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Beyond *Candida albicans*: Mechanisms of immunity to non-*albicans Candida* species

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Abstract

The fungal genus *Candida* encompasses numerous species that inhabit a variety of hosts, either as commensal microbes and/or pathogens. *Candida* species are a major cause of fungal infections, yet to date there are no vaccines against *Candida* or indeed any other fungal pathogen. Our knowledge of immunity to *Candida* mainly comes from studies on *C. albicans*, the most frequent species associated with disease. However, non-*albicans Candida* (NAC) species also cause disease and their prevalence is increasing. Although research into immunity to NAC species is still at an early stage, it is becoming apparent that immunity to *C. albicans* differs in important ways from non-*albicans* species, with important implications for treatment, therapy and predicted demographic susceptibility. This review will discuss the current understanding of immunity to NAC species in the context of immunity to *C. albicans*, and highlight as-yet unanswered questions.

Introduction

Fungi constitute a poorly understood and comparatively under-studied (and under-funded) form of infectious disease. To date, there are no vaccines to any fungal pathogens, and the correlates of immunity are not well defined. However, fungal infections are on the rise, in part due to increasing populations of immunocompromised individuals [1]. *Candida* species comprise the second most frequent cause of fungal infections worldwide. The *Candida* genus contains multiple species that show considerable phylogenetic and phenotypic variation. Our knowledge of immunity to *Candida* has almost exclusively been gleaned from studies on *C. albicans*, the most common disease-causing species. However, the prevalence of disease caused by non-*albicans Candida* (NAC) species is on the rise, and our understanding of immunity to these species is the subject of this review.

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Immunity to *C. albicans* has been studied intensively over the last decade, and a general picture of the essential components is now accepted [2]. Broadly, *C. albicans* is initially detected by C-type lectin receptors (CLRs), such as dectin-1, expressed dominantly on myeloid antigen presenting cells. In addition, an important antifungal contribution of epithelial cells is becoming appreciated, particularly during mucosal infection. Following fungal encounter, responding cells produce innate immune cytokines such as TNFα and IL-1β. These cytokines drive innate antifungal effector responses and trigger skewing of adaptive T cells to dominantly Th17 and Th1 populations. The Th1 and Th17 hallmark cytokines, IFNγ and IL-17, in turn act on neutrophils and macrophages to further amplify antifungal responses. Although this model is well substantiated for *C. albicans*, it is much less clear whether a similar picture is true of immunity to NAC species.

Infections caused by *Candida* species

Fungi belonging to the genus *Candida* are normally found as commensal organisms on mucosal and cutaneous surfaces throughout the human body. Only a subset of species are associated with disease, which include *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei* and *C. dubliniensis* [3, 4]. Mucocutaneous *Candida* infections are often mild or self-limiting, such as oral and vaginal candidiasis/thrush. However, these superficial infections can be associated with significant morbidity, such as in chronic mucocutaneuous candidiasis (CMC) and recurrent vaginal candidiasis. Additionally, *Candida* species cause potentially fatal systemic infection, where mortality rates are reported up to 80%. *Candida* species have also been associated with inflammatory bowel disease and asthma, though the link is not directly causal and is likely to be an exacerbating effect.

Although *C. albicans* remains the most frequently isolated species, the prevalence of NAC species is on the rise [4]. Risk factors for candidiasis vary by species. For example, *C. glabrata* is particularly associated with oral thrush in the elderly and denture wearers, whereas *C. dubliniensis* is frequently isolated from HIV+/AIDS individuals with oral thrush [5]. Neonates, transplant recipients and patients receiving parenteral nutrition are at increased risk of *C. parapsilosis* infection compared to other *Candida* species. Furthermore, geographical differences in *Candida* species prevalence are apparent. *C. albicans* and *C. glabrata* are prominent in North America and Europe, while *C. tropicalis* is typically the most frequently isolated *Candida* species in India and Latin America [6].

With the worldwide rise in fungal infections comes an increase in antifungal drug resistance [7]. Worryingly, antifungal drug resistance has been detected for all clinically relevant *Candida* species to some degree [6]. Moreover, the pattern of antifungal drug resistance differs among *Candida* species, making effective treatment with appropriate antifungal drugs challenging. A particular problem is present with *C. glabrata*, which is resistant to the most common drug classes, azoles and echinocandins [6–9].

The reasons underlying differences in *Candida* species prevalence and antifungal drug resistance are unclear. However, *Candida* species are heterogeneous, so understanding their phylogenetic differences may help to explain, and ultimately address, these disparities. The

most closely related species are *C. albicans*, *C. dubliniensis* and *C. tropicalis* whereas *C. glabrata* is more closely related to *Saccharomyces cerevisiae* [10]. Accordingly, the agglutinin-like sequence (Als) cell wall virulence genes are found in *C. albicans*, *C. dubliniensis* and *C. tropicalis* but not *C. glabrata* [11]. Substantial differences exist even among the most related *Candida* species. For example, Als3 is specifically expressed by *C. albicans* but not *C. dubliniensis* [12]. Genomic divergence among *Candida* species thus results in considerable phenotypic variation within the *Candida* genus.

Phenotypic differences among *Candida* species and consequences for immunity

Although *Candida* species cause grossly similar infections, multiple phenotypic variations exist, including include morphology, cellular size, cell wall composition, growth requirements and virulence factor composition (Table 1) [13, 14]. Each of these alterations may contribute to the development of a distinct immune response. Therefore, it cannot be assumed that a 'one size fits all' immune response to *Candida* species is operative.

Cell wall composition

The *Candida* cell wall is composed of an inner layer of chitin and β-1,3-glucan polysaccharides and an outer layer of mannans covalently associated with proteins [15, 16]. Many of the known pathogen-associated molecular patterns (PAMPs) derive from the cell wall [17], highlighting the importance of this structure in defense against *Candida*. Indeed, differences in cell wall composition and *Candida* recognition are known to impact the immune response. For example, variations in antigenic cell wall-associated proteins were detected among *C. albicans*, *C. tropicalis* and *C. guilliermondii* [18]. Moreover, a recent study identified a novel antigenic cell wall-associated protein of *C. tropicalis*, Kgd2p [19]. Although not tested in this study, the presence of species-specific antigenic proteins indicates that *Candida* species promote distinct immune responses. Ultrastructure analysis of *C. glabrata* versus *C. albicans* cell walls revealed ~50% more proteins, higher amounts of mannan and lower levels of total glucan in *C. glabrata* cell walls [20]. Conversely, *C. albicans*, *C. tropicalis* and *C. parapsilosis* contain higher chitin content than *C. glabrata* and *C. krusei* [21]. It has yet to be determined how or whether these cell wall differences among *Candida* species impact immunity.

Candida species morphology

C. albicans is polymorphic, existing in a unicellular yeast cells form, pseudohyphae and/or filamentous hyphae, and the transition between morphologies is a key virulence trait [17]. However, not all *Candida* species are polymorphic. Growth as true filamentous hyphae is usually associated only with *C. albicans* and *C. dubliniensis*. Some strains of *C. tropicalis* can also form true hyphae (Table 1), although many do not *in vitro* [22, 23]. Similarly, *in vitro* studies have shown that *C. parapsilosis*, *C. krusei* and *C. glabrata* do not form hyphae, though they have been reported to form pseudohyphae [24–27]. *C. albicans* can also switch between normal white yeast cell morphology and mating-competent opaque cell growth. Although white-opaque switching has been documented in other *Candida* species such as *C.*

dubliniensis and *C. tropicalis*, this morphological switch is poorly understood in NAC species [28, 29].

Pattern Recognition

C. albicans is recognized by different classes of PRRs. The C-type lectin receptors (CLRs) are the most important, and include dectin-1, dectin-2, dectin-3, mannose receptor (MR) and Mincle [30]. Although little is known about the PRRs involved in recognition of NAC species, several insights have begun to emerge.

Dectin-1 is a key antifungal receptor in host defense against *C. albicans* infection. Dectin-1 recognition of *C. albicans* triggers phagocytosis, cytokine and chemokine production, reactive oxygen species (ROS) production and neutrophil extracellular trap (NET) formation [31, 32]. *Dectin-1*$^{-/-}$ mice display heightened susceptibility to disseminated and mucosal *C. albicans* infection, although this varies by strain of fungus and genetic background of the host [33–36]. Similarly, loss-of-function *DECTIN1* mutations in humans are associated with increased *Candida* species colonization at mucosal surfaces and higher risk of *Candida* infection, as well as susceptibility to CMC [37, 38]. Some evidence supports a protective role for dectin-1 against *C. tropicalis* at mucosal and systemic sites. *Dectin1*$^{-/-}$ mice are more susceptible to colitis induced by dextran sulfate sodium (DSS) colitis, which was associated with resident *C. tropicalis* overgrowth and tissue invasion [39]. We recently demonstrated that *Dectin1*$^{-/-}$ mice were more susceptible to disseminated *C. tropicalis* infection than WT mice [22]. Little is known about whether dectin-1 participates in immunity to other NAC species, although phagocytosis of *C. parapsilosis* by neutrophils was not impaired following dectin-1 blockade *in vitro* [40]. Similarly, no difference in binding of *C. glabrata* was detected between WT and dectin-1$^{-/-}$ bone marrow macrophages [41].

Dectin-2 is another CLR that functions in many ways similarly to dectin-1. *Dectin2*$^{-/-}$ mice display increased susceptibility to disseminated *C. albicans* infection [42]. Concerning other *Candida* species, disseminated *C. glabrata* infection in *Dectin2*$^{-/-}$ mice was associated with a transient increase in kidney fungal burden and concomitant decreases in splenic TNFα, IFNγ and IL-17A production [43]. Additionally, *Dectin2*$^{-/-}$ macrophages and neutrophils were impaired in phagocytosis of *C. glabrata*, although killing was not affected [43]. However, given that WT or *Dectin2*$^{-/-}$ mice infected with *C. glabrata* do not succumb to disseminated infection, it is difficult to ascertain the importance of this CLR in protection against lethal *C. glabrata* infection. In contrast, *Dectin2*$^{-/-}$ mice were not impaired in their ability to survive a disseminated *C. tropicalis* infection [22]. Therefore, recognition of *Candida* species is far from uniform.

Another PRR garnering attention in the context of *C. albicans* infection is galectin-3. This soluble lectin receptor is found in many cell types, and possesses direct antifungal activity [44]. *Lgals3*$^{-/-}$ mice display increased mortality following disseminated *C. albicans* infection [45], demonstrating a role in antifungal immunity *in vivo*. Galectin-3 also appears to be involved in immunity to several NAC species. Both *C. albicans* and *C. tropicalis* were shown to induce secretion of galectin-3 by human gingival epithelial cells [46]. Moreover,

galectin-3 directly kills *C. albicans* and *C. glabrata in vitro.* However, not all *Candida* species are targeted, since no effects were detected on *C. guilliermondii* [44]. In a model of disseminated *C. parapsilosis* infection, no difference in mortality was detected between WT and *Lgals3*$^{-/-}$ mice. However, *Lgals3*$^{-/-}$ mice had elevated kidney fungal burdens, suggesting this lectin receptor is required for control of *C. parapsilosis in vivo* [45]. The role of galectin-3 in defense against additional NAC species remains to be determined.

Several different PRRs recognize microbes simultaneously in the context of the immune response to a large organism. Indeed, an interaction between dectin-1 and galectin-3 on macrophages in response to *C. albicans* appears to be required for optimal TNFα production [47]. Dectin-1 also cooperates with TLR2 to induce maximal downstream responses following zymosan stimulation [48]. One study reported that dectin-2 and dectin-3 synergize to trigger enhanced NF-κB activation following *C. albicans* stimulation [49]. Together, these *in vitro* studies indicate that signaling through multiple PRRs mediates optimal antifungal immunity *in vivo*. In this regard, mice lacking downstream signaling molecules used by several PRRs tend to be profoundly more susceptible to *C. albicans* infection than mice deficient in individual receptors. This concept is exemplified by CARD9, an adaptor activated by numerous CLRs, including dectin-1, dectin-2, dectin-3 and Mincle [49, 50]. CARD9$^{-/-}$ mice are severely susceptible to disseminated *C. albicans* infection [51]. Moreover, humans with mutations in *CARD9* present with severe CMC and systemic candidiasis, as well as other fungal infections [52–54]. Several *Candida* species were found responsible for candidiasis in these patients, including *C. albicans*, *C. dubliniensis* and *C. glabrata*. Along these lines, we observed that *Card9*$^{-/-}$ mice were profoundly more susceptible to disseminated *C. tropicalis* infection than *Dectin1*$^{-/-}$ mice [22], providing evidence that PRR cooperation is a requirement for immunity to NAC species.

The influence of *Candida* morphology on recognition

Fungal morphogenesis involves changes in cell wall composition, and therefore *C. albicans* morphotypes expose different putative recognition factors. For example, Als3 and hyphally regulated protein 1 (Hyr1) are hypha-specific cell wall proteins that contribute to *C. albicans* resistance to host defense mechanisms. Als3 is involved in adhesion and invasion of host cells and is also a receptor for ferritin, thus mediating iron acquisition [55]. Hyr1 helps resist phagocyte killing [56]. Moreover, both factors are vaccine targets, as vaccination of mice with recombinant Als3 or Hyr1 proteins improves clearance of *C. albicans* [57, 58]. Indeed, an experimental vaccine in clinical trials for vulvo-vaginal candidiasis (VVC) is based on Als3 [59, 60].

Not surprisingly, different *C. albicans* morphotypes induce altered downstream immune responses. For example, *C. albicans* yeast cells induce IL-12 in dendritic cells (DCs), whereas hyphae promote IL-4 production [61]. In macrophages, *C. albicans* yeast but not hyphae induce IFNγ production [62]. In another study, hyphae but not yeast-locked forms of *C. albicans* triggered IL-1β production by macrophages, which was associated with reduced mannan fibrils expression in hyphae compared to yeast cells [63]. Epithelial cells also respond differently to *C. albicans* yeast and hyphae. Yeast cells promote a tolerogenic epithelial cell response, whereas inflammatory response stimulated upon recognition of

invasive hyphae [64, 65]. Moreover, *C. albicans* yeast cells and hyphae are differentially recognized by dectin-1 and dectin-2 [35, 66, 67]. White-opaque switching is another morphological switch that impacts fungal recognition. One study demonstrated that neutrophils phagocytose white but not opaque cells *in vitro* [68].

The ability of different *C. albicans* morphologies to influence the immune response is controversial [34, 69–71]. There are contrasting reports on the ability of yeast and hyphal growth forms to activate downstream dectin-2 responses or promote Th17 responses [42, 63, 69, 71, 72], which may be explained by differences in fungal strains. Alternatively differences between *in vitro* and *in vivo* experimental conditions may be important, since the fungal cell wall is dynamic and the availability of *C. albicans* PAMPs differs markedly *in vitro* compared to *in vivo* settings [34, 70].

While our knowledge on the impact of *C. albicans* morphology on immunity is expanding, this area is yet to be probed with respect to other *Candida* species. However, it is plausible that the varying morphologies of NAC species also drive altered immune responses. Given the importance of morphogenesis in *C. albicans* pathogenicity, understanding the impact of other *Candida* species morphotypes on immune responses may prove an important avenue of research.

Cellular immunity to *Candida* species: the first line of defense

Neutrophils

Neutrophils are crucial components of immunity to both mucosal and systemic *C. albicans* infection [73, 74]. They are the first cell type to be recruited to sites of *C. albicans* infection and are regarded as the most potent cell type in killing the fungus. In humans, neutropenia is a major risk factor for systemic candidiasis and individuals with dysfunctional neutrophils are defective in *C. albicans* killing [75]. Depleting neutrophils renders mice highly susceptible to oral and disseminated *C. albicans* infection [74, 76]. Furthermore, neutrophils are involved in preventing dissemination of *C. albicans* from the gut [77].

Neutropenia is also a risk factor for invasive candidiasis caused by NAC species, such as *C. tropicalis* and *C. krusei* [78] [79–81]. Strikingly, invasive *C. tropicalis* infection is associated with higher mortality rates compared to *C. albicans* infection, though the basis for this is unclear [82]. A crucial role for neutrophils in host defense against disseminated *C. tropicalis* has been confirmed in mouse models [22, 83]. Moreover, reduced neutrophil responses during intra-abdominal *C. glabrata* infection were associated with increased peritoneal fluid fungal burden [84]. Therefore, neutrophils appear to be key components of antifungal immunity against most *Candida* species.

Numerous studies have investigated neutrophil phagocytosis and downstream responses of different *Candida* species, primarily *in vitro*. Several NAC species appear to be killed more efficiently than *C. albicans* [40, 85–87]. For example, killing of *C. tropicalis*, *C. parapsilosis*, *C. krusei* and *C. glabrata* by human neutrophils was higher than *C. albicans* killing [85, 86]. In this regard, *C. albicans* induced more neutrophil cell death compared to *C. glabrata* [88], suggesting that the observed differences may be due in part to an enhanced

capacity of *C. albicans* to kill neutrophils. Indeed, increased phagocytosis of *C. dubliniensis* relative to *C. albicans* uptake by human neutrophils was associated with reduced neutrophil damage, as well as elevated expression of neutrophil killing mechanisms such ROS and lactoferrin [89]. However, not all studies demonstrated a difference in neutrophil phagocytosis and killing of *Candida* species. For example, phagocytosis of serum-opsonized *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. glabrata* by neutrophils was similar [90]. Another study showed that *C. krusei* was phagocytosed less efficiently than *C. albicans* by human neutrophils [91]. Interestingly, *C. parapsilosis* may be more resistant to damage by neutrophils than *C. albicans* in some settings [87]. Overall, it is clear that neutrophils respond to *Candida* species differently, though the mechanisms responsible for these differences still remain poorly understood.

Monocytes/Macrophages

Monocytes/macrophages can directly kill *C. albicans*, and these cells produce cytokines and chemokines required for immune defense. Mice deficient in monocytes or tissue-resident macrophages display increased susceptibility to disseminated *C. albicans* infection [92–94].

Moreover, individuals with mutations in CX_3CR1, the signature chemokine receptor for tissue resident macrophages, were shown to be at increased risk of systemic candidiasis [95]. More efficient phagocytosis and killing of certain NAC species compared to *C. albicans* by macrophages has been reported, similar to neutrophils. *C. parapsilosis* is killed more efficiently than *C. albicans*, a process that involves production of oxygen radicals [96, 97]. Similarly, *C. glabrata* is phagocytosed at higher rates by macrophages than *C. albicans*, which was more lethal to macrophages [88, 97, 98]. In this regard, macrophage phagocytosis rate of *C. albicans* is dependent on fungal morphology, and *C. albicans* hyphae can lyse macrophages [98–100]. Therefore, differences in phagocytosis and killing of *Candida* species by macrophages may partly depend on *Candida* morphogenesis. Interestingly, *C. glabrata* can survive and replicate within macrophages, and be released intact [101]. This survival strategy of *C. glabrata* is based on intrinsic stress resistance and nutrient acquisition, and illustrates differences in the interaction of different *Candida* species with immune cells [102].

Not much is known regarding the physiological requirement of monocytes/macrophages in controlling NAC species. We observed that monocyte or macrophage depletion with clodronate liposomes increased the susceptibility of WT mice to disseminated *C. tropicalis* infection [22]. However, the effects were less profound than neutrophil depletion, suggesting that neutrophils are the dominant cell type required for protection against systemic infection. Notably, depletion of both neutrophils and monocytes by anti-Gr1 Ab treatment significantly increased susceptibility to infection compared to depletion of neutrophils or monocytes/macrophages alone. Therefore, the combined actions of neutrophils and monocytes are likely to be central to antifungal immunity against systemic *C. tropicalis* infection (Figure 1).

Dendritic cells

Although DCs can phagocytose and kill *C. albicans*, their primary role in antifungal immunity is to direct adaptive immune responses [103]. DCs produce cytokines involved in helper Th cell differentiation in response to *C. albicans*, which is dependent on *C. albicans* morphology and DC subset [61, 71]. A crucial role for DCs in immunity to *C. albicans* was recently demonstrated using CD11c-specific deletion of Syk. Syk is a kinase activated by CLRs acting upstream of CARD9, and its loss in DCs rendered mice more susceptible to disseminated *C. albicans* infection. Notably, this study indicated that DC cooperation with NK cells and neutrophils was required for protective immunity against *C. albicans* [104], suggesting that DCs perform important antifungal functions aside from their ability to promote adaptive immune responses.

With respect to NAC species, one report showed that *C. albicans*, *C. dubliniensis* and *C. glabrata* induced IFNβ expression by BMDCs, with *C. glabrata* inducing the highest levels [105]. Moreover, differences in generation of the DC "fungipod", a dorsal pseudopodial protrusion involved in DC function, were demonstrated among *Candida* species. *C. parapsilosis* displayed strong induction of fungipods compared to *C. albicans* and *C. tropicalis* [106]. However, little else is known about the activities of DCs in response to NAC species.

Epithelial cells

Epithelial cells are increasingly being appreciated as key components of immune responses. They are of particular significance for mucocutaneous *Candida* infections, where fungi normally reside as commensal microbes. Epithelial cells can phagocytose *C. albicans*. However, this does not result in killing of the fungus, and in fact has been shown to damage endothelial cells [107]. Oral and vaginal epithelial cells possess candidastatic capacity, which is cell-contact dependent [108–111]. Epithelial cells can also produce cytokines, chemokines and antimicrobial proteins, such as IL-6, IL-8, TNFα, CCL2 and S100A9, in response to *C. albicans* [112–114]. Moreover, epithelial cells can augment neutrophil antifungal activity *in vitro* [115], suggesting that these cell types are important in promoting optimal antifungal immunity, particularly at mucosal surfaces.

In general, NAC species induce weak cytokine and chemokine responses in epithelial cells. For example, *C. albicans* was able to induce efficient expression of IL-6, IL-8, CCL2 and adhesion molecules by endothelial cells *in vitro*, whereas *C. tropicalis* and *C. glabrata* did not [113]. Similarly, human oral epithelial cells produced GM-CSF and other pro-inflammatory cytokines in response to *C. albicans*, but to a much lower degree or not at all in response to *C. tropicalis* or *C. glabrata* [116]. In contrast, another group documented GM-CSF production by oral epithelial cells in response to *C. glabrata* rather than *C. albicans*. In the same study, oral epithelial cells were more resistant to killing by *C. glabrata* compared to *C. albicans* [117]. Clearly, much remains to be learned on the interaction between epithelial cells and NAC species.

Adaptive immunity to *Candida* species: call in the reinforcements

T lymphocytes

CD4$^+$ T cells are vital players in the response to *C. albicans*, particularly Th17 cells, as demonstrated dramatically by both knockout mice and humans with mutations in components of the IL-17 pathway. Deficiency in CARD9, IL-17RA, IL-17RC, Act1, IL-17A IL-23 and STAT3 drive susceptibility to a variety of *C. albicans* infections, including oral, cutaneous and disseminated candidiasis [118]. HIV$^+$/AIDS patients not only have reduced CD4$^+$ cell counts but lose Th17 cells disproportionally to other subsets [119, 120]. AIDS patients are exquisitely susceptible to OPC, with over 95% of patients experiencing oral thrush [121]. In humans, memory T cells specific for *C. albicans* are of the Th17 subset [122, 123]. A similar scenario is observed in mice subjected to recall *C. albicans* infections [124, 125] Furthermore, protective vaccine responses are associated with robust Th1 and Th17 responses [58, 126] Protection against oral and cutaneous candidiasis is more selectively associated with specific Th17 immunity, whereas both Th1 and Th17 responses participate against systemic infection [124, 127–130].

Evidence for an involvement of CD4$^+$ T cell responses in immunity to NAC species also exists. Sepsis caused by *C. parapsilosis* in an infant with ectodermal dysplasia and thymic hypoplasia was associated with reduced T cell numbers and reduced T cell proliferative capacity [131]. Both cross-reactive and distinct T cells are generated in response to different *Candida* species. Human T cells generated following stimulation with *C. albicans* cellular extract displayed cross-reactivity with *C. tropicalis* but not *C. glabrata* [132]. Despite the generation of CD4$^+$ T cell responses with distinct specificity, it seems that induction of IL-17A by CD4$^+$ T cells is a common feature of *Candida* species. *C. albicans* and *C. dubliniensis*, which are the most closely related phylogenetically, were found to trigger the most IL-17A, whereas the distantly related *C. glabrata* induced the least [125]. Given the protective role of IL-17 responses in immunity to *C. albicans*, it would be predicted that IL-17 immunity is similarly involved in responses to NAC species. However, IL-17-dependent responses were dispensable for protection against a mouse model of disseminated *C. tropicalis* infection. Rather, CARD9-dependent TNFα responses were crucial for protection [22]. Therefore, the dogma that IL-17 immunity is central to host defense against *Candida* may not hold true for all *Candida* species.

Innate lymphocytes

The recent recognition of various innate lymphocyte populations [133] has prompted reassessment of innate vs. adaptive immune responses in antifungal immunity to *Candida*. Such cell types include TCR-expressing subsets (NKT, γδ-T, ‘natural’ T cells) and TCR-negative cell types (NK, ILC1, ILC2, ILC3) [134]. Depletion of γδ T cells increased susceptibility to *C. albicans* infection, and γδ T cells enhanced macrophage nitric oxide production and candidacidal activity *in vitro* [135]. Since then, several other studies have confirmed a key role for γδ T cells in host defense against *C. albicans* infection, with a principle mechanism involving IL-17 production [136–138]. Additionally, we showed that “natural” Th17 cells protect against acute oral *C. albicans* infection in conjunction with γδ T cells [136]. Although ILC3 cells were suggested to be involved in antifungal immunity

against *C. albicans* [139], they were not evident in other analyses [136]. NK cells possess anti-*Candida* killing ability and have been implicated in protection against disseminated *C. albicans* infection [140, 141]. However, a protective role for NK cells against *C. albicans* infection is controversial and may depend on host immune status [142]. More recently, reduced numbers of NKT and mucosal-associated invariant T (MAIT) cells that showed a selective defect in IL-17 production were documented in individuals with mutations in *STAT3* [143]. *STAT3* mutations are consistently associated with CMC [118], implicating these poorly understood T cell populations in antifungal immunity to *Candida*.

Again, little is known about the role of innate lymphocyte populations and NAC species immunity. However, emerging data hints at differences. For example, nTh17 cells were not induced during oral *C. glabrata* exposure, in contrast to *C. albicans* [136]. Furthermore, we saw no apparent role for innate T cells, ILCs or NK cells in protection against disseminated *C. tropicalis* infection, based on the observation that *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice did not display increased susceptibility to systemic infection [22].

Antifungal mechanisms: soluble factors

Cytokines and chemokines

A myriad of cytokines and chemokines are associated with protection against *C. albicans* infection. In addition to IL-17 discussed above, these include factors that promote development and recruitment of neutrophils, such as GM-CSF, G-CSF, CXCL1 and CXCL2 [130, 144]. Similarly, cytokines that promote phagocyte killing and recruitment, such as TNFα, IL-6, IL-1β and IFNγ, are key in host defense against *C. albicans*. Indeed, recombinant GM-CSF and IFNγ therapy have been used in the clinic to protect against mucosal and systemic *C. albicans* infections, though the utility of this approach is still under investigation [145–147].

Similarities in the induction of cytokines and chemokines by different *Candida* species have been reported, at least *in vitro*. However, *C. glabrata* is generally associated with the activation of weak cytokine and chemokine responses. For example, *C. albicans*, *C. tropicalis* and *C. krusei* induced IL-1β production by BMDMs, whereas *C. glabrata* did not [148]. Similarly, *C. albicans* but not *C. glabrata* promoted epithelial cell production of IL-8 and IL-1α [117]. However, several studies suggest that *C. glabrata* may favor GM-CSF production, as this NAC species induced production of GM-CSF by both epithelial cells and BMDMs *in vitro* [101, 117].

In contrast to the above *in vitro* studies, disseminated *C. glabrata* infection is associated with the production of TNFα, IL-12p35 and IFNγ [43, 149]. TNFα appears to be central in controlling *C. glabrata* growth, as Ab blockade of TNFα but not other cytokines increased kidney fungal burden [149]. We recently showed that depletion of TNFα by etanercept treatment renders mice more susceptible to disseminated *C. tropicalis* infection compared to controls [22]. Therefore, TNFα may be a broadly applicable antifungal mechanism.

Certain cytokines enhance phagocyte killing of *Candida* species. G-CSF augments neutrophil damage of *C. albicans*, *C. parapsilosis* and *C. tropicalis*. Interestingly however,

IFNγ enhances neutrophil damage of *C. albicans* and *C. parapsilosis* but not *C. tropicalis* [87]. Overall, the impact of cytokines and chemokines in response to *Candida* are not identical.

Antimicrobial peptides and reactive chemical species

Other important antifungal events include the production of antimicrobial peptides (AMPs) and reactive chemical species, such as ROS. These soluble effectors directly kill *C. albicans*, and are primarily produced by phagocytic cells and epithelial cells. A major AMP associated with oral candidiaiss in mice is β-defensin 3 (BD3) [124, 130]. Moreover, deficiencies in BD1, S100A8 and S100A9 lead to heightened susceptibility to mucosal and systemic *C. albicans* infection [150–152]. *C. albicans* dissemination from the GI tract occurs in mice deficient in components of the ROS and RNS pathways [153]. In humans, Chronic Granulomatous Disease (CGD) patients that have defects in the NADPH oxidase system are at increased risk of invasive candidiasis and neutrophils from CGD patients are defective in killing opsonized *C. albicans* [154, 155].

Antimicrobial peptides including β-defensins, histatins, H1 histones and lactoferrin display antifungal activity against multiple *Candida* species [156–158]. Synthetic peptides can also kill *C. albicans*, *C. tropicalis* and *C. glabrata* strains *in vitro* [159] [160] [161]. In general, the antifungal activity of AMPs appears to vary among specific *Candida* strains rather than species. However, *C. glabrata* displays increased resistance to human BD2, BD3 and histatin compared to other species [162, 163].

Reactive chemical species are also implicated in immunity to NAC species. For example, $p47^{phox-/-}$ mice are significantly more susceptible to disseminated *C. glabrata* infection [164]. Moreover, myeloperoxidase $(MPO)^{-/-}$ mice were impaired in clearance of *C. albicans* and *C. tropicalis* from the lungs [165]. In contrast, clearance of lung *C. glabrata* was comparable between $MPO^{-/-}$ and WT mice. Therefore, although AMPs and reactive chemical species are involved in host defense against NAC species, considerable differences exist among *Candida* species.

Challenges to studying NAC species

It is clear that our understanding of immunity to NAC species is still immature. This is partly because *C. albicans* remains the dominant *Candida* species isolated in the Western world. However, other hurdles have made studying immunity to NAC species difficult. One issue is the paucity of NAC species-specific tools. As the *Candida* field has largely focused on *C. albicans*, a wealth of genetic mutants exist, such as morphotype-locked mutants, fluorophore-expressing reporters (e.g., GFP, Luciferase), and epitope-tagged strains for *in vivo* tracking [138, 166]. A parallel collection of genetic mutants does not yet exist for NAC species, although progress is being made for *C. glabrata* [167].

Another roadblock is that many NAC species are not usually pathogenic in mouse models of candidiasis, in contrast to *C. albicans*. For example, in a mouse model of disseminated candidiasis, WT mice did not succumb to *C. parapsilosis*, *C. krusei* or *C. glabrata* infection [168]. Similarly, *C. dubliniensis* is far less pathogenic than *C. albicans* in mouse models of

disseminated and gastrointestinal infection [169–171]. In a model of oral candidiasis, even WT mice immunosuppressed with high dose cortisone were able to clear *C. tropicalis*, *C. dubliniensis* and *C. glabrata* without any signs of disease (NW and SLG, unpublished observations). These differences in susceptibility to *Candida* infection may reflect phenotypic variation among *Candida* species discussed above, but could also be explained by immune differences between mice and humans. Regardless of the reason, the field lacks tractable animal models with which to study these important pathogens. However, advances have been made with a newly described murine model of intra-abdominal *C. glabrata* infection, which closely mimics human disease [84]. Nevertheless, the difficulty in studying immune responses to NAC species *in vivo* means that most information to date has been gleaned from *in vitro* approaches which do not necessarily recapitulate the physiological environment. For instance, strains of *C. tropicalis* that do not form hyphae *in vitro* have been identified, yet it is unknown whether this holds true *in vivo* [23]. In this regard, we observed that a *C. tropicalis* clinical isolate did not form filamentous hyphae *in vitro*, yet formed invasive hyphae in kidneys [22]. Developing faithful models to understand immunity to NAC species is key for future studies in this area.

Consequences for emerging biologics

The first biologics to be approved for clinical use targeted TNFα, and have been successful in treating rheumatoid arthritis and other autoimmune conditions for the last 2 decades. Although cases have been reported, anti-TNFα therapy is not commonly associated with heightened risk of *Candida* infections [172]. However, meta-analyses have indicated that candidiasis may be an under-recognized opportunistic infection associated with this therapy [173]. We recently showed that immunity to systemic *C. tropicalis* infection is TNFα-dependent [22]. One reason this infection is not commonly reported may be that, although anti-TNFα therapy is widely used in the Western world, this is not true in developing countries due to high costs. Given the geographical differences in prevalence between *C. albicans* and *C. tropicalis*, it is conceivable that the risk of *Candida* infection associated with anti-TNFα therapy is underestimated.

Antibodies targeting IL-17 (secukinumab) or IL-12/IL-23 (ustekinumab) have shown impressive effects for the treatment of psoriasis and were recently approved for clinical use [174]. Given the importance of IL-17 responses in immunity to *C. albicans* infection, an obvious potential risk factor is increased susceptibility to this fungus. Indeed, early reports have documented increased mucosal *Candida* infections in patients receiving sekukinumab, although the frequency of particular *Candida* species was low [175]. However, given our finding that the IL-17 pathway is not required for protection against disseminated *C. tropicalis* infection in mice [22], IL-17 pathway biologics may not increase susceptibility to all *Candida* species.

Perspective

The rise in resistance to antifungal drugs and the lack of new medications or vaccines against *Candida* has prompted interest in development of novel treatment strategies. One example is immunotherapies that could be used alone or in combination with current

treatments. The dogma on immunity to *Candida* infection is based almost entirely on our knowledge of immunity to *C. albicans*. As described here, important differences exist in immunity to *Candida* species. Given the rise in NAC species infections, it is pertinent to understand immunity to these emerging pathogens. Unraveling the similarities and differences in immunity to *C. albicans* and other *Candida* species will pave the way for appropriate immunotherapies and vaccines.

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Abbreviations

AMP	antimicrobial peptide
ILC	innate lymphoid cell
CARD9	caspase recruitment domain family member 9
CLR	C-type lectin receptor
OPC	oropharyngeal candidiasis
NAC	non-albicans Candida species
CMC	chronic mucocutaneous candidiasis
PRR	pattern recognition receptor
VVC	vulvo-vaginal candidiasis

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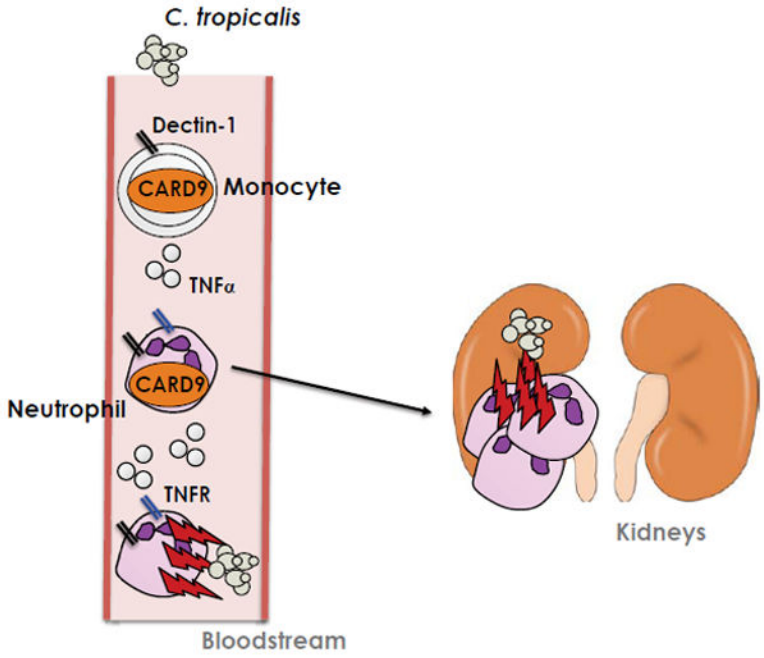

Figure 1. Model of immunity to disseminated *C. tropicalis* infection

C. tropicalis is rapidly recognized by neutrophils and monocytes following invasive infection. Recognition by dectin-1 and other PRRs activates CARD9, which is crucial for host defense against *C. tropicalis*. CARD9 activation triggers the production of TNFα by both neutrophils and monocytes, which acts upon neutrophils to augment antifungal killing of *C. tropicalis*. TNFR = TNFα receptor.

Table 1

Phenotypic differences among *Candida* species

Clinically relevant *Candida* species vary in morphological capacity, fermentative growth ability, yeast cell size and virulence factor composition.

Candida species	Morphology			Fermentation			Yeast cell size	Sap virulence factors
	Yeast	Pseudohyphae	Hyphae	Glucose	Maltose	Galactose	Diameter (μM)	Number
albicans	+	+	+	+	+	V	4–10	10
dubliniensis	+	+	+	+	+	V	4–10	8
tropicalis	+	+	+	+	+	+	5–11	4
parapsilosis	+	+	−	+	−	V	3–9	3
krusei	+	+	−	+	−	−	3–10	?
glabrata	+	+/−	−	+	−	−	2–4	?

*Yeast cell size is approximate.

Sap = secreted aspartyle proteinase. V = variable.