The role of pattern recognition receptors in the innate recognition of Candida albicans

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Candida albicans is both a commensal microorganism in healthy individuals and a major fungal pathogen causing high mortality in immunocompromised patients. Yeast-hypha morphological transition is a well known virulence trait of C. albicans. Host innate immunity to C. albicans critically requires pattern recognition receptors (PRRs). In this review, we summarize the PRRs involved in the recognition of C. albicans in epithelial cells, endothelial cells, and phagocytic cells separately. We figure out the differential recognition of yeasts and hyphae, the findings on PRR-deficient mice, and the discoveries on human PRR-related single nucleotide polymorphisms (SNPs).

Candida Albicans and Host Pattern Recognition Receptors (PRRs)

Humans encounter fungi every day, while only a few fungal species may cause infections. In the past 3–4 decades, with the advent of organ transplantation, haematopoietic stem cell transplantation, immunosuppression, chemotherapy, and the dissemination of HIV, the incidence of fungal infections has been rising. Presently, fungi have become the fourth main cause of hospital-acquired infections. Among the fungal pathogens, Candida spp is prominent, and Candida albicans is a major pathogen.

C. albicans is a commensal fungus that colonizes on gastrointestinal/genital mucosa of mammals without causing disease in most healthy individuals, but in case the host defense is weakened under certain circumstances can C. albicans become pathogenic. C. albicans may cause 2 types of infections: superficial infections (such as oral or vaginal candidiasis), and systemic infections (such as life-threatening bloodstream infections/candidaemia). Polymorphological transition is the widely known virulence trait of C. albicans, and the fungus can grow as white-phase yeast cells, GUT cells, opaque-phase cells, gray-phase cells, chlamydospores, ture hyphae, and pseudohyphae. C. albicans normally grows in white-phase yeast form when it colonizes on mammalian mucosal surfaces. Yeast-to-hypha transition usually indicates a pathogenic status. In accordance, the yeast form is tolerated by the host immune system, while the invasive hyphal form may induce robust immune responses.

The cell wall of C. albicans provides targets for host immune system to sense the pathogen and trigger immune response. The cell wall is a matrix of 3 components: chitin, glucans, and mannans. Chitin locates at the most inside of the cell wall and covalently linked to β-glucan. Chitin and β-glucan form hydrogen bonds with each other to construct a tough 3-dimensional inner layer network of microfibrils. The outer layer is constituted by O-linked and N-linked mannosyl polymers (mannans), with highly glycosylated cell wall proteins attached. Although the basic components of the cell wall are similar, the precise structure and chemical properties are different in different forms of C. albicans, which may facilitate host immune system to recognize different cell forms.

Host innate immunity to C. albicans critically requires pattern recognition receptors (PRRs). PRRs is fundamental in discriminating self from non-self via recognizing vital conserved chemical signatures of pathogens, called pathogen-associated molecular patterns (PAMPs). As for C. albicans, amounts of cell wall components are PAMPs, including β-glucan, mannans, and cell wall proteins. Besides, some intracellular components, such as specific DNA and RNA can also be recognized as PAMPs. For all kinds of pathogens, 4 major classes of PRRs have been identified: Toll-like receptors (TLRs), C-type lectin receptors (CLRs), Nod-like-binding oligomerization domain (NOD)-like receptors (NLRs) and retinoic-acid-inducible gene I (RIGI)-like receptors (RLRs). TLRs can be divided into cell-membrane-associated receptors (TLR1, TLR2, TLR4, TLR5, and TLR6) and endosomal receptors (TLR3, TLR7, TLR8, and TLR9). CLRs are mainly membrane-bound receptors. NLRs and RLRs are both intracellular receptors. In addition, some circulating proteins, such as mannose-binding lectin (MBL), are also considered as PRRs. TLRs and CLRs play major roles for the recognition of C. albicans PAMPs; NLRs are also involved in the recognition; while little is known about the role of RLR in the recognition of C. albicans PAMPs up to now (Table 1). TLR2, TLR4, and TLR9 directly recognize phospholipomannan (PLM), O-linked mannosyl residues, and CpG DNA, respectively in C. albicans. TLR7 is required for the recognition of single-stranded RNA of C. albicans. Of note, some CLRs are involved in the...
recognition of \textit{C. albicans}, including Dectin-1, Dectin-2, Dectin-3 (originally named murine macrophage C-type lectin, MCL), the dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN), the macrophage mannose receptor (MR), Galectin-3, and the macrophage-inducible C-type lectin (Mincl). Dectin-1 recognizes \((1,3)-\text{glucan}\), while the rest CLRs recognize different mannose-relative structures. MBL is considered a soluble CLR. It mediates opsonization and uptake of \textit{Candida} by phagocytes via binding to both \textit{Candida} mannan and the C1q receptor on the surface of phagocytes. NLRs are involved in the recognition of intracellular pathogens. Interestingly, NOD1 and NOD2, 2 main NLRs important in bacterial peptidoglycans recognition, are not involved in the recognition of \textit{C. albicans}. Nevertheless, NLRP3 plays an important role in \textit{C. albicans}-induced inflammation. Several other NLRs, such as NLRP10 and NLRC4, are also revealed to be related to anti-\textit{C. albicans} responses. NLRP10 is required to control the disseminated \textit{C. albicans} infection, and NLRC4 functions within the mucosal stroma to control oral \textit{C. albicans} infection.

After recognizing \textit{C. albicans} PAMPs, the recognition signals can be transduced through multiple pathways (Fig. 1). In TLRs signaling pathway, 2 crucial signaling adaptors, MyD88 and TRIF (also known as TICAM-1) are involved. MyD88 binds to almost all TLRs except TLR3. TRIF binds to TLR3 and TLR4. The activation of MyD88 and TRIF lead to MyD88-dependent pathway and the MyD88-independent (TRIF-dependent) pathway respectively. In contrast, CLRs are mostly associated with the spleen tyrosine kinase (SYK) (Fig. 1), which activates MAPK (mitogen-activated protein kinase). Dectin-1 signals are associated with Syk directly, while Dectin-2 and Mincl couple Syk via the common \(\gamma\)-chain of Fc receptor. Of note, in the Syk signaling pathway, CARD9 plays a crucial role to induce cytokine induction. Raf-1 is another kinase involved in CLRs signal transduction, which can be activated by Dectin-1 or DC-SIGN. Interestingly, most PRRs, if not all, activate the transcription factor NF-\(\kappa\)B or IRE3/7 to induce immune responses. (Fig. 1).

Innate immunity is the first defense of host against \textit{C. albicans}, where several types of cells work against the pathogen: epithelial cells, endothelial cells, and phagocytic cells. These types of cells work in cooperation to sense, kill, and present antigens of the invasive \textit{C. albicans}. They express specific PRRs, which determine their specific interactions with \textit{C. albicans}. Here, we summarize the role of PRRs in recognition of \textit{C. albicans} in each cell type.

### PRRs of Epithelial Cells

Mucosal epithelial cells are engaged in the first line of anti-fungal defense. Mucosal epithelial cells not only function as a passive physical barrier to restrain pathogen from invading, but also sense the pathogen and trigger immune responses. As key cells in innate immunity, mucosal epithelial cells express a wide range of PRRs, including TLR1-6 and TLR8-10, Dectin-1, Galectins, and NOD1. Although epithelial cells from different sites express similar TLRs, the expression levels may be different. For example, TLR2 mRNA is most abundant in human female genital tract, fallopian tubes and cervical tissues, followed by the endometrium and ectocervix. The expression of TLR4 in the epithelial cells of the human female genital tract is controversial. Some observed the presence of TLR4, while others reported the absence. In normal human intestinal epithelial cells, TLR2 and TLR4 are expressed at low level. The differential expression of PRRs at different sites may be related to the different microenvironments and the different roles of PRRs. For example, TLR2 is revealed to be associated with epithelial growth, survival, and repair. Of note, although epithelial cells express a wide range of PRRs, not all PRRs are engaged in \textit{C. albicans} recognition, and only certain TLRs and CLRs on epithelial surfaces are reported to be engaged. After culturing epithelial cells with \textit{C. albicans} yeasts, TLR2, TLR4, TLR6, and TLR9 genes’ expression were activated. Nevertheless, the activation of human epithelial cell immune response is not likely to be initiated by TLRs, as blocking of these receptors with antibodies didn’t alter the epithelial cytokine profile. Dectin-1 and Dectin-2 are 2 confirmed receptors for \textit{C. albicans} recognition. However, only Dectin-1 is found expressed in epithelial cells. Although some studies on other fungal pathogens have revealed the up-regulation of Dectin-1 in human epithelial cells upon fungal infection, few studies work on the role of Dectin-1 in \textit{C. albicans} recognition in epithelial cells up to now.

MAPK and NF-\(\kappa\)B pathways are crucial in epithelial cells response to \textit{C. albicans}. MAPK pathway is revealed to identify the invasive \textit{C. albicans}, while NF-\(\kappa\)B pathway is in charge of anti-fungal responses. The activation of the pathways would lead to series of biological effects, and the effects can be divided into 2 categories. One is to activate weak but direct anti-fungal defense by secreting antimicrobial peptides (such as \(\beta\)-defensins and LL-37). The antimicrobial peptides can recruit immune cells to sites of infection/proliferation and additionally can bind

### Table 1. Pattern recognition receptors and \textit{C. albicans} PAMPs

| Family | Receptor | PAMP | References |
|--------|----------|------|------------|
| TLRs   | TLR2     | Phospholipomannan | [22] |
|        | TLR4     | O-linked mannans | [24] |
|        | TLR7     | Single-stranded RNA | [26,27] |
|        | TLR9     | \(\text{Cpg DNA}\) | [25] |
| CLRs   | Dectin-1 | \(\beta-(1,3)-\text{glucan}\) | [28] |
|        | Dectin-2 | High-mannose structures | [110-112] |
|        | Dectin-3 | \(\alpha\)-mannan | [29] |
|        | Mannose receptor | N-linked mannan | [24] |
|        | MINCLE   | \(\alpha\)-mannan | [114] |
|        | Galectin-3 | \(\beta-(1,2)-\text{mannosides}\) | [107,108] |
|        | DC-SIGN  | N-linked mannan | [151] |
| NLRs   | NLRP3    | \(\beta\)-glucan | [33] |
|        | NLRC4    | Unknown | [39] |
|        | NLRP10   | Unknown | [38] |
| Others | Mannose-binding lectin | Mannan | [30] |
|        | SCARF1   | \(\beta\)-glucan | [121] |
|        | CD36     | \(\beta\)-glucan | [121] |
|        | Complement Receptor 3 | \(\beta-(1,3)-\text{glucan}\) | [116] |
to PRRs and influences responses. The other is to secrete a profile of pro-inflammatory cytokines and chemokines, which facilitates epithelial cells to cooperate with other types of cells at mucosal surface, including dendritic cells and neutrophils. C. albicans stimulates epithelial cells to produce IL-1α/β, IL-6, GM-CSF, GM-CSF, TNF-α, and IL-8, while IL-12, IFN-γ, IL-4, and IL-13 are not included. For example, IL-8 was released at high level by C. albicans-infected human oral epithelial cells and it actively recruits neutrophils into mucosal tissues, leading to an anti-fungal defense. In primary human keratinocytes, IL-22 plus TNF-α effectively inhibit the growth of C. albicans and maintain the survival of epithelia. In addition, human vaginal epithelial cells could express S100 calcium-binding proteins to recruit polymorphonuclear neutrophils (PMNs) to the C. albicans-infected vagina. Recently it was shown that S100A8 alarmin is sufficient, but
not necessary, to induce PMN migration during experimental vaginal candidiasis. 87

**PRRs of Endothelial Cells**

Endothelium forms a semi-permeable barrier between blood/lymph and the surrounding tissues. Once hematogenously disseminated candidiasis initiates, *C. albicans* must adhere to and invade the endothelial cell lining to infect the deep tissues. 88 Endothelial cells express many PRRs. In detail, immune responsive endothelial cells in healthy arteries express low levels of TLR2 and TLR4. 89,90 Human umbilical vein endothelial cells (HUVECs) express TLR3 and TLR9. 91-93 Human dermal microvascular endothelial cells express MR. 94 Besides, Galectin-3 was detected on cultured signaling, NF-k activation of primary human endothelial cells through TLR3 signaling. 95 The expression of Dectin-1 on endothelial cells is controversial. In contrast to its major role on phagocytic cells for fungal β-glucan recognition, Dectin-1 is generally believed not expressed by endothelial cells previously. 88,96 However, a recent study observed Dectin-1 on HUVECs. 97

*C. albicans* has a family of specialized proteins (adhesins) with agglutinin-like sequence (ALS). The family contains 8 members (Als1-7 and Als9), and Als3 is vital for *C. albicans* adherence and invasion. 11 Some studies using HUVECs revealed that the ALS proteins mediate the adherence to endothelial cells. After adherence, *C. albicans* invades endothelial cells through endocytosis. Als3 and Ssa1 on the surface of *C. albicans* hyphae bind to N-cadherin and other receptors on the surface of endothelial cell, which mediates the endocytosis. 98-100 In contrast to the ALS proteins and endocytosis, the interaction between *C. albicans* PAMPs and PRRs on endothelial cells was rarely investigated. A study revealed that *C. albicans* triggers proinflammatory gene expression in primary human endothelial cells through TLR3 signaling, NF-kB, and p38 MAPK pathways in response to *C. albicans* invasion. 96 While, CLR3 on endothelial cells rarely studied.

**PRRs of Phagocytic Cells**

Phagocytic cells, including neutrophils, monocytes/macrophages, and dendritic cells (DCs), are believed to be most effective for controlling and clearing *C. albicans* infection. Neutrophils are considered principal effector cells, followed by monocytes/macrophages. 101 Monocytes/macrophages can also present antigens, but they only play an integral role in anti-*Candida* defense in infection locations. DCs are professional antigen-presenting cells (APCs), which ingest *C. albicans* PAMPs and present antigens via major histocompatibility complex (MHC) class II molecules. Till now, most findings on the interaction between PRRs and *C. albicans* PAMPs are obtained through investigations on phagocytic cells.

**PRRs of neutrophils and monocytes/macrophages**

Neutrophils and monocytes/macrophages are effective in killing invasive fungal cells. They are rapidly recruited at the infection locations. 102-105 Monocytes mainly recognize invading fungi in circulation, expressing high levels of TLRs and moderate levels of CLRs. 21 When monocytes reside at infected tissues and differentiate into macrophages, they keep on expressing TLRs and up-regulate the expression of CLRs. 21 As the expression of PRRs in macrophages can be influenced by cytokines and some other factors, the levels of PRRs in macrophages are variable. 21 Neutrophils express TLRs, CLRs, and phagocytic receptors including complement receptor 3 (CR3) and Fcγ receptors (FcγRs). 21 Collectively, in these phagocytic cells, TLRs (including TLR2, TLR4, and TLR6), CLRs (including Dectin-1, Dectin-2, MR, Galectin-3, and Mincle), and other fungal-relevant receptors (including FcγR, CR3, CD36, and SCARF1) are expressed, which play roles in recognize various PAMPs from *C. albicans*.

Some PRRs recognize *C. albicans* mannan. MR on the surface of macrophages recognizes the N-bound mannans, 24 and TLR4 recognizes the O-bound mannans. 106 TLR2 and TLR6 interact with phospholipomannan (PLM) directly to initiate proinflammatory cytokine production in the mouse macrophage-like cell line J774. 23 Galectin-3 on the surface of murine macrophages can bind to the β-1, 2-mannosides of *C. albicans*. 107,108 In human neutrophil, Galectin-3 plays an important role in phagocytosing *C. albicans* hyphae, but not *C. albicans* yeasts. 109 Dectin-2 is another PRR for phagocytic cells to recognize *C. albicans* mannan. 110-112 By using mouse leukemic monocyte macrophage cell line RAW 264.7, Dectin-2 is found mainly involved in the recognition of *C. albicans* hyphae and induce intracellular signals through FcγR. 49 A recent study revealed that Dectin-3 recognized α-mannans on the surfaces of *C. albicans* hyphae and induced NF-κB activation in bone marrow-derived macrophages from C57B/L6 mice. 29 Dectin-3 constantly forms heterodimers with Dectin-2 for recognizing *C. albicans* hyphae. Compared to their respective homodimers, Dectin-3 and Dectin-2 heterodimers bound α-mannans more effectively, leading to potent inflammatory responses against fungal infections. 29 Another study indicated that Dectin-3 can mediate endocytosis. 113 Mincle, another C-type lectin, is expressed predominantly on macrophages. It is shown to play a role in murine macrophage responses to yeast-form *C. albicans*. 114 Similar to Dectin-2, Mincle recognizes *C. albicans* by selectively binding α-mannose with the association of FcγR. 114 In human monocyte and neutrophil, Mincle expression is up-regulated upon *C. albicans* stimulus and further immune responses are thereby regulated. 115

CR3 and Dectin-1 are revealed to recognize *C. albicans* β-glucans. CR3 is a widely expressed β2-integrin. In human kidney 293 fibroblastoid cell line, CR3 mediates recognition of both the yeast and hyphal forms of *C. albicans*. 116 Moreover, the phagocytosis of *C. albicans* by human polymorphonuclear leukocytes (PMN) is mainly mediated by CR3. 117 Dectin-1 is a myeloid-expressed receptor for β-glucans recognition and expressed systematically on phagocytic cells. On *C. albicans* yeasts, budding and cell separation may expose β-glucans, thereby Dectin-1 can recognize *C. albicans* yeasts easily. 118,119 Dectin-1 is revealed to be important for the activation of murine PMN by *Candida*. 120 Besides, some investigations indicated that CD36 and SCARF1 may bind *C. albicans* β-glucan. 121 SCARF1 is expressed on macrophages and endothelial cells. To test the ability of SCARF1 to
bind and phagocytose fungi, investigators isolated the SCARF1 cDNA from a human endothelial cell cDNA library and established a stable Chinese hamster ovary (CHO) cell line expressing SCARF1 (CHO-SCARF1). They found that CHO-SCARF1 cells bind C. albicans in a β-glucan–dependent manner. Moreover, CD36 is a class B scavenger receptor that is a sensor for endogenous molecules and microbial products that signal via TLR2. CHO-CD36 cells bind C. albicans also in a β-glucan–dependent manner. CD36-deficient macrophages showed an ~50% reduction in binding C. albicans relative to WT macrophage, and CD36−/− macrophages stimulated with C. albicans had a marked reduction in the expression of IL-1β, TNF, IL-12p40, MIP-2, MIP-1α, MIP-1β, and RANTES.

The chitin recognition receptors have also been investigated. On human peripheral blood mononuclear cells (PBMCs) and murine macrophages, purified chitin from C. albicans could block the recognition of C. albicans yeast cells. A recent study revealed that purified chitin particles derived from C. albicans led to the selective secretion of the anti-inflammatory cytokine IL-10 on murine bone marrow-derived macrophages, and NOD2, TLR9 and MR are essential fungal chitin-recognition receptors for this response.

The recognition of C. albicans by PRRs is generally thought to occur at the phagocytic cell surface and this process leads to the phagocytosis of C. albicans and the formation of an intracellular vacuole called phagosome. Dectin-1, CR3, MR, Dectin-2, and possibly TLR2 have been identified as receptors involved in phagocytosis of C. albicans. For example, Galectin-3 antibody significantly inhibited neutrophil phagocytosis of C. albicans hyphae, and exogenous galectin-3 increases phagocytosis of C. albicans yeast. Actually, PRRs not only mediate the opsonised fungi uptake, but also the recognition of C. albicans components at the phagosomes. Dectin-1 not only controls internalization of β-1,3-glucan containing phagosomes and triggers proinflammatory cytokines, but also acts as a master regulator for subsequent phagolysosomal maturation through Syk activation. TLR9 and TLR7 are both endosomal receptors, and not expressed on cell surface. TLR9 mediate the sensing of C. albicans unmethylated genomic DNA. By using TLR9 knockout (TLR9KO) macrophages, TLR9 is revealed to be activated by fungal DNA and modulate macrophage anti-fungal effect. TLR7 is required for the recognition of single-stranded RNA from C. albicans and the mice lacking TLR7 were hypersusceptible to systemic C. albicans infection. Of note, inflammasome plays an important role in antifungal immune response. Inflammasome is a cytoplasmic proteolytic multimeric protein complex expressed in myeloid cells, and consists of NLRs and several adaptors. Two NLRs, NLRP3 and NLRC4, are implicated in mediating responses to C. albicans, while only NLRP3 is involved in preventing subsequent dissemination of this pathogen. C. albicans are able to trigger proinflammatory cytokine IL-1β and IL-18 production via NLRP3 inflammasome in murine monocytes, macrophages and dendritic cells. Consistently, downregulation of NLRP3 by RNA interference strongly reduced the secretion of bioactive IL-1β. Pyroptosis is an inflammasome-mediated programmed cell death. In bone marrow-derived macrophages and murine J774 macrophages, NLRP3 can be triggered by C. albicans, leading to NLRP3-mediated pyroptosis.

As multiple PRRs are involved in the recognition of C. albicans, it is reasonable that "cross-talk" can occur between these receptors. Dectin-1 is shown to collaborate with TLR2, 4, 5, 7 or 9 to synergistically influence the secretion of many cytokines (inducing IL-23, while repressing IL-12). In human PBMCs, Dectin-1/TLR2 pathway was able to amplify MR-induced IL-17 production, a vital cytokine upon C. albicans stimulus. This finding provides an evidence for the interaction between C-type lectin receptors and TLRs. Galectin-3 on the surface of murine macrophages specifically recognizes C. albicans, which needs the association of TLR2 for signaling. Interestingly, Galectin-3 also works in association with Dectin-1 on macrophages. When macrophages expressing Dectin-1 are exposed to C. albicans mutants with increased exposure of β-glucan, the loss of Galectin-3 dramatically accentuates the failure to trigger an appropriate TNF-α response. Moreover, the collaboration in immune response may also involve other cell receptors, such as peroxisome proliferator-activated receptor (PPAR)-γ and CD44. PPAR-γ is expressed in various immune cells and acts as a transcriptional repressor to inhibit the transcription of many proinflammatory cytokines. PPAR-γ has been implicated in the negative regulation of IFN-β production in TLR3- and TLR4-stimulated peritoneal primary macrophages. CD44 is a major hyaluronan receptor distributed in different tissues and alerts cell-to-cell injury. CD44 is found to regulate TLR2-mediated immune responses in murine bone marrow-derived macrophages. The collaborations between the receptors, downstream signaling pathways, and cytokine production are complicated. More studies are needed to reveal much more underlying “cross-talk.”

After recognition of invasive fungi, neutrophils and monocytes/macrophages use a number of oxidative and non-oxidative mechanisms to kill extracellular and internalized fungi. The respiratory burst is thought to be a major anti-fungal defense mechanism. Besides producing reactive oxygen intermediates, the production of reactive nitrogen intermediates is another oxidative system possessing fungicidal activity. This system can be induced by PRRs and cytokines, leading to the killing of fungi. The interaction between phagocyte PRRs and C. albicans plays an important role in determining the cytokine and chemokine profiles. For example, Dectin-1 induces the production of inflammatory mediators, including eicosanoids, TNF-α, IL-1β, IL-6, IL-23, CCL2, CXCL1 and CCL3. Fungal recognition by Dectin-2 can induce the production of numerous cytokines, including TNF-α, IL-1Ra, IL-2, IL-10, IL-6, IL-1β, IL-12 and IL-23, and possibly cysteine leukotrienes. Similarly, fungal recognition by Mincle induces the production of cytokines, including MIP-2, KC, IL-10 and TNF-α.

**PRRs of dendritic cells (DCs)**

DCs are specific phagocytic cells, existing in tissues in contact with external environment, such as the skin and mucosal surface.
Besides ingesting and killing \textit{C. albicans}, DCs mainly act as professional antigen-presenting cells (APCs), which bridge innate and adaptive immunity by shaping the T cell response following PRR-dependent cytokine production. Only DCs are able to prime naive T cells to generate life-long memory immunity. DCs express a myriad of PRRs involved in \textit{C. albicans} recognition, including TLRs, CLRs, FcyR, and CR3. The expression of PRRs on DCs is variable in different situations. For example, immature DCs express high level of FcyR, CRs, and TLRs, while mature DCs express less. Human plasmacytoid DCs express endosomal TLR7 and TLR9, but lack the expression of TLR4.\textsuperscript{144} However, whether the differences influence the recognition of \textit{C. albicans} is rarely investigated.

The PRRs on DCs for \textit{C. albicans} recognition are similar with those on phagocytic cells. Here, we emphatically summarize the findings on DCs. TLR2 and TLR4 can recognize a 65 kDa cell surface mannoprotein (MP65) from \textit{C. albicans}.\textsuperscript{145} After the recognition via TLR2 and TLR4, DCs increase the secretion of TNF-\alpha, IL-6, IL-12 and the expression of CD14 and FcyR.\textsuperscript{145} TLR1 was indicated not involved in the recognition of \textit{C. albicans}, while TLR6 might play a role in modulating the balance between Th1 and Th2 cytokines.\textsuperscript{146} The TLR6 knock-out mice displayed a defective production of IL-10 and an increased IFN-\gamma release.\textsuperscript{146} These results indirectly suggest that DCs might regulate adaptive immunity through TLR6. Whether the phagosomal TLRs (such as TLR3 and TLR7) on DCs were involved in recognizing RNA of \textit{C. albicans} is still unclear. Nevertheless, murine conventional DCs mount a type-I IFN response against \textit{C. albicans} requiring phagosomal TLR7-mediated IFN-\beta signaling.\textsuperscript{147} Moreover, it is suggested that \textit{C. albicans} activates murine bone marrow-derived myeloid DCs through a TLR9-mediated signaling pathway.\textsuperscript{25} Dectin-1 was well characterized on DCs. It was found that Dectin-1 was high expressed on the DC cell line XS52, but less on the macrophage cell line J774.\textsuperscript{148} A recent study showed that Dectin-1 on mouse renal DCs senses \textit{C. albicans} and induces IFN-\beta production through Dectin-1-Syk-IRF5 signaling.\textsuperscript{149} Dectin-2 also contributes to DCs activation.\textsuperscript{142} Dectin-2 is important in murine immune defense against \textit{C. albicans} by inducing Th17 cell differentiation via Fcy chain and Syk-CARD9-NF-\kappaB-dependent signaling pathway.\textsuperscript{51} Although Dectin-2 was found to bind hyphal components of \textit{C. albicans} preferentially, both yeast and hyphal \textit{C. albicans} can induce Th17 differentiation.\textsuperscript{51} DC-SIGN also plays roles in the immune response to \textit{C. albicans}. It was demonstrated that DC-SIGN is able to bind \textit{C. albicans} in human monocyte-derived DCs.\textsuperscript{150} The binding was shown to be time- as well as concentration-dependent, and live as well as heat-inactivated \textit{C. albicans} were bound to the same extent.\textsuperscript{150} Interestingly, N-linked mannan, but not O-linked or phosphomannan, is specifically recognized by DC-SIGN on human DCs and directly influences the production of the proinflammatory cytokine IL-6.\textsuperscript{151} Galectin-3 on murine bone marrow-derived DCs was recently found to be able to modulate Th17 responses to \textit{C. albicans}.\textsuperscript{152} Galectin-3 is encoded by GAL3 gene. Under condition that \textit{C. albicans} was mixed with gal3+/- or gal3+/+ DCs for 3 days, and then intravenously injected into wild-type mice, the levels of IL-6, TGF-\beta, IL-23, and IL-17 in mice receiving gal3/- DCs were significantly higher than those receiving gal3+/- DCs,\textsuperscript{152} indicating the modulatory role of Galectin-3. MR is widely expressed on DC subsets and has been shown to play a role in the recognition of \textit{Candida}.\textsuperscript{153} A recent study revealed that MR promotes DCs to form “fungipod” upon contacting yeast-form \textit{Candida}. “fungipod” is a dorsal pseudopodial protrusion and phagocytic structure of DCs, and the formation of this structure is propelled by the robust actin cytoskeleton growth at the DC-yeast contact site. MR is required for the formation of “fungipod,” while Dectin-1 is not.\textsuperscript{154} Of note, not all \textit{Candida} species can induce the formation of “fungipod.” The human pathogen \textit{C. parapsilosis} induces DC fungipod formation strongly, but the response is species specific since the related fungal pathogens \textit{C. tropicalis} and \textit{C. albicans} induce very few and no fungipods, respectively. Besides, NLRC3 is also involved in \textit{C. albicans} recognition of DCs. In mouse BM-DCs, \beta-glucan can activate NLRC3 inflammasome, and this activation is dispensable for antigen specific Th1 and Th17 polarization.\textsuperscript{35}

Previously, it is a general thought that DCs have little effect on innate resistance to fungal infection. However, a recent study revealed that selective loss of Syk in DCs abrogates innate resistance to acute systemic \textit{C. albicans} infection in mice,\textsuperscript{155} which indicates that a single kinase in DCs might orchestrate a complex series of molecular and cellular events in innate resistance to \textit{C. albicans}. Actually, full protection against most pathogens requires an adaptive response, which is initiated and directed by DCs.\textsuperscript{156} DCs respond to \textit{in situ} and released \textit{C. albicans} PAMPs via PRRs (MR, Dectin-1, TLR2, Galectin-3 etc.)\textsuperscript{134} The PAMPs of \textit{C. albicans} are then taken up, processed, and presented in an MHC class II-restricted fashion to naive T cells. An \textit{in vitro} study showed that the addition of \beta-glucan to the DCs promoted the activation and maturation of human DCs.\textsuperscript{157} DCs would present the \textit{C. albicans}-specific antigens to T cells. In addition to priming T cell responses via antigen presentation, DCs also shape T cell responses through secretion of cytokines.\textsuperscript{158} The presentation of \textit{C. albicans} antigen by DCs leads to the activation of CD4+ and CD8+ T cells.\textsuperscript{159,160} CD8+ T cells process direct cytolytic activity and inhibit the growth of \textit{C. albicans} hyphae in \textit{vivo},\textsuperscript{160} while CD4+ T-cells are thought to be predominant in adaptive response to \textit{C. albicans} infection. CD4+ T cells are mainly polarized into specific subsets characterized as Th1, Th2, Th17 or Tregs, each of which is dictated by the cytokines and microenvironment.\textsuperscript{159} In contrast to the phenotype of Th2, which is closely associated with increased growth and dissemination of the fungus, Th17/Th1 cells are important in reactions against \textit{C. albicans}.\textsuperscript{161} IL-23 promotes terminal differentiation and expansion of the Th17 cells,\textsuperscript{162} and accumulating evidence indicates that Th17 cells are key cells in the response to \textit{C. albicans} infection.\textsuperscript{45,163,164} Th17 cells secrete numerous cytokines including IL-17A, IL-17F and IL-22, and play vital roles for immune protection against \textit{C. albicans} at the majority of mucosal sites in the body.\textsuperscript{165,166} The importance of Th17 cells in anti-\textit{Candida} responses is not only portrayed by data from mice models, but also from human patients. Patients with deficiency in Th17-mediated adaptive immunity frequently suffer from chronic mucocutaneous candidiasis.\textsuperscript{167-171}
Differential Recognition of Yeasts and Hyphae

Invasive hyphal form of \textit{C. albicans} is more pathogenic and tends to induce robust immune responses, while yeast form is more likely to lead to commensalism. More specifically, \textit{C. albicans} hyphae are believed as an infection form to penetrate the epithelial cell layers, whereas yeast cells are generally found either on the epithelial cell surface or at the local tissues after the penetration.\textsuperscript{173,174} Host cells discriminate the morphologies of \textit{C. albicans} and response accordingly. Furthermore, there is a threshold for the amount of \textit{C. albicans} that can be tolerated by the host.\textsuperscript{175} A study revealed that oral epithelial cells orchestrate an innate response to \textit{C. albicans} via NF-\kappaB and a biphasic MAPK response. Activation of NF-\kappaB and the first MAPK phase, constituting c-Jun activation, is independent of morphology and due to fungal cell wall recognition. Activation of the second MAPK phase, constituting MKP1 and c-Fos activation, is dependent upon hypha formation and fungal burdens and correlates with proinflammatory responses. MAPK/MKP1/c-Fos activation may be critical for identifying and responding to the pathogenic switch of commensal microbes.\textsuperscript{17}

An open question is what exact PAMPs on different forms of \textit{C. albicans} are presented to immune cells. To date, this question is partly answered. Glucans are key fungal PAMPs.\textsuperscript{18,19,118} A recent study revealed that glucans from \textit{C. albicans} hyphae are different from those from yeast cells. Hyphal glucan induces robust immune responses in human PBMCs and macrophages via a Dectin-1-dependent mechanism. In contrast, \textit{C. albicans} yeast glucan is a much less potent stimulus.\textsuperscript{176} On ordinary yeast cells, cell wall \beta-glucan of \textit{C. albicans} is largely shielded by outer wall components.\textsuperscript{118} Nevertheless, the yeast budding and cell separation create permanent scars, which expose \beta-glucan to trigger antimicrobial responses.\textsuperscript{118} Unmasking of \textit{C. albicans} \beta-glucan to PRRs during yeast-to-hypha switch may lead to robust immune responses. A recent study demonstrated that phospholipids phosphatidylerine (PS) is an component masking \beta-glucan of \textit{C. albicans}.\textsuperscript{177} The mutant species lacking PS exhibits increases in exposure of \beta-(1-3)-glucan, which leads to greater binding by Dectin-1 in both yeast and hyphal forms.\textsuperscript{177} The unmasking of \beta-(1-3)-glucan results in increased elicitation of TNF-\alpha from macrophages in a Dectin-1-dependent manner.\textsuperscript{177} In addition to glucans, PLMs of \textit{C. albicans} are able to evoke a proinflammatory state in murine macrophage, which, however, in part depends on their glycosylation status.\textsuperscript{178} Thus, it can be inferred that the PRRs described above might be able to discriminate the subtle differences of PAMPs after morphological transition and lead to corresponding immune responses. Further studies are expected to reveal the detailed mechanism of PRRs-PAMP interactions during morphological transitions.

The Roles of PRRs: Findings Using PRR-Deficient Mice

In the sections above, the roles of PRRs in the recognition of \textit{C. albicans} in various cell types are discussed in detail. In this section, we update the findings using \textit{in-vivo} murine models (Table 2).

TLR2-/- mice infected with \textit{C. albicans} intraperitoneally or intravenously exhibit significantly decreased survival compared with the wild-type mice. And this effect is associated with decreased production of TNF-\alpha and chemokines.\textsuperscript{179} Accordingly, in an intraperitoneal model of candidiasis, fungal clearance is delayed in mice lacking TLR2.\textsuperscript{180} However, a few other studies showed controversial results. Upon intravenous \textit{C. albicans} infection, mice lacking TLR2 have an improved fungal clearance and better survival compared to wild-type mice.\textsuperscript{181,182} The susceptibility of TLR4-lacking mice to \textit{C. albicans} infection depends on the \textit{C. albicans} infection route and growth form. TLR4-defective C3H/HeJ mice have been reported to be more susceptible to disseminated candidiasis.\textsuperscript{183} Similar results were obtained in models of intragastic infection and intravenous re-infection.\textsuperscript{182} However in intravenous infection models, TLR4-/- mice survived longer upon \textit{C. albicans} hyphae infection,\textsuperscript{182} while no difference was observed between the TLR4-/- and wild-type mice upon \textit{C. albicans} yeasts infection.\textsuperscript{183} TLR7-deficient mice are more susceptible to systemic infections by low doses of \textit{C. albicans}. However, when challenged with higher doses, no significant difference was observed between TLR7-deficient mice and wild-type mice.\textsuperscript{27} Similarly, using high dose challenges, TLR9-/- mice showed no significant alteration in survival upon clinical \textit{C. albicans} isolate infection.\textsuperscript{25,27} However, increased susceptibility to systemic candidiasis and impaired fungal clearance in TLR9-/- mice were observed upon challenge with a lower dose of \textit{C. albicans}.\textsuperscript{27}

Taylor PR et al.\textsuperscript{184} investigated \beta-glucan recognition and control of fungal infection using Dectin1-/- mice, and revealed that cytokine release, phagocyte recruitment, phagocytosis and microbial killing are all impaired in the Dectin1-/- mice compared with wild-type mice in disseminated candidiasis model. However, another study carried out by Saigo S et al.\textsuperscript{185} using Dectin1-/- mice suggested that Dectin-1 is not required for host defense against \textit{C. albicans}. The different conclusion may be caused by different experimental design. Saigo inoculated much more \textit{C. albicans} to the mice intravenously (1 \times 10\textsuperscript{5} or 5 \times 10\textsuperscript{5} \textit{C. albicans}) than Taylor PR et al did (1 \times 10\textsuperscript{4} or 1 \times 10\textsuperscript{5} \textit{C. albicans}), which may lead to the different conclusions. Dectin-3-deficient mice are highly susceptible to \textit{C. albicans} infection.\textsuperscript{29} With a low dose of \textit{C. albicans} infection, the survival rate of Dectin-3-deficient mice is significantly lower than wild-type mice. But with a higher dose, only a slight difference was observed regarding the survival rate of wild-type mice and Dectin-3-deficient mice.\textsuperscript{29} MR/- mice have also been used in studies. After challenging MR-/- mice and wild-type mice intraperitoneally with \textit{C. albicans}, no significant difference was found in survival between the mice. However, MR-/- mice has higher average fungal burdens in some of the organs but exhibited more competence in inflammatory cell recruitment and antibody production.\textsuperscript{179} Galectin-3-deficient mice (gal3-/-) were more susceptible to \textit{C. albicans} infection than wild-type (WT) mice. More specifically, gal3-/- mice died significantly faster and exhibited a trend toward increased fungal burden and increased abscess formation in infected brains compared to WT mice.\textsuperscript{186}
Table 2. Comparison of PRR-deficient mice and human PRRs genetic polymorphisms

| Gene  | Genotype | Effect | Reference | SNPs or haplotypes | Effect | Reference |
|-------|----------|--------|-----------|-------------------|--------|-----------|
| TLR1  | —/—      | Unknown| /         | R80T, S248N, I602S| Significantly increased susceptibility to candidemia in whites; decreased secretion of IL-1β, IL-6, and IL-8 from PBMCs of volunteers with polymorphisms | [195] |
| TLR2  | —/—      | Decreased production of TNF-α and chemokines; influence fungal clearance | P631H | No associations with susceptibility to candidemia; Increased susceptibility to RVVC; decreased secretion of IFN-γ and IL-17, while no influence on secretion of IL-1β, IL-6, and TNF-α from PBMCs of volunteers with polymorphisms | [195,197] |
| TLR3  | —/—      | Unknown| /         | L412F             | Increased prevalence of chronic candidiasis; decreased secretion of IFN-γ and TNF-α from PBMCs of volunteers with polymorphisms | [196] |
| TLR4  | —/—      | Susceptibility to candidiasis varies depending on *C. albicans* strains and infection routes | A299G | No associations with susceptibility to RVVC | / |
| TLR6  | —/—      | Unknown| /         | S249P             | No associations with susceptibility to candidemia | [195] |
| TLR7  | —/—      | Increase susceptibility to systemic candidiasis by low doses *C. albicans* | Unknown | Unknown | / |
| TLR9  | —/—      | Increase susceptibility to systemic candidiasis by low doses *C. albicans* | Promoter | No associations with susceptibility to candidemia | [195] |
| Dectin-1 | —/—       | Impairement of cytokine release, phagocyte recruitment, phagocytosis and microbial killing to candidiasis | Y238X | Increased susceptibility to mucocutaneous fungal infections (like RVVC); decreased secretion of IL-17, TNF-α, IL-6 from PBMCs of volunteers with polymorphisms | [198] |
| Dectin-3 | —/—       | Increase susceptibility to systemic candidiasis by low doses *C. albicans* | Unknown | Unknown | / |
| MR    | —/—      | No significant difference in susceptibility to systemic candidiasis | Unknown | Unknown | / |
| Galectin-3 | —/—       | Increase susceptibility to systemic candidiasis | Unknown | Unknown | / |
| NLRP3 | —/—      | Increase susceptibility to systemic candidiasis | Unknown | Unknown | / |
| NLRP10 | —/—      | Increase susceptibility to systemic candidiasis | Unknown | Unknown | / |
| MyD88 | —/—      | Increase susceptibility to systemic candidiasis | Promoter, 3’UTR | No associations with susceptibility to candidemia | [195] |
| CARD9 | —/—      | Increase susceptibility to systemic candidiasis | S12A, Q295X | No associations with susceptibility to RVVC (S12A); Increase susceptibility to chronic mucocutaneous candidiasis (Q295X); decreased proportion of Th17 cells in RVVC patients with mutated (Q295X) CARD9 | [198,170] |
NLRP3 has been found critical for the control of C. albicans infections. Mice deficient in NLRP3 displayed diminished serum IL-1β, reduced survival and higher fungal burdens in kidney, spleen, liver, and lung upon C. albicans infection. In a murine model of oral C. albicans infection, NLRP3 inflammasome was necessary to prevent systemic dissemination of C. albicans. The NLRP3 inflammasome modulates not only the innate immunity, but also the adaptive immunity. After exposed to disseminated candidiasis, the mice deficient in NLRP3 inflammasome display diminished Th1/Th17 responses, followed by increased fungal outgrowth and lower survival. In addition, NLRP10 was found essential for protective anti-fungal adaptive immunity against C. albicans. NLRP10-deficient mice had increased susceptibility to disseminated candidiasis, which is indicated by decreased survival and increased fungal burdens. Further investigation revealed that NLRP10-deficient mice also displayed a defect in the generation of Th1/Th17 responses.

As many PRRs share same adaptors for signal introduction, the mice lacking these adaptors also influence host responses to C. albicans. MyD88 is an important adaptor of TLRs for signal introduction. Moreover, MyD88 is also the receptor of IL-1, IL-18, and IL-33. Thus, MyD88 plays a key role in innate immune system. Mice lacking MyD88 are hypersensitive to systemic C. albicans infection. TRIF is another important signaling adaptor of TLRs. In intra-gastric infection models, mice lacking TRIF fail to prevent C. albicans from infecting peripheral organs. Some data support that TRIF pathways promote tolerance to C. albicans, whereas MyD88 is engaged in anti-fungal response. CARD9 plays an essential role in Dectin1-Syk-CARD9 pathway. CARD9-/- mice are more susceptible to disseminated candidiasis. Collectively, MyD88, TRIF, and CARD9 are all important in response to C. albicans infection based on findings on gene knockout mice.

More in-vivo studies are still needed to better understand the role of PRRs. Firstly, the conclusions on the role of some specific PRRs are still inconsistent. The inconsistence may be caused by the differences in experimental design and materials. Another example is that there are conflicting results regarding the presence of Dectin-1 on human PBMCs because of internalization of β-glucan coupled with the corresponding Dectin-1 receptors. More in-vivo studies are needed to reveal the exact roles of PRRs. One more example is that live C. albicans and heat-killed C. albicans may lead to different Th17 responses. In mammalian cells, 2 pathways of tryptophan metabolism have been described. One pathway leads to the L-kynurenine synthesis and thereafter to niacin as the end metabolite. The second pathway is mediated by the enzymatic activity of tryptophan hydroxylase, producing 5-hydroxytryptophan, followed by further metabolization into serotonin and melatonin. Under conditions that PBMCs were incubated with C. albicans, live C. albicans can shift tryptophan metabolism away from kynurenines and toward 5-hydroxytryptophan metabolites. Five-hydroxytryptophan metabolites inhibit IL-17 production. Thus, live C. albicans may inhibit host Th17 responses, and experiments using live C. albicans, heat-killed C. albicans or PAMPs may lead to different conclusions. Secondly, more in-vivo research data are needed to better understand oral/vaginal candidiasis and host immune responses. Presently, most in-vivo studies use disseminated candidiasis animal models, while few studies focus on oral or vaginal candidiasis. C. albicans colonizes on gastrointestinal or genital mucosa as a constituent of microbiota. The situation at local mucosa is rather complicated. For example, a recent report revealed that Lactobacillus crispatus modulates epithelial cell defense against C. albicans through TLR2 and TLR4, IL-8 and human β-defensins 2 and 3. It can be inferred that more in-vivo studies with the consideration of microbiota on mucosa will shed new insights into the interaction between C. albicans and host immunity. Thirdly, some studies have opened a door to study the collaborations/coordinations among PRRs, while more in-vivo studies are needed to provide more meaningful information.

The Roles of PRRs: Studies on Human SNPs

Regarding the immunity against C. albicans, differences do exist between human and mice (Table 2). Although studies using murine models have provide a lot of information on the role of PRRs, findings on human beings are especially valuable. After analyzing SNPs in genes encoding TLRs, MyD88 and Mal in patients with candidemia and controls, TLR1 SNPs (R80T, S248N, I602S) were found associated with candidemia susceptibility, while no association was revealed between the susceptibility and SNPs in TLR2, TLR4, TLR6, TLR9, MyD88 and Mal. Another study revealed that L412F, a TLR3 SNP, is associated with increased prevalence of chronic candidiasis. By testing patients’ PBMCs for secretion of cytokines, cells carrying the L412F variant showed reduced IFN-γ and TNF-α secretion in response to C. albicans. A study on patients with recurrent vulvovaginal candidiasis (RVVC) revealed that a non-synonymous polymorphism in TLR2 (P631H) significantly increase susceptibility to RVVC, while SNPs in TLR1, TLR4, and CARD9 did not affect the susceptibility to RVVC. The Dectin-1 Y238X polymorphism was revealed to express defective Dectin-1. Patients with the homozygous mutation are more susceptible to mucocutaneous fungal infections (RVVC or onychomycosis). After performing genetic studies on a family with susceptibility to fungal infections, a homozygous Q295X mutation in CARD9 is associated with susceptibility to chronic mucocutaneous candidiasis. These studies indicate that PRRs are actively involved in anti-fungal response in humans, and the roles of PRRs in humans and mice are different. There is no doubt that TLR2 is essential in defense against C. albicans in mice. In contrast to the findings on mice, the study on human SNPs suggested that mutations of TLR2 did not increase the risk to candidemia. Few studies reported the importance of TLR1 and TLR3 in defense against C. albicans in murine models, but the mutations...
of TLR1 or TLR3 increase the susceptibility to *C. albicans* in humans. Mice lacking MyD88 are hypersensitive to systemic *C. albicans* infection, but humans with autosomal recessive MyD88 deficiency are resistant to fungal infections normally.

Of note, it is still immature to make conclusions on the role of most PRRs in human and further studies are necessary. Firstly, only a small number of patients/volunteers are included in most studies up to now, and the evidence is not as solid as we expected. Secondly, the roles of PRRs in different sites of human bodies may be different. For example, patients with mutations of TLR1, but not TLR2, were found susceptible to candidemia, while a -non-synonymous polymorphism in TLR2, but not TLR1, significantly enhances susceptibility to mucocutaneous *C. albicans* infection.

### Conclusions and Future Perspectives

The roles of many PRRs in innate recognition of *C. albicans* have been investigated. Some *in-vitro* studies indicate that TLRs and CLRs play a non-negligible role in *C. albicans* recognition, while NLRs (especially NLRP3), and some other receptors (such as FcYR, CR3, CD36, and SCARF1) are involved in. Nevertheless, further studies are expected to reveal the different recognition mechanisms between yeast and hyphal cells, and more *in vivo* studies are necessary to better understand the exact roles of PPRs. Beside, the cross-talks between various PRRs as well as between epithelial cells and phagocytic cells should draw more attentions. Of note, there are some crucial questions remain unanswered. For example, what are the differences between human and mice regarding innate recognition of *C. albicans*?

Further studies on the role of PRRs will open up new avenues for preventing and treating Candida infections.

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No potential conflicts of interest were disclosed.

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