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Interplay between *Candida albicans* and the Mammalian Innate Host Defense

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***Candida albicans* is both the most common fungal commensal microorganism in healthy individuals and the major fungal pathogen causing high mortality in at-risk populations, especially immunocompromised patients. In this review, we summarize the interplay between the host innate system and *C. albicans*, ranging from how the host recognizes, responds, and clears *C. albicans* infection to how *C. albicans* evades, dampens, and escapes from host innate immunity.**

Candida species, the most common human fungal pathogens, rank as the fourth-greatest cause of nosocomial bloodstream infections, with up to 40% mortality in epidemiological studies (118). *Candida* species colonize asymptomatically in around 30 to 50% of individuals in a population at any given time, but under conditions when the host defense of the individuals is weakened, they can cause both mucosal and systemic infections (14). Risk factors, such as neutropenia, systemic antibiotic exposure, a central venous catheter, and a prolonged intensive care unit (ICU) stay, predispose individuals to invasive and even life-threatening systemic candidiasis (118).

In the past decades, a sustained effort to unravel the interplay between the host immune system and *Candida* species has been carried out. On the one hand, ample knowledge has been gained regarding the host defense mechanisms against *Candida* species, ranging from recognition to signal transduction and fungal clearance/killing. On the other hand, the mechanisms through which *Candida* evades the host defense armory were also investigated extensively. In this review, we aim to bring these two fields together and present a comprehensive view of the interplay between *Candida* and host innate defenses, with a specific focus on how yeast- to hyphal-phase morphological transition contributes to recognition by the host and to the triggering of a protective immune response against *Candida* infection. While the incidence of non-*albicans Candida* species as etiologic agents of invasive candidiasis increased in the last decades (42), *Candida albicans* remains the most prevalent species in both mucosal and systemic infections. Most of the *Candida*-host interaction studies have investigated the interaction of *C. albicans* with the immune system, and therefore, this review will focus on this pathogen.

RECOGNIZING THE INTRUDER

PRRs. The first fundamental aim of host innate immunity is to distinguish self from nonself. Since Medzhitov and Janeway proposed the concept of pattern recognition (66), a plethora of pattern recognition receptors (PRRs) that recognize so-called pathogen-associated molecular patterns (PAMPs) have been identified. Several excellent reviews have extensively discussed how innate immune systems recognize *Candida* species (32, 78, 80). In this review, we will therefore only point out the key receptors and their specific fungal ligands (Fig. 1).

The *Candida* cell wall structure is composed of chitin, β-glucans, and mannoproteins. The polysaccharide structures of the cell wall of *C. albicans* are recognized by two classes of membrane-bound PRRs: the Toll-like receptors (TLRs) and the C-type lectin receptors (CLRs). The first PRRs discovered to recognize *C. albicans* were the TLRs, with TLR2 recognizing phospholipomannan (48), while the O-linked mannan has been shown to be recognized by TLR4 (79, 101). In contrast, other TLRs, such as TLR1 and TLR6, play a secondary role, and they do not seem to be essential for antifungal defense in candidiasis (81). The second major PRR family that recognizes *Candida* PAMPs is the CLRs. While β-glucans are recognized by dectin-1 (12), the N-linked mannan is recognized by the macrophage mannose receptor (79). Dectin-2 was initially reported to recognize the high-mannose structure in hyphae (63, 95), but recently, α-mannan on both yeast and hyphae was shown to be recognized by dectin-2 as well (93). DC-SIGN is another important receptor on the dendritic cells (DCs) that recognizes *Candida* mannan (16). Galectin-3 has been shown to play a role in recognizing the β-mannosides of *C. albicans* (47). Besides these, several additional C-type lectin receptors (CLRs), such as Mincle (13) and SCARF1/CD36 (65), were reported to be involved in *Candida* recognition, but the specific ligands are yet to be identified. Last but not least, MBL (mannose-binding lectin), a soluble CLR, mediates *Candida* opsonization and uptake via binding to *Candida* mannan and to the surface C1q receptor on the phagocyte (11).

In addition to the recognition of fungal PAMPs by membrane-bound receptors, several PRRs were shown to recognize *Candida* intracellularly. TLR9 has been demonstrated to recognize *C. albicans* DNA and induce cytokine production in dendritic cells (70). However, there was no difference in susceptibility between wild-type and TLR9$^{-/-}$ mice in a model of disseminated candidiasis, suggesting a redundant role of TLR9 for systemic anti-*Candida* defense (106). Although TLR9 is recruited to *C. albicans* containing phagosomes, one study showed that the macrophages from TLR9$^{-/-}$ mice produce higher tumor necrosis factor alpha (TNF-α), suggesting a modulatory role of TLR9 in host anti-*Candida*

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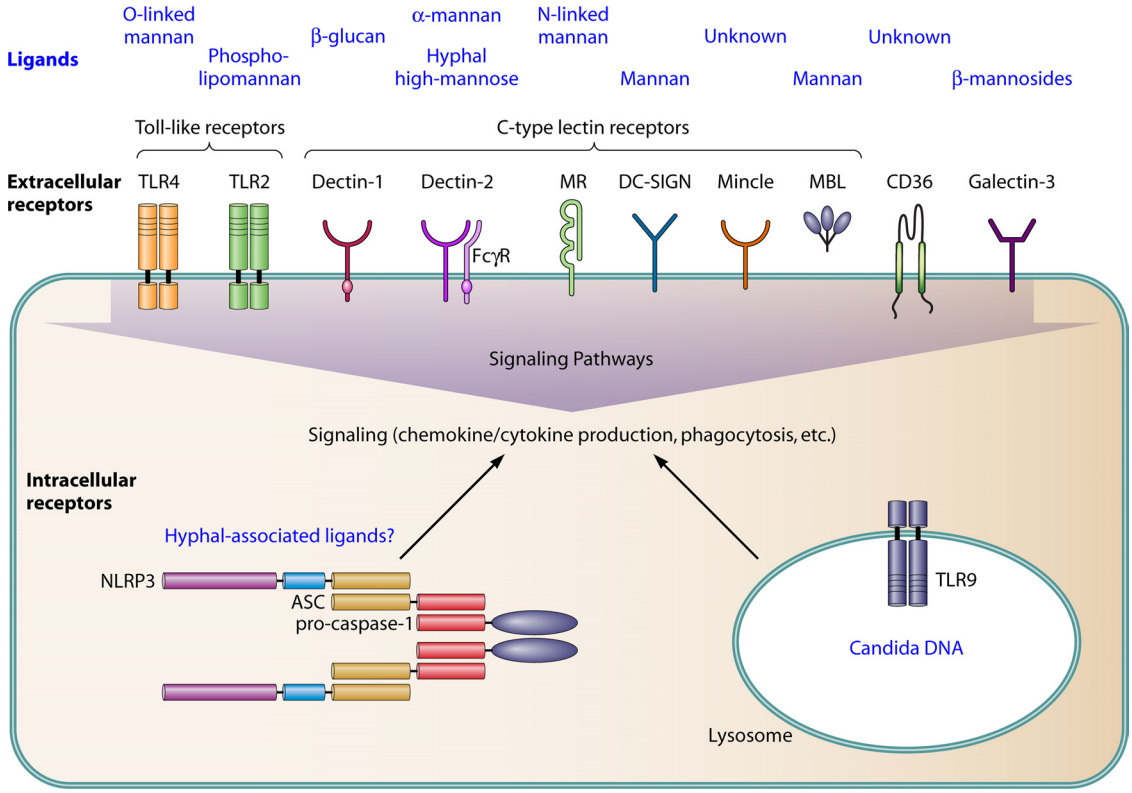

FIG 1 Major pattern recognition receptors (PRRs) and their corresponding *Candida* PAMPs. *Candida* cell wall components are mainly recognized extracellularly by Toll-like receptors and C-type lectin receptors on the host cell surface and lead to different downstream signaling, such as chemokine/cytokine production and phagocytosis. Once *Candida* is internalized/phagocytosed, the fungal PAMPs can further activate TLR9 or NLRP3 inflammasome activation.

innate immune response (50). Receptors of the nucleotide-binding domain, leucine-rich, repeat-containing receptors (NLRs) are PRRs recognizing intracellular PAMPs, and one of their main functions is to activate caspase 1 within a protein complex called the inflammasome, leading to processing and activation of cytokines of the interleukin 1 (IL-1) family (10). Among the NLRs, NLRP3 (NLR family pyrin domain containing 3) has been suggested to play an important role for anti-*Candida* host defense. It has been reported that NLRP3 and ASC gene knockout mice were more susceptible to both systemic (41, 52) and mucosal (43) *Candida* infections, suggesting a role of the NLRP3 inflammasome for anti-*Candida* defenses. Intriguingly, caspase 1 knockout mice are not more susceptible to disseminated candidiasis (67), arguing for the presence of alternative inflammasome-independent mechanisms for the production of bioactive IL-1β. Therefore, further investigations of the role of NLRP3 and ASC in inflammasome-independent function are warranted.

Danger recognition receptors. In addition to PRRs, danger recognition receptors have been proposed to activate host defenses by recognizing endogenous danger signals. The protease-activated receptors (PARs) are G protein-coupled receptors that are activated upon proteolytic cleavage of their N-terminal tail. Instead of directly sensing the PAMPs, PARs function as danger-sensing receptors that are activated either by a protease from a host, e.g., elastase and cathepsin G from neutrophils, or by proteases from *Candida* species, e.g., secreted aspartic proteases. It has been shown that PAR1 expression was upregulated in mice infected with *Candida* and that the cross talk between PAR1 and TLR2 can promote *Candida*-induced inflammation (71). However, in an attempt to translate these findings from mice to humans, we were not able to find direct evidence of the involvement of PAR1/PAR2 in *C. albicans*-induced proinflammatory cytokines in human peripheral blood mononuclear cells (PBMCs) (17). Nevertheless, this does not yet exclude an *in vivo* role of PARs in *Candida* infections. Therefore, future studies of the role of PAR during *Candida* infection in different niches are needed.

CELL TYPES INVOLVED IN HOST INNATE DEFENSES AGAINST *CANDIDA* INFECTION

Epithelial cells. The mucosal epithelium is the first line of defense against *Candida* species. It has been long acknowledged that the epithelium has a function as a passive physical barrier to restrain *Candida* from invasion of the underlying tissue. However, recent studies have broadened our knowledge about the active role played by epithelial cells in triggering immune responses. Oral epithelial cells express most of the TLRs, with the exception of TLR5 and TLR7 (113), to recognize invading microorganisms. Upon recognition of the invading *Candida* species, epithelial cells secrete antimicrobial peptides, such as β-defensins (2) and LL-37 (53), to clear/control fungal infection directly. For example, in response to *Candida parapsilosis*, human gingival epithelial cells upregulate TLRs and antimicrobial peptides, such as hBD-1 (human β-defensin 1) and hBD-2, to inhibit fungal growth (5). Similar results were also observed when *Candida famata* was used to stimulate oral epithelial cells (6).

In addition, both oral (100) and vaginal (8) epithelial cells can

inhibit *Candida* growth in a contact-dependent manner. Although proinflammatory cytokines produced by epithelial cells have no direct antifungal effects (55), they serve as signals to mucosal inflammatory cells to boost their antifungal function. Weindl and colleagues have shown in a reconstituted human epithelial model that epithelial cells were protected from *Candida* infection when neutrophils were present (113). By addition with anti-TNF-α antibody, the protective effect was partially inhibited. Therefore, epithelial cells may "sound the alarm" by inducing the production of cytokines and chemokines to recruit/activate other immune cells.

Cytokines produced from immune cells also play an important role in epithelial immunity against *Candida* infection. It has been shown that IL-22, the key cytokine produced by the T helper 22 subset of lymphocytes (Th22), synergistically induces the production of hBD2, S100A7, and CXCL-10 together with TNF-α in keratinocytes (26). The IL-22 and TNF-α combination also renders a protective effect of increasing epidermal integrity against *C. albicans* infection (26). This highlights the cross talk between epithelial and immune cells in anti-*Candida* infection.

Site-specific differences in anti-*Candida* immunity also need to be taken into account. Oral and vaginal candidiasis are the two most commonly found *Candida* infections in humans. It is generally considered that innate and cell-mediated immunity are important for mucosal antifungal defense, as exemplified by the high prevalence of oropharyngeal candidiasis (OPC) in AIDS patients due to the loss of CD4 T cells (30). The role of cell-mediated immunity for host defense at the level of the vaginal mucosa is less clear, and no solid evidence for the protective role of the innate immunity against vaginal infection was found (29). Moreover, vaginal epithelia were shown to express S100A8 and S100A9, which recruit polymorphonuclear neutrophils (PMNs) to the infected vagina, upon *Candida* infection (120). However, unlike the protective role of PMNs in oral candidiasis (96), the infiltrated PMNs in the vagina are associated with symptomatic vaginal infection (31).

Phagocytic cells. (i) Polymorphonuclear neutrophils. Phagocytes are believed to be the most effective cell type for controlling and clearing *Candida* infection. Among the phagocytes, PMNs play a critical role in host defense against both mucosal and disseminated candidiasis (109). Several proinflammatory cytokines, such as IL-6 (92, 108), IL-8 (7), and TNF-α (82), have been reported to be responsible for the recruitment of PMNs to the site of infection. Recently, IL-17 has been shown to be crucial to stimulate granulopoiesis (97) and recruitment of neutrophils to the site of infection (121). Several studies, though not all, have shown that mice deficient in IL-17 or the IL-17 receptor are more susceptible to systemic (45) or mucosal (22) *Candida* infection. In contrast, others have suggested a deleterious role of IL-17 through overwhelming inflammatory reactions (24). In humans, Th17 responses are severely defective in patients with chronic mucocutaneous candidiasis (107). Similarly, patients with hyper-IgE syndrome also suffer from oral and mucocutaneous candidiasis due to a defective Th17 response (21). Another line of evidence on the role of Th17 for antifungal defense as well as for the occurrence of chronic mucocutaneous candidiasis in patients with IL-17F or IL-17 receptor deficiencies comes from the dectin-1/CARD9/Th17 pathway (89). Patients with defective dectin-1 (28) and/or downstream adaptor CARD9 (38) suffer from mucocutaneous candidiasis. Therefore, the Th17 response is less likely to be deleterious and is instead protective in human mucosal antifungal responses.

In addition to proinflammatory cytokines, the hematopoietic growth factors granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are critical for recruitment and activation of PMNs (51, 54). In addition to their direct killing of *C. albicans*, it was demonstrated that PMNs are the only cell type in blood which can inhibit *C. albicans* germ tube formation (33).

Phagocytes, and especially PMNs, kill *Candida* cells both intracellularly and extracellularly. Once *Candida* cells are phagocytosed by phagocytes, the engulfed microorganisms are processed through fusion with lysosomes into phagolysosomes. The engulfed *Candida* cells are killed within the phagolysosome by hydrolytic enzymes, antimicrobial peptides, and the reactive oxygen species (ROS) (3). The formation of the candidacidal radical peroxynitrite ($ONOO^-$) due to superoxide anion (O_2^-) and nitric oxide release is another mechanism of intracellular killing (110). Recently, a novel extracellular mechanism of killing *Candida* species was shown to be exerted by neutrophils. Upon encountering *Candida*, in addition to direct killing through phagocytosis, neutrophils inhibit *Candida* growth by releasing neutrophil extracellular traps (NETs) which contain the antifungal peptide calprotectin (104).

(ii) Mononuclear phagocytes—monocytes/macrophages. The role of mononuclear phagocytes in disseminated candidiasis is less well established. In a mouse model of macrophage depletion, a slower clearance of *Candida* from the bloodstream was observed (90), suggesting the involvement of macrophages in host defenses against systemic *Candida* infections. However, one study using depletion of monocytes has suggested that mice with monocytopenia are equally as susceptible to *Candida* as control mice, reinforcing the dominant role played by PMNs in terms of anti-*Candida* infection by the host (109). It was proposed that the low candidacidal activity of macrophages is due to the reduced myeloperoxidase activity and decreased superoxide generation during the macrophage differentiation (94). In addition to the oxidative candidacidal mechanism, macrophages adherent to type 1 collagen matrices were more capable of killing ingested *Candida* by enhancing the fusion of yeast-containing phagosomes with the lysosomes (83). This implies that macrophages in contact with the extracellular matrix might be more efficient than macrophages in an *in vitro* experimental setup for killing *Candida*.

(iii) Dendritic cells. As professional antigen-presenting cells, DCs reside and patrol in the skin and mucosal surface, and they ingest *Candida* once tissues are invaded. *Candida* species are internalized by DCs via MR and DC-SIGN (15, 16), leading to the processing and presentation of *Candida*-specific antigens via major histocompatibility complex (MHC) class II molecules. DCs discriminate between yeast- and hyphal-phase forms of *C. albicans* and induce T helper cell differentiation. Ingestion of yeasts primes T helper type 1 cells (Th1), whereas ingestion of hyphae inhibits IL-12 and Th1 differentiation, favoring Th2 differentiation. Thus, DCs bridge the innate and adaptive antifungal responses by recognizing different morphologies of *Candida* (25).

SOLUBLE FACTORS

In addition to the aforementioned cell-mediated antifungal responses, several blood soluble factors, such as complement and antibodies, contribute to host anti-*Candida* immunity. The com-

plement system can be activated through three pathways: the classical pathway (CP), the alternative pathway (AP), and the lectin pathway (LP). All three pathways can be activated by *Candida* (98, 123, 124). The opsonized *Candida* cells can be more efficiently ingested by phagocytes through the interaction between the CR3 and C3b, which is deposited on the *Candida* surface (62), or between the Fc receptor and the anti-*Candida* antibody (4). In contrast, the thick fungal cell wall prevents the killing mechanisms mediated by the membrane attack complex.

Apart from the role of mediating phagocytosis through surface opsonization, we have identified a crucial role of anaphylatoxin C5a in augmenting *C. albicans*-induced IL-6 and IL-1β production in PBMCs (18). By using the specific blocking antibody against C5a or the C5a receptor antagonist, a clear reduction of cytokine production induced by *C. albicans* in the presence of serum was observed. Moreover, by using serum isolated from patients with various complement deficiencies, we demonstrated a crucial role of C5, but not the membrane attack complex, for *C. albicans*-induced IL-6 and IL-1β. These findings reveal a central role of anaphylatoxin C5a in augmenting host proinflammatory cytokine production upon contact with *C. albicans*. It was also demonstrated that C5-deficient mice are more susceptible to systemic *C. albicans* infection, resulting in a higher fungal burden in the organs (73). A recent study using computational analysis proposed that different combinations of *C5* and *C1r/s* alleles can predict the survival of different mouse strains in the systemic *Candida* infection model (86). This implies that reduced C1 deposition in the susceptible mice resulted in reduced C5 binding and activation.

EVASION OF *CANDIDA* FROM THE HOST DEFENSE MECHANISMS

As a commensal microorganism surviving in various host niches, *Candida* species encounter a continuously hostile environment in terms of host immune system, pH, nutrition acquisition, and competition with the other microorganisms in the microflora. Here we will specifically focus on the strategies employed by *Candida* to escape/evade host innate defenses (Fig. 2).

Yeast- to hyphal-phase transition. *C. albicans* is a dimorphic fungus. The morphological switch between the yeast phase and the hyphal phase is considered to be the main virulence factor of *C. albicans*. Through the dissection of the molecular mechanisms responsible for the yeast- to hyphal-phase transition, several transcriptional factors responsible for the morphological transition have been identified. These transcriptional factors are activated by different environmental stimuli and have been reviewed previously (117). Nonfilamentous *C. albicans* strains with defective transcriptional factors, such as *efg1* and *cph1*, have been shown to be avirulent or less virulent in mice infection models (56). This highlights the fact that morphological transition is an important virulence factor for *C. albicans*. In the systemic infection model in mice, *C. albicans* was readily recognized and phagocytosed in the bloodstream. Once the yeast form of *C. albicans* is phagocytosed, the production of carbon dioxide within the macrophages induces the adenyl cyclase and cyclic AMP (cAMP)-dependent protein kinase A pathway, thereby activating *Efg1p*, which is the major transcription factor responsible for the yeast- to hyphal-phase transition. Formation of hyphae will eventually lead to the piercing and killing of macrophages by *C. albicans* hyphae (37, 61). In the oral experimental candidiasis model, as another example of how yeast- to hyphal-phase transition subverts host innate immunity, hyphal formation was also shown to inhibit human-defensin expression (57).

Intriguingly, hypha-locked mutants and yeast-locked mutants have both been demonstrated to be less virulent than wild-type strains (9, 74). This implies that the morphological switch from yeast phase to hyphal phase, and vice versa, accounts for the full virulence of *C. albicans*. While hyphae might be regarded as an invasive form required for piercing through phagocytes and invading the epithelium barrier, the yeast form is also needed for the free dissemination in the systemic infection.

Epithelium invasion. *C. albicans* invades the epithelial barrier via two different routes: active tissue invasion and passively induced endocytosis. Recently, Wachtler and colleagues performed an extensive study to elucidate the genes involved in the active penetration of the epithelium by *C. albicans* at different stages, including epithelial attachment, tissue invasion, and eventually, tissue damage (111). Many hypha-associated genes, including *ALS3*, *HWP1*, *ECE1*, *SOD5*, *PHR1*, and *PRA1*, are upregulated in *C. albicans* cells in contact with epithelial cells. Hyphae are the invasive form of *C. albicans* found within epithelial cells in the invaded tissue (91). Therefore, upregulation of hypha-associated genes upon contact with epithelial cells might be crucial for active penetration of epithelial cells by *C. albicans*. In addition to active penetration, *C. albicans* can also cause transepithelial infection through induced endocytosis. It is demonstrated that ALS-3 mimics host cadherins and induces endocytosis through binding to E-cadherin on oral epithelial cells (87). This endocytosis process is passive and does not require cell viability, because even the killed *C. albicans* cells can be endocytosed by the epithelial cells. Once *C. albicans* is inside the epithelial cells, it forms hyphae, leading to piercing of the cells through the function of *EED1* (epithelial escape and dissemination 1). An *eed1*-deficient strain failed to maintain hyphal formation and was trapped within the cells (122). In addition to invasion of epithelial cells, *C. albicans* is able to downregulate epithelial TLR4 expression, which in turn increased the vulnerability of epithelial cells to *C. albicans* infection (113).

Escape from phagocytosis. (i) Shielding of the surface PAMPs. To phagocytose *Candida* species, the host cells first need to "sense" the microorganism, a process which is achieved through recognizing the PAMPs of *Candida*. One mechanism through which this step is prevented is the shielding of important PAMPs from recognition by PRRs. It has been shown that β-glucan is shielded by the outer cell wall components, thus preventing the recognition of dectin-1 (35). In line with this, live *C. albicans* induced small amounts of cytokines in human peripheral blood mononuclear cells, yet heat-killed *C. albicans* cells in which the architecture of the cell wall is disrupted induced significant amounts of cytokines through the recognition of the now-exposed β-glucan by dectin-1 (39). McKenzie and colleagues have also demonstrated that mutants deficient in O-linked and N-linked mannans were more readily phagocytosed by macrophages (64). However, during a live infection model, β-glucans are exposed in the damaged *Candida* cells by the action of host factors, demonstrating the continuous "arms race" between the host and the pathogen (116).

(ii) Complement inhibition and degradation. *C. albicans* possesses several strategies to interfere with complement activation in order to avoid phagocytosis or to reduce production of proinflammatory cytokines. It has been shown that secreted aspartic pro-

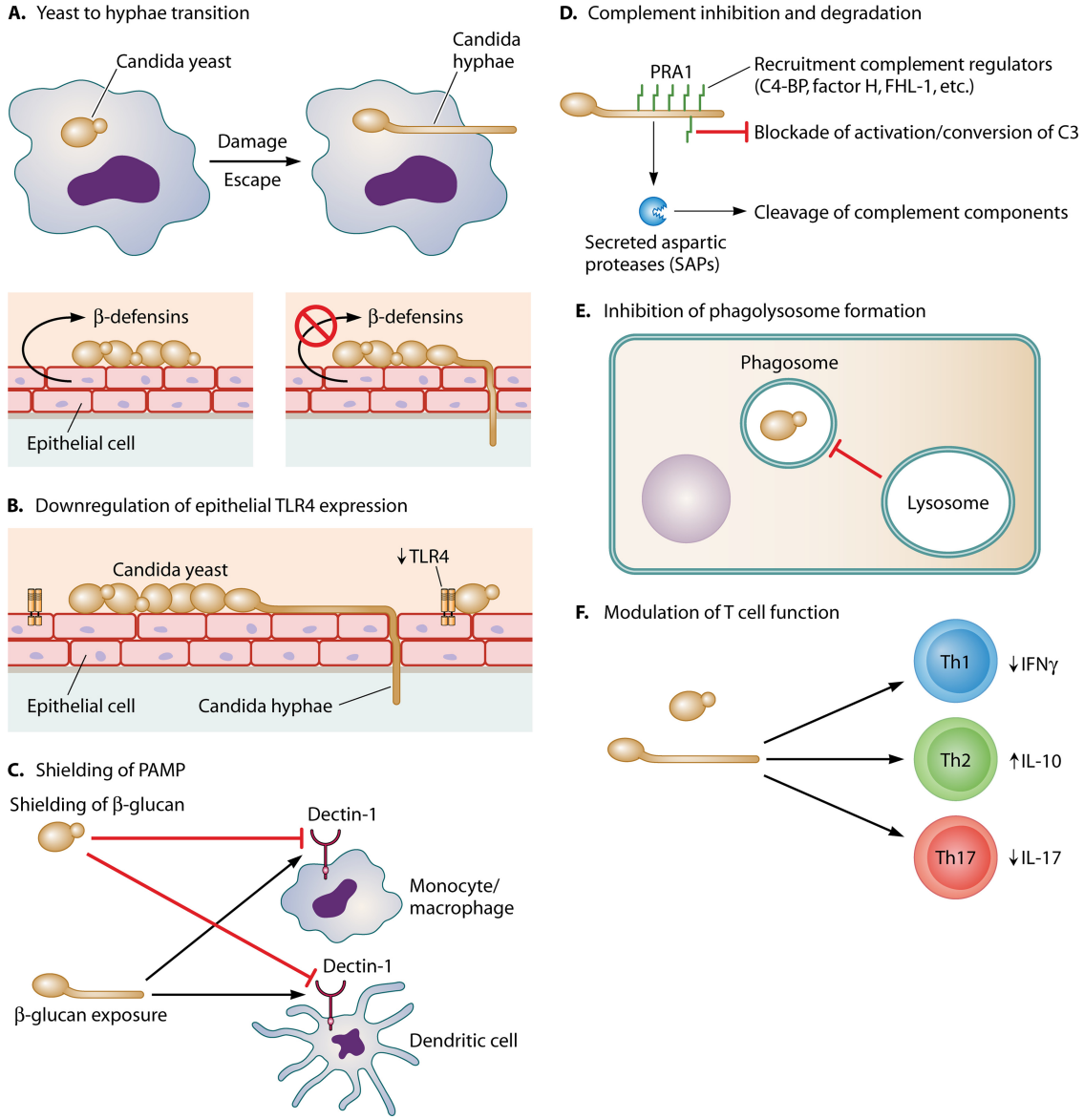

FIG 2 *Candida albicans* host innate system evasion strategies. (A) Yeast- to hyphal-phase transition. (B) Downregulation of epithelial TLR4 expression. (C) Shielding of PAMP from PRR recognition. (D) Inhibition or degradation of complement system. (E) Inhibition of phagolysosome formation. (F) Modulation of T cell function.

tease degrades C3b, thus inhibiting the opsonization of *Candida* species by human serum *in vitro* (40). Furthermore, *C. albicans* may also bind the complement regulatory proteins, such as the complement regulator C4b-binding protein, factor H, FHL-1, and the plasminogen-binding surface protein, on the cell surface in order to inhibit the activation of the complement system (68, 69, 88). A recently identified *C. albicans* surface protein, Pra1, has been shown to bind factor H and the C4b-binding protein to regulate complement activation (58, 60) and subsequently block the activation and conversion of C3 (59). On the other hand, strikingly, Pra1 also serves as the primary ligand recognized by CR3 and facilitates phagocytosis (99). This demonstrates once more the complex interplay between *Candida* and host innate immune systems.

(iii) Inhibition of phagolysosome formation. An important step in the process of killing of a pathogen is the fusion of the phagosome containing the microorganism with the lysosomes. It has been recently reported that *C. albicans* can modulate intracellular membrane trafficking by inhibiting the formation of phagolysosomes. Live *C. albicans*, but not heat-killed *C. albicans*, was able to inhibit phagolysosome formation, implying that this is an active inhibition dependent on the viability of the fungi. Interestingly, wild-type *C. albicans* is more capable of controlling phagosomal composition than the nonfilamentous mutants (27). This is also in line with the fact that morphological transition is one of the critical virulence factors of *C. albicans*. However, the genetic background of *C. albicans* strains also plays an important role in the ability to survive within the phagosome. Tavanti and colleagues have reported that *C. albicans* isolates with the c karyotype are more resistant to intracellular killing and more able to

replicate and escape from THP-1 cells than isolates with the b karyotype (103). It is expected that a further dissection of the underlying mechanisms through which *C. albicans* prevents the phagolysosome fusion may be translated into potential novel antifungal intervention strategies.

(iv) ROS inhibition. ROS production is a major antifungal mechanism in phagocytes. To counteract the oxidative stress, *Candida* species possess several defensive armories. *C. albicans* catalase has been suggested to counteract the respiratory burst, and a *C. albicans* Δ*cat1* mutant is less virulent and was cleared faster than a wild-type strain in an experimental model (76). Similarly, the *C. albicans* surface superoxide dismutase has also been implicated for counteracting the ROS production from the phagocytes (34). In line with this, Wellington and colleagues have demonstrated that *C. albicans* and *Candida glabrata*, but not *Saccharomyces cerevisiae*, can actively suppress ROS production in a murine macrophage cell line. Interestingly, although the recognition of a fungal cell wall is needed for the ROS production, as demonstrated by the stimulation of macrophages with heat-killed *Candida* or caspofungin-treated *Candida*, the *Candida* viability is needed for the suppression effect, implying an active role for live *Candida* in suppressing the ROS production (114). *Candida* vacuole formation was also suggested to play a role in resistance against stress and in hyphal growth (84). The Δ*vps11* strain is defective in vacuole biogenesis and, as a consequence, more sensitive to oxidative stress and severely retarded in filamentous growth. However, although the partially functional *vps11hr* strain bears a similar defect in hyphal formation, the *vps11hr* strain shows survival patterns similar to those of the wild-type strain in the macrophage J774A.1 cell line (85).

(v) Farnesol. Farnesol was first identified as a quorum-sensing molecule (QSM) that repressed the yeast- to hyphal-phase transition of *C. albicans* in an autoregulatory manner (44). Recently, farnesol has also been suggested to be a virulence factor of *C. albicans*. It has been demonstrated that farnesol might decrease macrophage viability through induction of ROS (1). Furthermore, farnesol has been suggested to protect *C. albicans* from oxidative stress via upregulating CAT1, SOD1, SOD2, and SOD4 (115). In an *in vivo* infection model, the pretreatment with exogenous farnesol led to inhibition of Th1 cytokine gamma interferon (IFN-γ) and IL-12 and enhanced Th2 cytokine (77).

On the other hand, farnesol also seems to function as a danger signal that activates antifungal defenses. Exogenous farnesol upregulates TLR2 expression in epithelial cells, which results in more IL-6 and β-defensin 2 expression upon *C. albicans* stimulation (23). It has also been demonstrated that murine macrophages produced more IL-6 when stimulated with wild-type *C. albicans* than with a farnesol-deficient strain (36). In addition, the conditioned medium of *C. albicans* cultures has been demonstrated to potentiate IL-6 and IL-8 production in human PBMCs (17), and it has been suggested that this may be attributed to the presence of farnesol.

Modulating cytokine production by soluble factors. A lot has been learned in the past decades about the mechanisms through which *Candida* induces the production of cytokines in the host, yet little is known about the active role of *C. albicans* in exploiting host cytokine production for its own benefit.

Live *C. albicans*, but not *Candida krusei*, has been demonstrated to inhibit IL-12 and IFN-γ production from human PBMCs (119). This IL-12 inhibitory effect was dependent on the viability of *C. albicans*, because both heat-killed *C. albicans* and *C. krusei* induced similar amounts of IL-12. Further studies showed that IL-12 inhibitory activity is due to the secretion of a glycoprotein (112) and signaling through the selective activation of extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) (102). However, the identities of this soluble glycoprotein and the receptor responsible for the IL-12 inhibition signaling are unknown.

Recently, we have also reported the active role played by soluble factors released by *C. albicans*. We have demonstrated that although conditioned medium from *C. albicans* culture by itself did not induce host cytokine production, it may amplify host IL-6 and IL-8 production (17). On the other hand, the conditioned medium downregulated host IFN-γ synthesis yet upregulated IL-10 production, thus shifting the T helper cell response from a beneficial Th1 response to a detrimental Th2 response (17). Further investigations about which soluble factor(s) is responsible and how are warranted.

Inhibition of IL-17 production. IL-17 has been suggested to be an important component of host defense against *Candida* infection (22, 45). *Candida* cell wall components, especially mannans and β-glucans, are recognized by CLRs, such as MR, dectin-1, and dectin-2, leading to inflammasome activation, IL-1β production, and subsequent induction of IL-17 (105). Recently, it was demonstrated that *C. albicans* can actively inhibit host IL-17 production by altering host tryptophan metabolism. Tryptophan metabolism is regulated by two distinct enzymes: indoleamine 2,3-dioxygenase (IDO) and tryptophan hydroxylase. By inhibiting IDO expression, *C. albicans* could shift tryptophan metabolism, leading to fewer kynurenines and more 5-hydroxytryptophan metabolites. The increased 5-hydroxytryptophan levels subsequently inhibit host IL-17 production (20).

RECOGNITION OF *CANDIDA* COLONIZATION VERSUS INVASION—THE ACHILLES' HEEL OF *C. ALBICANS*

C. albicans is a commensal microorganism in healthy individuals, but it is capable of causing serious infections if the protective mucosal barrier is breached. Therefore, immune discrimination between *Candida* colonization and invasion is of particular significance.

A biphasic MAPK response has been proposed to be responsible for discrimination between *C. albicans* yeasts and hyphae by the epithelial cells (72). Moyes and colleagues have demonstrated that during the commensal stage of *C. albicans*, c-Jun was activated in the epithelial cells upon recognition of fungal cell wall components. The activation of c-Jun is independent of fungal morphology and leads to NF-κB activation but not to production of proinflammatory cytokines. However, activation of the second MAPK phase, consisting of MKP1 and c-Fos activation, is dependent on hyphal germination and an increased fungal burden and thus induces a potent inflammatory response. A subsequent study further demonstrates that *C. albicans* cell wall glycosylation was indirectly required for induction of proinflammatory cytokine production, but not for activation of the MAPK/MKP1/c-Fos pathway, in epithelial cells (75). This reveals a possible mechanism of epithelial discrimination between fungal colonization and invasion.

In addition, hyphal formation was identified to be the key event for triggering inflammasome activation and IL-1β secretion in murine macrophages (46). Since IL-1β is indispensable for

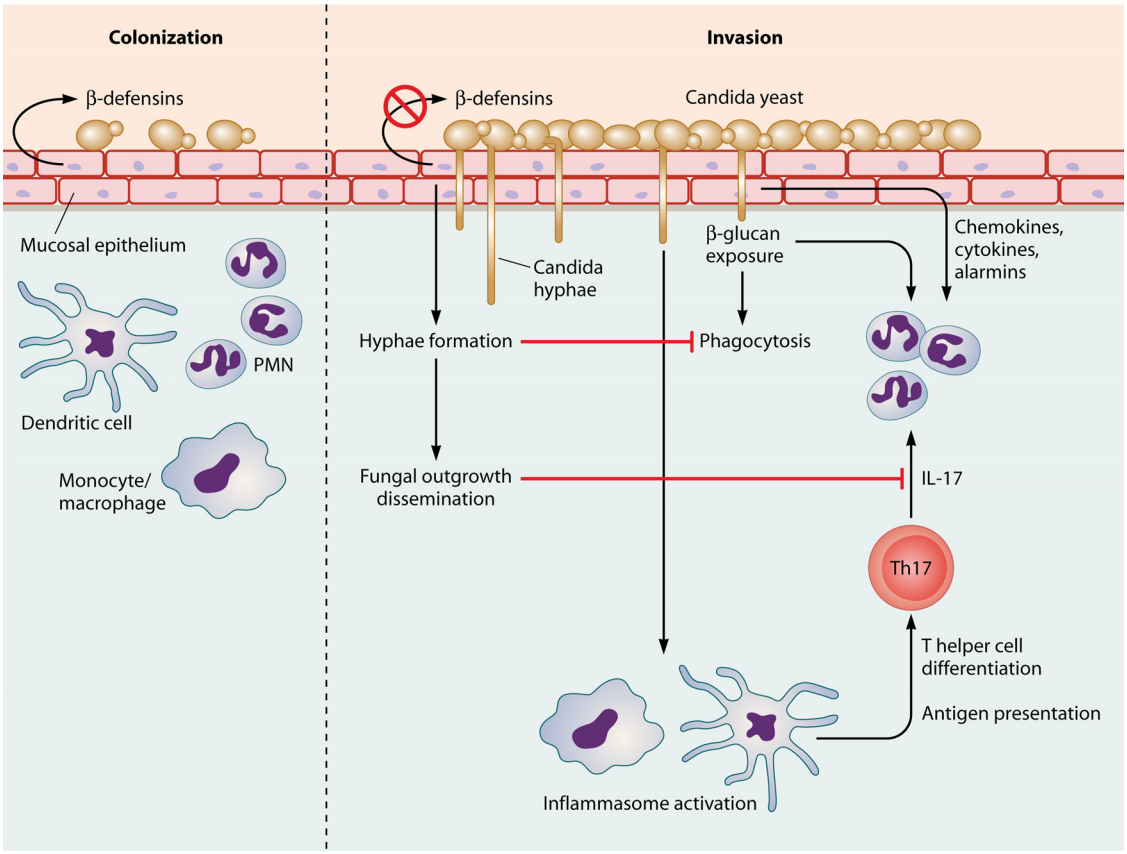

FIG 3 Schematic diagram of the interplay between *Candida albicans* and host innate immune systems at the mucosal surface. Black lines denote host defense mechanisms. Red lines denote *Candida* invasion/escape mechanisms.

Th17 differentiation, the recognition of invasive hyphae might be the crucial step for macrophages to discriminate between *Candida* colonization and invasion. We have demonstrated that *Candida* hyphae may specifically activate the inflammasome through the exposure of fungal PAMPs, such as β-glucans, that are originally shielded in yeast (19), because β-glucan was demonstrated to induce both IL-1β mRNA transcription and inflammasome activation (49, 52). Subsequently, the inflammasome activation and IL-1β production are crucial for Th17 differentiation and IL-17 production, and yeast-locked *C. albicans* strains defective in hyphal formation fail to induce IL-17 production. Therefore, macrophages serve as a gatekeeper to induce protective Th17 responses against *C. albicans* invasion by recognizing invading hyphae.

Yeast- to hyphal-phase transition has been demonstrated to be the crucial virulence factor for *C. albicans* and is important for tissue invasion and for escaping from phagocytes. This, however, also puts *C. albicans* at risk to be more efficiently recognized by the host and induces an additional array of host defense mechanisms (Fig. 3).

CONCLUDING REMARKS AND FUTURE DIRECTIONS

In the past decades, much has been learned about the mechanisms through which host innate immunity recognizes, responds to, and defends against *Candida* species. In addition, many of the fungal virulence factors that contribute to pathogenesis have been identified, and sustained efforts have been made to study the interplay between *Candida* and the host defense. However, one can envisage that the interaction between *Candida* and the host in real life will be more complicated, and important questions remain to be answered. One such topic is represented by the mechanisms through which the sensing of invading *Candida* species by the epithelial cells prepares and educates the innate cells in the fight against invasion. It is expected that the cross talk between epithelial cells and immune cells will draw more attention in the years to come. Similarly, much remains to be investigated on the pathways through which the morphology of *Candida* facilitates its pathogenicity. Moreover, several crucial questions related to mucosal antifungal immunity remain unanswered. For example, what are the differences between the host immune responses at the oral mucosa and those at the vaginal mucosa, and what are the consequences of the deregulation of antifungal mucosal immunity for autoinflammatory diseases, such as Crohn's disease and ulcerative colitis? These are only a few of the questions that need to be answered in the future in order to get an overall view of the interplay between *Candida* and host innate immune defense.

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