, they are of greater concern due to their extremely high mortality rate<sup>1</sup>. Cryptococcal meningitis, disseminated candidiasis, and invasive pulmonary aspergillosis, for example, can result in 30-80% mortality during treatment and are 100% fatal if the diagnosis is missed<sup>1</sup>. Worryingly, recent decades have seen drastic increases in the incidence of invasive fungal infection, which is due primarily to modern medical practices, such as immunosuppressive therapy, and the HIV/AIDS pandemic.

The ability of healthy individuals to cope with the continual exposure to fungal pathogens, indicates that our immune system has effective mechanisms for preventing infections with these organisms. Although our understanding of these mechanisms has lagged behind those of other pathogens, substantial progress has been made over the last few years, and it is hoped that we will ultimately be able to use our growing knowledge to develop novel immunotherapeutic approaches for the treatment of these devastating diseases. One fundamental insight was the realization that C-type lectin receptors (CLR) play central roles in immunity to fungal pathogens. In this review, we will highlight the importance of CLR in antifungal immunity and explore the roles and mechanisms utilized by these receptors to induce and modulate innate and adaptive responses. We will also demonstrate how these

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receptors can collaborate with other PRR and discuss strategies used to target these receptors to drive tailored immune responses for vaccines.

## The key role of CLRs

To date, four families of PRR have been shown to recognize pathogens and are capable of inducing cellular responses: the Toll-like (TLR), Nod-like (NLR), RIG-I like (RLR) and CLR receptor families. The RLR and NLR are not thought to contribute directly to fungal recognition, although certain NLRs can be activated by fungi through unknown mechanisms, as discussed below. The TLRs are the best-characterized family of PRR with regards to other types of pathogens, and they also have been implicated in fungal recognition. Mice lacking MyD88, a central signaling adaptor utilized by many TLRs (but also IL-1R) are susceptible to infections with several fungal species, including *Candida albicans*, *Paracoccidioides brasiliensis*, *Aspergillus fumigatus* and *Cryptococcus neoformans*. Furthermore, a number of TLRs have been implicated in fungal recognition, including TLR1, TLR2, TLR4, TLR6, TLR7 and TLR9 (2,3). However, there is contradictory evidence surrounding the individual role of these PRRs, particularly in mouse models, which may be due to variable recognition of different isolates of the same fungal pathogen, as shown for *C. albicans*<sup>4</sup>. Polymorphisms in TLRs have also been linked to human susceptibility in the context of immunosuppression<sup>5</sup>, but immunocompetent individuals which lack MyD88 and other critical downstream signaling components do not show a predisposition to fungal diseases<sup>6</sup>. Never the less, there is emerging evidence that the interaction of TLRs with other PRR is an integral component of anti-fungal immunity (discussed below).

In contrast to the TLRs, CLR and their signaling pathways are essential for anti-fungal immunity. CLR are part of a heterogeneous superfamily of soluble and transmembrane proteins defined by a characteristic C-type lectin domain<sup>7</sup>, and they bind to most, if not all, fungal species that cause disease in humans. These receptors recognize the major carbohydrate structures that are found in fungal cell walls, including  $\beta$ -glucan and mannan<sup>8</sup> (Figure 1). Interestingly, no PRR has yet been identified which recognizes chitin, another major cell wall-component which has demonstrable immunomodulatory activities<sup>9</sup>.

Of particular interest are several CLR which can induce intracellular signaling upon fungal recognition, including Dectin-1, Dectin-2, the mannose receptor (MR), DC-SIGN, and Mincle<sup>10</sup>. While Dectin-1 recognizes  $\beta$ -glucan, the other receptors bind various, largely undefined, mannose-based structures found in the mannan layer of the fungal cell wall (Figure 1). The responses mediated by these receptors include fungal binding and phagocytosis, induction of antifungal effector mechanisms, and the production of various soluble mediators, including cytokines, chemokines and inflammatory lipids<sup>2</sup>. Notably, these receptors also direct and modulate the development of adaptive immunity, particularly T<sub>H</sub>1 and T<sub>H</sub>17 responses<sup>11-17</sup> (see below).

Dectin-1, Dectin-2 and Mincle utilize the signal transduction kinase Syk, which activates MAPK, NFAT, and through the PKC $\delta$ -CARD9-Bcl10-MALT1 axis, NF- $\kappa$ B<sup>11,18-21</sup> (Figure 2). Dectin-1 signals directly via Syk, whereas Dectin-2 and Mincle couple to Syk via the Fc receptor common  $\gamma$ -chain<sup>22-24</sup>. Both Dectin-1 and DC-SIGN can activate Raf-1 kinase to modulate NF- $\kappa$ B activity, although the proximal mechanisms involved are unclear<sup>12,13</sup>. Interestingly, Dectin-1 signaling is only activated following clustering into a “phagocytic synapse”, from which the regulatory tyrosine phosphatases, CD45 and CD148, are excluded<sup>25</sup>. The signal transduction pathway utilized by the MR is as yet undefined. In mouse models, genetic deletion of these CLR (including Dectin-1, Dectin-2, Mincle, MR) and their downstream signaling components (including PKC $\delta$  or CARD9) results in

defective immunity to several fungal pathogens<sup>14,15,18,20,26-29</sup>. Importantly, in humans, polymorphisms in Dectin-1 and mutations in CARD9 have been identified that result in susceptibility to fungal infections, especially mucocutaneous candidiasis<sup>30,31</sup>. Interestingly, the phenotype of the CARD9-affected individuals was more severe than that of Dectin-1<sup>30,31</sup>, indicative of an involvement of other PRRs.

Individual CLRs can recognize many fungal pathogens and there is clear overlap in the substrate specificities of some of these receptors. Yet, there is still some specificity in recognition by these receptors, due, in part, to the exposure of different carbohydrate structures by the different fungal species or morphological forms of the same organism. For example, Dectin-1 can only recognize the yeast form of *Candida*, because exposed  $\beta$ -glucans become masked by mannan upon formation of hyphae<sup>32</sup>. Another example is the MR, which has been implicated in the recognition of most fungi *in vitro*, yet in mice this receptor appears only to be required for protective immunity to infections with *C. neoformans*<sup>29,33</sup>. Furthermore, and similar to the TLRs, CLR recognition can be fungal strain dependent, such as occurs with Dectin-1<sup>10</sup> and Dectin-2<sup>34</sup>, which has implications for our understanding of human susceptibility to these infections.

## CLR-dependent control of anti-fungal immune responses

Phagocytic cells, particularly macrophages and neutrophils, are essential elements of protective antifungal immunity, and loss of these cells or defects in their antimicrobial effector mechanisms results in susceptibility (reviewed in 2). CLR mediate many of these effector functions and promote inflammatory responses, which are critically required for controlling fungal infections<sup>10</sup>. Dectin-1, for example, induces the respiratory burst and the production of inflammatory mediators, including eicosanoids, TNF, IL-1 $\beta$ , IL-6, IL-23, CCL2, CXCL1 and CCL3<sup>10,35,36</sup>. In mouse models of infection with *C. albicans* and *A. fumigatus*, loss of Dectin-1 resulted in a failure to mount protective inflammatory responses (defective neutrophil and monocyte recruitment, defective production of cytokines such as IL-6, G-CSF etc) and a failure to control fungal growth<sup>26,37</sup>.

All of the signaling CLRs that recognize fungi (Dectin-1, Dectin-2, MR, DC-SIGN, MINCLE) are capable of inducing or modulating T<sub>H</sub>1 and T<sub>H</sub>17 responses, the latter of which is now considered to be a hallmark of antifungal adaptive immunity<sup>39</sup> (Figure 3). Although T<sub>H</sub>1 responses are essential for the control of systemic fungal infections, in part through the activation of phagocytes by IFN- $\gamma$ , T<sub>H</sub>17 responses appear to be primarily required for protection at the mucosa<sup>40,41</sup>. Indeed, various defects in T<sub>H</sub>17 immunity, including mutations in STAT1, STAT3, IL-17 and IL17RA have been linked to susceptibility to mucocutaneous infections in man, especially chronic mucocutaneous candidiasis (CMC)<sup>42-46</sup>. Furthermore, other diseases characterized by susceptibility to CMC, such as autoimmune polyendocrine syndrome 1, are also associated with alterations in T<sub>H</sub>17 immunity<sup>47,48</sup>. How T<sub>H</sub>17 responses drive protection at the mucosa is unclear, but they are thought to involve IL-17-mediated neutrophil recruitment and IL-22-mediated induction of antimicrobial peptide production by epithelial cells<sup>41</sup>. T<sub>H</sub>17 responses may also be involved in controlling systemic infections with some fungi, such as *Candida* (see Saijo *et al*, 2010<sup>14</sup> for an example), although there is evidence to suggest that these responses may contribute to pathology and susceptibility in certain settings<sup>49</sup>.

CLRs and their signaling pathways play essential but varied roles in the development of these antifungal immune responses. Notably, CARD9 deficiency renders both mice and humans susceptible to infection with *Candida* and results in ablated T<sub>H</sub>17 and altered T<sub>H</sub>1 responses<sup>11,31</sup>. Reduced T<sub>H</sub>17 responses also correlated with susceptibility to mucocutaneous infections in Dectin-1-deficient humans<sup>30</sup>. In mice, deficiency of Dectin-1

or Dectin-2 results in susceptibility to infection with *Candida*, but only loss of Dectin-2 resulted in significant alterations in T<sub>H</sub>17 responses<sup>14,15</sup>. Loss of both Dectin-1 and Dectin-2, however, also led to profound reductions in T<sub>H</sub>1 responses, further demonstrating the importance of receptor cooperation<sup>15</sup>. Interestingly, Dectin-2 is capable of inducing T<sub>H</sub>2 immunity in response to house-dust mite allergens<sup>50</sup>, but whether this receptor, or other CLRs, are able to induce this type of response to fungi needs to be ascertained, as T<sub>H</sub>2 immunity is generally considered to contribute to fungal susceptibility<sup>40</sup>.

There have also been significant insights into the mechanisms that are utilized by CLRs to drive adaptive immunity. Stimulation of Dectin-1, for example, induces dendritic cell (DC) maturation and the expression of polarizing cytokines, such as IL-1 $\beta$ , IL-6 and IL-23, which favor T<sub>H</sub>17 differentiation<sup>11</sup>. Furthermore, Dectin-1 stimulated DC were able to convert a subset of Treg cells into IL-17 producers<sup>51</sup>, and Dectin-1 (along with TLR2) could amplify MR-induced T<sub>H</sub>17 responses<sup>17</sup>. The activation of the NF- $\kappa$ B subunit, c-Rel, by Malt1 (which forms a complex with CARD9 and Bcl-10, discussed above) induces the production of IL-1 $\beta$  and IL-23, and this is essential for Dectin-1 and Dectin-2-mediated T<sub>H</sub>17 differentiation<sup>34</sup>. In fact, Dectin-2 appears to selectively activate c-Rel<sup>34</sup>, whereas Dectin-1 also activates other NF- $\kappa$ B subunits, including the non-canonical RelB, promoting both T<sub>H</sub>1 and T<sub>H</sub>17 responses *in vitro*<sup>12,34</sup>. However, during pulmonary infection with *Aspergillus*, Dectin-1 actively suppresses IL-12 and IFN- $\gamma$  production, favoring T<sub>H</sub>17 differentiation<sup>52</sup>.

CLRs can also influence the function of  $\gamma\delta$  and  $\lambda$ NKT cells (Figure 3).  $\gamma\delta$  T cells are potent innate sources of IL-17 and produce this cytokine in response to IL-23 and IL-1 $\beta$  without TCR triggering<sup>53</sup>. Importantly, this IL-17 is produced in large amounts and prior to the development of adaptive T<sub>H</sub>17 responses<sup>53</sup>. CCR6<sup>+</sup>  $\gamma\delta$  T cells express TLR1, TLR2 and Dectin-1, and triggering of these receptors directly induced IL-17 production in these cells; a response which could be amplified by IL-23 (ref 54). *C. albicans* hyphae, but not yeast, are able to recruit and stimulate  $\gamma\delta$  T cells *in vivo*<sup>54</sup>.  $\lambda$ NKT cells, in contrast, do not respond directly to fungi, although they are required for the control of fungal pathogens *in vivo*<sup>55,56</sup>. Here, IL-12 production by DC, following stimulation of Dectin-1 or TLRs, enabled CD1d-restricted self-reactive  $\lambda$ NKT cells to produce IFN- $\gamma$ <sup>56</sup>. Although Dectin-1 normally suppresses IL-12 production by DC, as discussed above, co-culture with  $\lambda$ NKT cells potently restored production of this cytokine<sup>56</sup>. Such  $\lambda$ NKT responses could be initiated by several fungal species, including *A. fumigatus*, *C. albicans*, *Histoplasma capsulatum* and *Alternaria alternata*<sup>56</sup>. Thus, the CLR-mediated responses of  $\gamma\delta$  and  $\lambda$ NKT cells may represent key early steps in the development of protective anti-fungal immune responses.

## CLR and TLR collaboration

The recognition of intact pathogens involves multiple PRR and we are just starting to understand the “crosstalk” that can occur between these receptors<sup>57</sup>. As we have seen, fungi are recognized by several CLR and TLR, all of which are required for optimal antifungal responses<sup>58</sup>, and there are now several examples where direct interactions between these receptor families have been demonstrated to occur. Indeed, collaborative responses induced by Dectin-1 and TLR-2 were one of the first such interactions described<sup>59,60</sup>. Dectin-1 can collaborate with multiple MyD88-coupled TLRs to synergistically induce many cytokines, including TNF, IL-10 and IL-23, whilst repressing others, such as IL-12<sup>61-64</sup>. Other examples include MR-mediated production of IL-17, which was dependent on TLR2 and Dectin-1, and DC-SIGN, which does not directly induce cytokine responses but interacts with multiple TLRs to augment proinflammatory responses to fungi<sup>13,17</sup>. How these collaborative responses are mediated is still unclear, but may involve physical interactions upon ligand binding and modification of intracellular signaling cascades, by inclusion of components such as Raf-1, for example<sup>13,65,66</sup>. Having a better understanding of these

mechanisms are likely to reveal novel targets for pharmacotherapy and the development of vaccine adjuvants.

The importance of PRRs crosstalk in the development of protective anti-fungal immunity is exemplified by our recent work with *Fonsecaea pedrosoi*. This pathogen is one of the main causative agents of chromoblastomycosis, a severe and chronic fungal disease of the skin which is very difficult to treat<sup>67</sup>. Notably, *F. pedrosoi* was recognized by CLRs, including Mincle, but was not detected by TLRs<sup>68</sup>. The lack of co-stimulation of both PRR pathways resulted in defective inflammatory responses<sup>68</sup>. However, exogenous administration of purified TLR ligands restored the cooperative inflammatory responses and led to pathogen clearance in mouse models, responses which were dependent on signaling cascades mediated through both Syk/ CARD9 and MyD88 pathways<sup>68</sup>. Remarkably, a similar approach also appears to work in humans; the topical application of TLR agonists to chromoblastomycosis lesions resulted in a rapid resolution of the infection when tested in a small group of patients (GDB unpublished results). Such defects in PRR cooperativity may also underlie chronic infections caused by other fungi, including *Pneumocystis*. In fact, treatment with heat-killed *E. coli* has been shown to clear *P. carinii* infection in mice, in part through the restoration of inflammatory responses<sup>69</sup>.

## Fungi, CLRs and the inflammasome

The inflammasome is a cytoplasmic proteolytic multimeric protein complex, involving NLRs and several adaptors, which is required for the processing and activation IL-1 $\beta$  and IL-18 in response to pathogens<sup>70</sup>. Both cytokines are essential for protective anti-fungal immunity, particularly for driving the development of anti-fungal T<sub>H</sub>17 and T<sub>H</sub>1 responses<sup>71</sup>. Several inflammasome components are implicated in mediating these responses to fungi, including the adaptor ASC (associated speck-like protein), caspase-1 and two NLRs (NLRP3 and NLRC4)<sup>71-76</sup> (Figure 4). Both NLRs are required for controlling mucosal infections with *Candida*, but only NLRP3 is involved in preventing subsequent dissemination of this pathogen<sup>75,77</sup>. While CLRs and TLRs can induce pro-IL1 $\beta$  in response to fungi, how the NLRs actually sense these pathogens to trigger caspase-1 activation is still unclear<sup>75</sup>. Activation of the NLRP3 inflammasome in response to both *A. fumigatus* and *C. albicans* requires Syk kinase, as well as the respiratory burst and potassium efflux, which is suggestive of a direct involvement of CLRs<sup>72,76</sup>.

More recently, a non-canonical inflammasome has been identified whose functioning is completely dependent on Dectin-1<sup>78</sup> (Figure 4). Here Dectin-1-mediated recognition of fungi induces both pro-IL1 $\beta$  and production of IL-1 $\beta$  through caspase-8 activation<sup>78</sup>. Syk-dependent signaling from this receptor induces a CARD9-Bcl-10-MALT1 scaffold which drives NF- $\kappa$ B activation, as described before, but this scaffold can also associate with ASC and caspase-8 to form the non-canonical inflammasome<sup>78</sup>. Unlike the NLR inflammasomes, activation of the caspase-8 inflammasome did not require particle internalization. In DC, various strains of *A. fumigatus* and *C. albicans* appeared to induce IL-1 $\beta$  primarily through this pathway, although some strains also induced the caspase-1 pathway in these cells<sup>78</sup>.

## Enhancing vaccine efficacy

CLRs, especially those limited to particular DC subsets, have been of interest as vaccine targets. One approach has been antibody-mediated targeting of these receptors<sup>79,80</sup> and Dectin-1, Dectin-2, MR and DC-SIGN have all been examined in this way and shown to variably enhance CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses to experimental antigens<sup>81-84</sup>. However, any direct contribution of these receptors to the subsequent immune responses was not examined. Another strategy has been to use carbohydrate ligands of CLR to drive vaccine responses<sup>85,86</sup>. This has been tested with several carbohydrates, including various mannose-

based ligands aimed at targeting the MR and DC-SIGN (although the actual receptor specificity in these studies is always questionable), as well as  $\beta$ -glucans aimed at targeting Dectin-1. In all cases, like antibody-mediated targeting, the complexing of these antigens with carbohydrates enhanced CD4<sup>+</sup> and CD8<sup>+</sup> T-cell responses<sup>80,87</sup>. Remarkably,  $\beta$ -glucan particles have also been used to systemically target macrophages following oral administration, but in this case complexed with siRNA<sup>88</sup>.

There has also been considerable interest in using these carbohydrates to develop anti-fungal vaccines, for which there is a desperate need as there are currently no vaccines that are available clinically<sup>1,89</sup>. Several approaches have been tested, including, for example, a conjugate vaccine composed of the  $\beta$ -glucan laminarin fused to diphtheria toxoid<sup>90</sup>. This vaccine induced anti- $\beta$ -glucan antibodies which were protective against a range of fungi including *Candida*, *Aspergillus* and *Cryptococcus*<sup>90,91</sup>. Very recently, the particulate  $\beta$ -glucan, curdlan, was shown to act as a T<sub>H</sub>17-polarizing adjuvant when used with a novel epitope from *C. albicans*, which provided protection against infection with several species of *Candida*<sup>92</sup>. Interestingly, the acquisition of vaccine immunity using a live attenuated pathogen, *Blastomyces dermatitidis*, also required T<sub>H</sub>17 immunity; a response that was induced through MyD88 but not Dectin-1, although the role of other CLRs was not examined<sup>93</sup>. Mannose-based anti-fungal vaccines have also been tested in various models with various degrees of success, although mannosylation notably was essential for driving effective T cell responses against a recombinant *C. neoformans* protein<sup>85,94</sup>.

## Conclusions

The data reviewed here highlight the central role of CLR in anti-fungal immunity. These receptors are essentially required for the binding and uptake of fungi by phagocytes, the induction of antifungal effector mechanisms, the production of inflammatory mediators, and the direction and modulation of adaptive immune responses. While the functions of CLR have been extensively studied in myeloid cells, it is likely that these receptors are also expressed in the epithelium. Indeed, a recent study has shown that expression of Dectin-1 can be induced in bronchial epithelial cells *in vitro* and stimulate antimicrobial and inflammatory responses in response to *Aspergillus*<sup>95</sup>. Having a better understanding of the function of CLR on non-myeloid cells is likely to provide important insights into protective host responses, given that the majority of our normal interactions with fungi occur at the epithelium<sup>96</sup>.

The ability of CLRs to drive adaptive immunity, particularly T<sub>H</sub>17 responses, has been of particular interest as these hallmark responses are essential for protection against fungal infections. The ability of CLR to stimulate adaptive immunity also represents a strategy for vaccination, and methodologies that utilize the antigenicity and adjuvanticity of CLR could provide powerful solutions for protecting against fungal and other diseases in the future. Further enhancement could potentially be achieved by taking advantage of the synergism that these receptors display when co-stimulated with other PRRs, particularly the TLRs.

Most CLR can recognize endogenous ligands (although few of these ligands have actually been identified) and these receptors are therefore likely to also have homeostatic roles. One of the best examples is the MR, which has a well established role as a regulator of serum glycoprotein homeostasis<sup>97</sup>. Furthermore, while largely associated with fungi, there is also evidence that CLR are involved in immunity to several other pathogens. DC-SIGN, MR, Dectin-1, Dectin-2 and Mincle, for example, have all been implicated in anti-mycobacterial immunity<sup>98</sup>. Considering the number of CLR in our genomes and their conservation during evolution<sup>99</sup>, it would not be surprising if these receptors are found to be far more extensively involved in anti-microbial immunity in the future.

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discovery of mutations in CARD9 in humans which result in susceptibility to fungal infections (see Glocker et. al., 2009<sup>31</sup>)

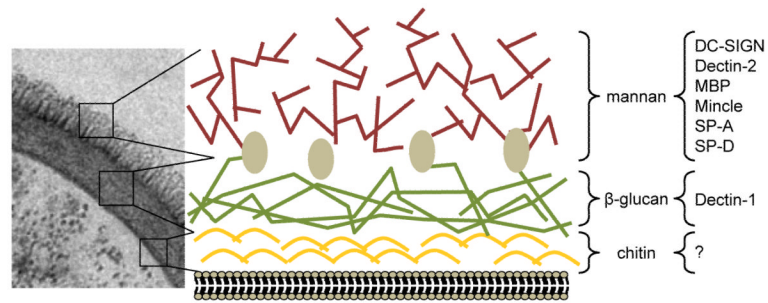
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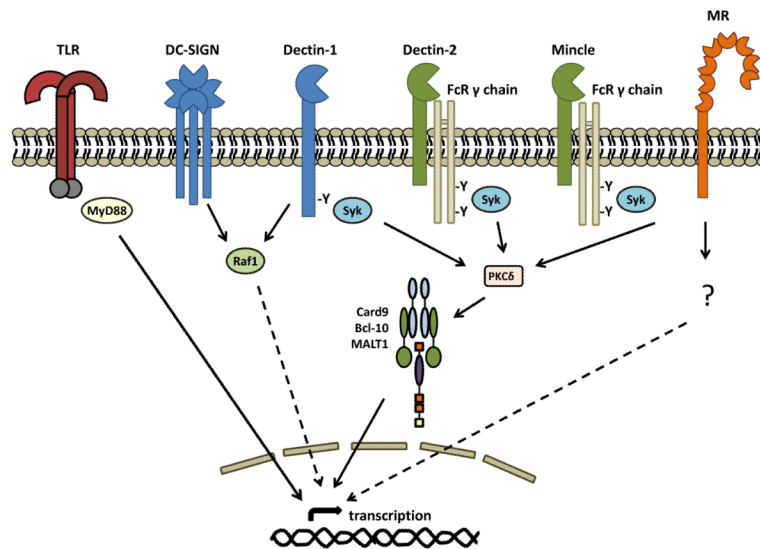
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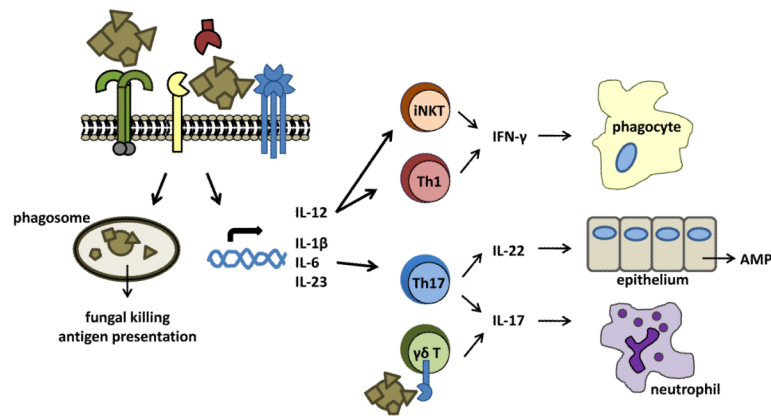
**Figure 1.**

Structure of the fungal cell wall. By EM, the various carbohydrate-rich layers of the fungal cell wall (in this example *C. albicans*) can be observed, which consist of mannan (mannosylated proteins),  $\beta$ -glucan and chitin, as indicated. Although providing a rigid framework, which gives these pathogens their shape and protection from the environment, the cell wall is a dynamic structure which changes significantly, particularly during the morphological transitions that many fungi can undergo (yeast to hyphae, for example). Furthermore, some of the internal components, such as  $\beta$ -glucans, can be exposed on the fungal surface in specific areas, such as the bud scar in *C. albicans*<sup>32</sup>. The composition of the cell wall also varies between different fungal species. Several CLR have been identified which recognize these cell-wall structures, including transmembrane and soluble CLRs. The latter group, consisting of Surfactant Protein (SP)-A, SPD and mannose-binding lectin (MBP), opsonise fungi and facilitate their recognition, but were not discussed in the text (For a review of these molecules see Vautier et al. 2012<sup>38</sup>). The micrograph was kindly provided by Jules Ene and Neil Gow.



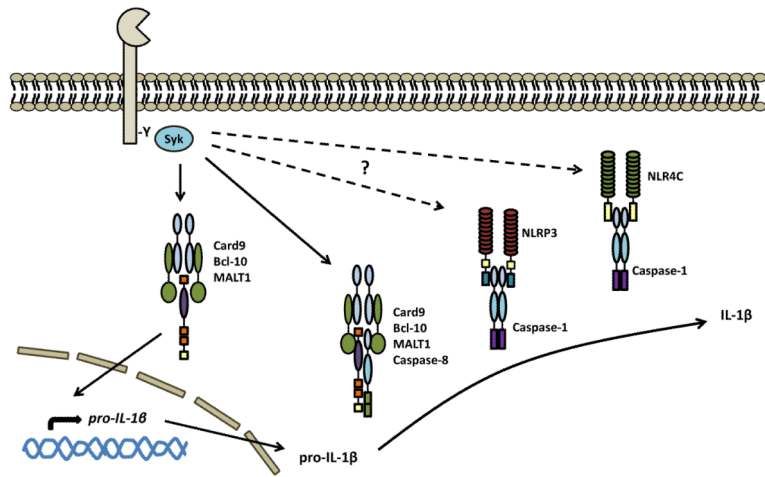
**Figure 2.**

Transmembrane CLR involved in antifungal immunity and their intracellular signaling pathways. Dectin-1, Dectin-2 and Mincle induce intracellular signaling via tyrosine (Y)-based activation motifs (immunoreceptor tyrosine-based activation motifs or ITAMs) which recruit and activate Syk-kinase either directly, or indirectly through the Fc $\gamma$ R adaptor chain. Signaling through protein-kinase C (PKC) $\delta$ , this pathway activates the Card9-Bcl10-Malt1 complex inducing gene transcription and the production of various inflammatory mediators. DC-SIGN and Dectin-1 can signal via the Raf-1 kinase pathway which modulates (dotted line) other signaling pathways, including those induced by the Toll-like receptors (TLR) and the Dectin-1/ Syk pathway. The mannose receptor (MR) can also induce intracellular signaling, but the mechanisms involved are unknown. CLR signaling can collaborate with that of the TLR (red bi-arrow), to synergistically induce or repress the induction of various cytokines and chemokines. CLR can also mediate fungal phagocytosis and induction of anti-microbial effector mechanisms (not shown).



**Figure 3.**

Integration of CLR-mediated signaling directs adaptive immunity. CLR-mediated recognition of fungi drives their uptake and killing by phagocytes, and directs the development of protective Th1/Th17 responses. Induction of IL-12 drives IFN- $\gamma$  production by Th1 and  $\alpha$ NKT cells, which is critically required for the activation of phagocytes. Remarkably, production of IFN- $\gamma$  by self-reactive  $\alpha$ NKT cells occurs following CLR-mediated induction of IL-12 on antigen-presenting cells. On the other hand, induction of IL-1 $\beta$ , IL-6, and IL-23 promotes Th17 differentiation, which drives the production of IL-17 and IL-22. These cytokines are critically required for neutrophil recruitment and epithelial antimicrobial peptide (AMP) production and provide protection against fungal infections, particularly at the mucosa. Notably, the production of IL-17 can also be directly induced by CLR-mediated signaling on  $\gamma\delta$  T cells, without TCR triggering.



**Figure 4.**

CLRs mediate inflammasome activation. Fungi can activate the NLRP3 and NLRC4 inflammasomes, inducing the caspase-1-mediated cleavage of pro-IL-1 $\beta$  and production of bioactive IL-1 $\beta$ . While CLR, such as Dectin-1, can drive the induction of pro-IL-1 $\beta$ , it is unclear how the intracellularly-located NLR actually sense fungi. Activation of these receptors may directly involve CLR, as this process was found to require Syk kinase (as well as fungal uptake, the respiratory burst and potassium efflux). More recently, Dectin-1 has been shown to be able to activate the noncanonical caspase-8 inflammasome, which interacts directly with the Card9-Bcl-10-MALT1 complex. Activation of caspase-8 by recruitment to this signaling complex results in the cleavage of pro-IL-1 $\beta$ . Assembly of these inflammasomes also involves other components, including ASC (not shown).