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Review Article

Candida Immunity

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The human pathogenic fungus *Candida albicans* is the predominant cause of both superficial and invasive forms of candidiasis. *C. albicans* primarily infects immunocompromised individuals as a result of either immunodeficiency or intervention therapy, which highlights the importance of host immune defences in preventing fungal infections. The host defence system utilises a vast communication network of cells, proteins, and chemical signals distributed in blood and tissues, which constitute innate and adaptive immunity. Over the last decade the identity of many key molecules mediating host defence against *C. albicans* has been identified. This review will discuss how the host recognises this fungus, the events induced by fungal cells, and the host innate and adaptive immune defences that ultimately resolve *C. albicans* infections during health.

1. Introduction

Current estimates indicate that there approximately 600,000 species of fungi on Earth [1]; however, only 0.1% (600 species) of these fungi are thought to be human pathogens [2, 3]. These range from mild infections of the skin and cutaneous tissues (e.g., dermatophytes, *Malassezia* species, and *Sporothrix schenckii*) to invasive life-threatening systemic infections (e.g., *Candida* species, *Aspergillus fumigatus*, *Cryptococcus neoformans*, and *Histoplasma capsulatum*) [4]. However, fungal infections only really became recognised as being of clinical importance in the second half of the 20th century with the onset of the AIDS epidemic. Together with advances in medical treatments such as cancer therapy and allogeneic transplantation, there has been a dramatic increase in the prevalence of fungal infections over the past three decades. This is the combined result of reduction of the $CD4^+$ lymphocyte population of the cell-mediated immune system and the use of immunosuppressive intervention therapies. This trend is likely to continue over the coming decades, particularly as further improvements are made in healthcare for immunocompromised patients.

The predisposition of certain patient groups to opportunistic fungal infections led to a notable increase in research into pathogenic fungi, predominantly on *Candida* species, *Cryptococcus neoformans,* and *Aspergillus fumigatus* [5]. This resulted in the unravelling of many fundamental biological processes that take place during host-fungal interactions, particularly with regard to *Candida* species. *Candida* species are one of the most common fungal pathogens of humans and the causative agents of superficial and invasive candidiasis, giving rise to severe morbidity and mortality in millions of individuals worldwide. Vaginal candidiasis alone affects ~75% of women at least once during fertile age [6, 7], equating to ~30 million infection episodes per year. *Candida* infections are also a common oral manifestation of human immunodeficiency virus (HIV) infection, with 50% of HIV+ patients and 90% AIDS patients suffering from oral candidiasis [8–10]. With ~4 million cases of HIV per year, this equates to ~2 million oral candidiasis cases. *Candida* species also cause mucosal diseases in the edentulous and elderly individuals, such as *Candida*-associated denture stomatitis. Furthermore, depending on the study, *Candida* infections are also the 3rd or 4th most common hospital-acquired blood stream infection, being more deadly than most bacterial infections including Gram-negative septicaemias such as Enterococci (*Escherichia coli*) and *Pseudomonas* spp. [11, 12]. Therefore, *Candida* pathogens carry an immense health burden and represent a major socioeconomic challenge for worldwide communities.

The most common fungi endogenous to humans are *Candida* species. The most abundant is *Candida albicans*,

a polymorphic fungus that resides as a commensal of mucosal tissues in approximately 40–80% of individuals and is represented by a mixed strain population [13]. Epidemiological and mycobiome studies reveal that other *Candida* species also reside in mucosal tissues, including *C. glabrata*, *C. parapsilosis*, *C. tropicalis,* and *C. krusei* [14–16], all of which are also important opportunistic pathogens of humans [17]. Given that the majority of life-threatening systemic *Candida* infections are acquired across the mucosae (predominantly gut), it is of paramount importance to understand the basic biological mechanisms that normally restrict *Candida* species to mucosal surfaces. Therefore, understanding the mechanisms involved in host-*Candida* interactions in both mucosal and systemic compartments is of fundamental importance, particularly those involved in discriminating between the commensal and pathogenic forms of *Candida* species and in initiating immune responses. Given that *C. albicans* is regarded as the most pathogenic *Candida* species, this review will provide a brief overview of *C. albicans* virulence followed by a detailed analysis of how this fungus interacts with the host immune system.

2. *C. albicans* Virulence and Pathogenicity

All pathogenic microorganisms have developed mechanisms that allow successful colonisation or infection of the host [18]. However, unlike bacteria, which often develop unambiguous ways of causing host infections, *C. albicans* has more advanced mechanisms in order to cause disease and overcome host defences. *C. albicans* is highly adapted to humans as a commensal organism and, accordingly, has developed an effective battery of strategies and factors that are required primarily to colonise host tissues, but which have potential to cause disease under suitable predisposing conditions. Notably, transition from harmless commensal to disease-causing pathogen is finely balanced and can be attributable to the delicate interplay of an extensive repertoire of virulence determinants [19]. Therefore, *C. albicans* has evolved to possess general attributes that contribute to survival, fitness, and persistence within the host, as well as specific virulence factors associated with adhesion, invasion, cell damage, and induction/evasion of host responses [4, 19–28]. However, the virulence factors expressed or required by *C. albicans* to cause disease will vary depending on the infection site (e.g., mucosal or systemic), the stage of infection, and the nature of the host response. Although many factors have been suggested to be virulence attributes for *C. albicans*, hypha and biofilm formation, cell wall-associated adhesins, invasion, and damage induction are still thought to be the most significant fungal processes [4, 21, 29–33].

Perhaps the most widely accepted virulence attribute of *C. albicans* is hypha formation leading to invasion [34–36]. However, the role of morphogenesis in *C. albicans* virulence has been debated for many years [37]. The populist view is that hyphal cells are invasive (and by extrapolation more pathogenic) and that yeast cells are noninvasive (and, therefore, less pathogenic or commensal in nature). In reality, both yeast and hyphal cells contribute to *C. albicans* infection of different organs; for example, filamentation is observed in the kidney but less so in the spleen or liver during invasive candidiasis [38]. Although there is no clear evidence which morphology predominates during the commensal phase in humans, the expression of hypha-associated genes is regularly detected during asymptomatic carriage [39–43]. Thus, the concept of fungal burdens with regard to hypha formation and infection is important to keep in mind, but it should be noted that hypha-associated genes are expressed by yeast cells under certain conditions [44, 45]. Furthermore, the expression of hypha-associated genes by *C. albicans* yeasts colonising the murine gastrointestinal tract after removal of the bacterial flora has been demonstrated [44, 46].

With the above precautions in mind, it is generally accepted that hypha formation is required for full virulence in *C. albicans*. As such, many of virulence factors that promote *C. albicans* pathogenicity appear to be inextricably linked to hypha formation (e.g., adhesion, biofilm formation, invasion, and damage induction). Furthermore, wild-type *C. albicans* strains unable to produce true hyphae or mutants lacking either key regulators of hyphal development (e.g., *efg1*Δ, *ras1*Δ, *hgc1*Δ, *eed*Δ, and *ume6*Δ) or hypha-associated adhesins (e.g., *als3*Δ and *hwp1*Δ) exhibit strongly reduced adhesion to host cells and are attenuated in virulence [24, 34–36, 47–51]. Indeed, the transcription factor, Efg1, is thought to be an important regulator of gastrointestinal colonisation [52, 53].

Notably, hypha formation, invasion, and damage induction are closely linked. Invasion of *C. albicans* into host cells requires hyphae and appears to be mediated by two key processes: induced endocytosis and active penetration [34, 47, 54–58]. Induced endocytosis is hostdriven and only hyphal cells appear to be endocytosed by host cells [34, 57]. Active penetration on the other hand is fungal-driven and is mediated by hyphal extension and the production of hypha-associated factors, including hydrolytic enzymes such as secreted aspartic proteinases (e.g., Sap4-6) [21, 47, 55, 59]. However, although important, hypha formation is probably not the only factor that contributes to tissue destruction. Irrespectively, these processes will promote invasion and subsequently the induction of damage to host cells. These are just some examples of how *C. albicans* virulence attributes are linked and contribute to fungal pathogenicity. The reader is guided to the following reviews for more in-depth discussion of the virulence factors that contribute to *C. albicans* pathogenicity [4, 21–29, 32, 33, 60–62].

Given the serious morbidity and potentially life-threatening infections *C. albicans* can cause, it is essential that the host possesses mechanisms to recognise and discriminate between the commensal and pathogenic states of *C. albicans* in order to raise an appropriate and protective host immune response. The remainder of this review will concentrate on the host innate and adaptive defence mechanisms that detect and control this fungal pathogen.

3. Innate Immune Recognition of *Candida*

Host immune recognition of *Candida* occurs via several mechanisms comprising innate and adaptive immunity.

Table 1: Fungal pattern recognition receptors.

PRR	Location	Recognition molecules	Role in fungal response
TLRs			
TLR1/2	Surface	Zymosan/β-glucans?	Probably
TLR2	Surface	Phospholipomannan; zymosan	Yes
TLR2/6	Surface	Zymosan/β-glucans?	Probably
TLR3	Endosomal	dsRNA	Possibly
TLR4	Surface/cytoplasmic	*O*-linked mannan	Yes
TLR9	Endosomal	Unmethylated CpG fungal DNA	Yes
C-type lectins			
Dectin-1	Surface	β-1,3 glucan; mannan; zymosan	Yes
Dectin-2/3	Surface	High mannose structures; α-mannan	Yes
Mannose receptor	Surface	*N*-linked mannan, N-acetylglucosamine	Yes
Mincle	Surface	α-Mannan	Probably
DC-SIGN	Surface	High (*N*-linked) mannose structures	Possibly
Galectins	Cytoplasm/nucleus; extracellular	β-1,2 mannosides (variety of complex N-glycans)	Probably
NLRs			
NLRP3	Cytoplasmic	Variable (zymosan; β-glucan)?	Yes
NLRC4	Cytoplasmic	Variable (zymosan; β-glucan)?	Yes

Table adapted from [63].

The adaptive immune system recognises specific antigenic moieties, leading to the development of a targeted immune response (see Section 5). In contrast, innate immune recognition is nonspecific and broad and is the first line of host defence against potentially dangerous microbes. These nonspecific responses are immediately activated upon recognition of a microbe in a preprogrammed fashion and play an essential role in controlling fungal burdens and preventing disease. Innate immunity comprises of a series of soluble (complement) and cellular (neutrophil, macrophage) components that act in concert to prevent the vast majority of pathogens from establishing an invasive infection. Further, it has become increasingly evident that these responses function to activate adaptive immunity as well as acting together with other homeostatic processes to provide further protection.

Innate immune recognition of *Candida* occurs via the recognition of pathogen-associated molecular patterns (PAMPs). PAMPs are motifs or molecules that are common between different types of fungi. Unlike antigens, individual PAMPs are not specific to a single *Candida* species but rather are shared between many different species and fungal genera. These microbial PAMPs are recognised by host germ-line encoded pattern recognition receptors (PRRs) [64] and provide a preprogrammed mode of fungal recognition, allowing for instant recognition of common fungal components. Table 1 lists the current *Candida* PAMPs and the PRRs that recognise them. The majority of fungal PAMPs are cell wall associated and include β-glucans, *N*- and *O*-linked mannans, and phospholipomannans [65]. These are recognised by three key PRR families: toll-like receptors (TLRs), C-type lectin receptors (CLRs), and nucleotide-binding domain leucine-rich receptors (NLRs) [63, 65–70]. These PRRs are expressed either on the surface, in endosomes or in the cytoplasm of host cells, including dendritic cells, monocytes, macrophages, polymorphonuclear leukocytes (PMNs), T cells, B cells, and epithelial cells. Activation of these PRRs by PAMPs leads to triggering of intracellular signalling pathways, such as MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathways, and ultimately to enhanced transcription of a multitude of genes involved in host immune defences, including chemokines, cytokines, inflammatory mediators, and antimicrobial peptides. As such, PRRs are critical mediators between innate and adaptive immune responses.

3.1. Receptor Molecules in Candida Recognition. The human genome encodes for ten TLR genes (TLR1–10) whilst the murine genome encodes twelve (TLR1–9, 11–13). All TLRs are characterized as type I transmembrane receptors possessing an extracellular leucine-rich repeat domain that recognises the target PAMP and a Toll/interleukin-1 receptor- (TIR-) domain containing cytoplasmic domain that transmits the activation signal, which has high similarity to the type 1 interleukin-1 (IL-1) receptor. The TLR family is an evolutionarily conserved group of PRRs that respond to a variety of bacterial, viral, and fungal PAMPs as well as some endogenous factors released when host cells are damaged. The extracellular domains of TLRs recognise a variety of microbial PAMPs, including lipopolysaccharide (LPS), peptidoglycan, proteins (including triacylated proteins and flagellin), and modified nucleic acids (unmethylated CpG rich DNA, double and single stranded RNA) [71–76].

3.1.1. TLR Recognition of Candida. A fundamental role for TLRs in antifungal host defence was first discovered when

Drosophila deficient in the Toll receptor were observed to be highly susceptible to *A. fumigatus* infection [77]. As a result, the vast majority of the initial antifungal immunity research targeted how fungal cells were recognised. This led to the identification of several PRRs involved in recognition of different cell wall polysaccharides of fungi and *C. albicans* in particular, including TLR2 (phospholipomannan), TLR4 (*O*-linked mannan), and mannose receptor (MR) (*N*-linked mannan) [65, 66, 78]. Ultimately, these studies culminated in the discovery of a new PRR, dectin-1 (dendritic cell-associated C-type lectin-1), which recognises fungal β-1,3 glucan [79]. Notably, these fungal PRRs can function both independently and in conjunction with one another. For example, dectin-1 and TLR2 act synergistically to recognise fungal yeasts, with dectin-1 inducing phagocytosis whilst TLR2 induces cytokine production [80–82]. Dectin-1 also synergises with TLR4 signalling [82]. In addition, TLR1 and TLR6 form heterodimers with TLR2 [83] but do not appear to play a major role in *C. albicans* recognition in a mouse model of invasive candidiasis [84]. It appears that depending on the coreceptor involved, coligation of TLR2 may either enhance TLR2-dependent responses [85] or modulate its PAMPs specificity as in the case with galectin-3 [86].

Although these are main receptors utilised by macrophages and neutrophils to recognise *C. albicans*, other receptors have also been identified including dectin-2 [87], mincle (macrophage inducible CTL) [88], DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin) [89, 90], and galectin-3 [86]. The role of these PRRs is currently not fully established; however, dectin-2 and DC-SIGN are thought to play an important role in the recognition of high mannose structures [91] and galectin-3 in the recognition of β-1,2 mannosides [86]. Interestingly, galectin-3 coimmunoprecipitates with dectin-1 [92], which suggests that galectin-3 may facilitate interactions between TLR2 and dectin-1 signalling. TLR recognition of other medically important fungi have also been studied but are less well characterised, although it appears that TLR3 recognises *A. fumigatus* conidia and TLR4 recognises *C. neoformans* glucuronoxylomannan, with TLR9 recognising *A. fumigatus*, *C. neoformans,* and *C. albicans* [93].

3.1.2. TLR Signalling. PAMP recognition by TLRs results in the activation of intracellular signalling pathways (Figure 1) through interaction of the cytoplasmic TIR domains with different adapter proteins: myeloid differentiation primary response gene (88) (MyD88), MyD88-adapter-like (MAL), TIR-domain containing adapter-inducing interferon-β (TRIF), and TRIF-related adaptor molecule (TRAM) [71–76, 94–97]. This TLR-adapter interaction leads to the activation of the IRAK (IL-1 receptor associated kinase) proteins and TRAF6 (TNF receptor associated factor-6). In turn, this leads to activation of the major signalling pathways including NF-κB, MAPK, and IRF (interferon regulatory factor) pathways. MAPK activation comprises three pathways: p38, JNK (c-Jun N-terminal kinase), and ERK1/2 (extracellular signal-regulated kinase1/2). Ultimately, signalling pathway induction leads to the activation and nuclear localisation of transcription factors including NF-κB, AP-1 (activating protein 1), and IRF-3 and IRF-7. The outcome of this activation cascade is to induce gene expression and secretion of various proteins involved in immune defence including cytokines, chemokines, antimicrobial peptides, and other inflammatory mediators, all of which function to trigger innate and adaptive immune responses. It should be noted that the vast majority of studies defining the TLR-mediated pathways have been performed using myeloid or lymphoid cells, but detailed analysis of TLR-mediated pathways in other cell types, and specifically epithelial cells, may yet identify novel and unusual mechanisms of pathogen (fungal) recognition and control at mucosal surfaces.

3.1.3. Role of TLRs during Candida Infection. Although mice lacking the TLR signalling adapter protein MyD88 are susceptible to fungal infection [65, 98–100], the precise role of individual TLR receptors in combating *Candida* infections is less clear. This is probably due to differences in study design, where different fungal species, morphotypes, and routes of infection have been assessed [70]. Consequently, studies using TLR knockout mice have revealed significant differences in the putative roles of different TLRs in systemic or mucosal immune responses against fungal infections [101]. For example, while some studies indicate that TLR2 and TLR4 influence susceptibility to murine disseminated candidiasis [100, 102–104], not all studies support this assertion [105, 106]. TLR7 may be required for fungal RNA recognition in the autophagosome, which is required for IFN-β release and is associated with prolonged *C. glabrata* infection [107]. TLR9 recognises *C. albicans* DNA (unmethylated CpG sequences) resulting in cytokine production in dendritic cells [108]; however, TLR9 knockout mice do not appear to be more susceptible to *C. albicans* infection, despite producing decreased levels of IL-12 and increased amounts of IL-4 and IL-10 [100, 108–110]. Notably, specific TLRs (TLR2, TLR4, TLR6, and TLR9) appear to harbour different roles depending on which arm of the innate immune response they engage with, for example, promotion of adaptive responses by facilitating antigen presentation in dendritic cells [111].

Several studies have associated common genetic variants (polymorphisms) in TLR genes with susceptibility or predisposition to systemic candidiasis or chronic mucocutaneous candidiasis (CMC). These include polymorphisms in TLR1 (R80T, N248S, and S602I) [112, 113] and TLR3 (L412F) [114, 115]. Polymorphisms in TLR4 (D299G) and TLR2 (D753Q) have also been identified as possible susceptibility markers for systemic candidiasis [116] but these could not be substantiated in a larger study [113]. Currently, most of the data available suggests a strong role for TLRs in antifungal defence but identifying specific roles for each TLR has been overshadowed by redundant signals induced by other PRRs [112].

3.1.4. C-Type Lectin Receptors. C-type lectin receptors (CLRs) are a superfamily of heterogeneous binding proteins that are characterised by the presence of an extracellular

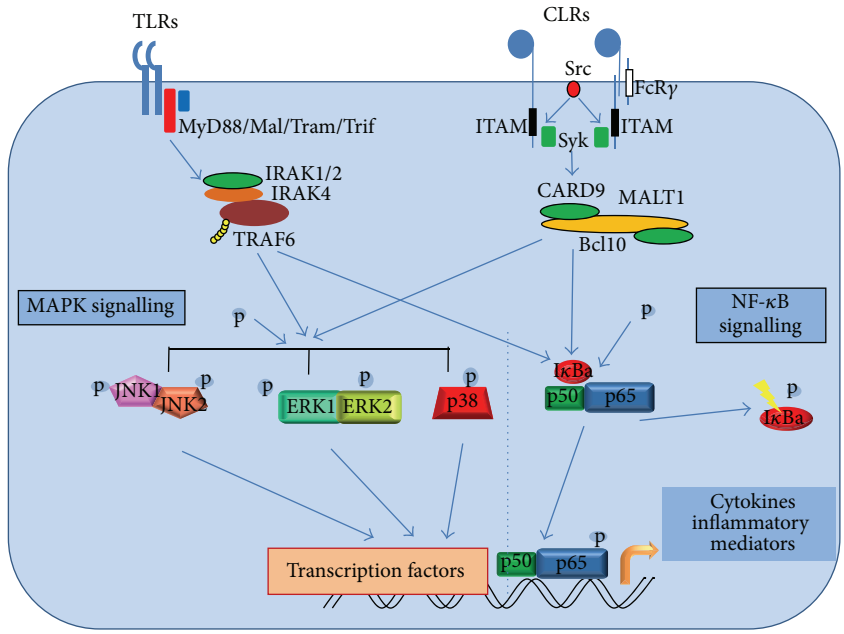

FIGURE 1: Signal pathway activation by TLRs and CLRs. TLRs and CLRs activate MAPK and NF-κB signal pathways to varying extents, thereby allowing different innate immune responses to be generated. TLRs utilise TIR-domain containing adapter proteins such as MyD88, Mal, TRAM, and TRIF. CLRs signal using ITAM domains within their cytoplasmic region (e.g., dectin-1) or associate with an ITAM-containing transducing protein (e.g., dectin-2 with FcRγ). Dectin-1 utilises Src kinases and Syk kinase to activate a complex containing CARD9, MALT1, and Bcl10 to activate the downstream signal pathways. Figure adapted from [63].

carbohydrate-recognition domain (CRD) or a C-type lectin-like domain (CTLD) [117]. The role of CLRs in antifungal immunity has been the subject of intense study in recent years and several key CLRs have now been demonstrated to display critical functions in *Candida* recognition, uptake, and killing and also contribute to the initiation and/or modulation of the immune response to fungi [65, 118, 119]. Currently, the key CTLs in *Candida* recognition appear to be dectin-1, dectin-2, and MR.

CLRs signal through activation of ITAM/ITIM (immunoreceptor tyrosine-based activation/inhibition motif) cytoplasmic domains (Figure 1). This can be achieved via their own cytoplasmic domain, as with dectin-1, or through use of coreceptor cytoplasmic domains, for example, DAP12 (DNAX activation protein of 12 kDa) and FcRγ (Fc receptor gamma chain), as with dectin-2. CLR ligation leads to the activation of different adaptors to those activated by TLRs, predominantly Src family kinases such as Src, Lyn, and Fyn. With regard to dectin-1, this leads to activation of spleen tyrosine kinase (SYK) and the downstream activation of the CARD9/Bcl10/MALT1 (caspase recruitment domain family/B cell CLL-lymphoma 10/mucosa associated lymphoid tissue lymphoma translocation gene 1) signalling complex. Irrespective of the CLR pathways and adapters used, the ultimate consequence is the activation of similar signalling pathways as those activated by TLRs, predominantly NF-κB and MAPK.

3.1.5. Dectin-1. Dectin-1, (also known as CLEC7a) is the main CLR identified as playing a major role in fungal recognition by the host immune system [120] and is a type II transmembrane protein that belongs to a subgroup of CLRs called natural killer (NK) receptor-like CLRs. The target ligands of dectin-1 are β-1,3 glucan polymers, which comprise a major part (~60%) of fungal cell walls. The intracellular region of dectin-1 contains a modified ITAM motif containing a single tyrosine residue instead of the usual two (hence the terms hemITAM or hemi-ITAM). Activation of the dectin-1 leads to phosphorylation of this domain and phosphorylation of SYK and activation of the Bcl10-CARD9-MALT1 complex as mentioned above. This leads to activation of both the canonical and noncanonical NF-κB pathways [121] as well as nuclear factor of activated T cells (NFAT) pathway [122]. Dectin-1 can also induce signalling via Raf-1 in a SYK-dependent fashion [121] and is associated with phospholipase C and A2 activation [68].

One of the major functions of dectin-1 binding appears to be the induction of phagocytosis [123]. However, a unique feature of dectin-1 is its ability to be activated or suppressed by its target ligand. To fully activate dectin-1, cells need to be exposed to insoluble β-glucan particles. Notably, exposure of dectin-1 to soluble β-glucan appears to block activation. This seems to be due to the apparent need to form a "phagocytic synapse," whereby phosphatases that normally suppress ITAM motifs are accumulated. This exclusion subsequently permits the phosphorylation of the intracellular hemITAM motif [124], thereby enabling phagocytosis. Dectin-1 has also been shown to synergise with both TLR2 and TLR4, resulting in the induction of tumour necrosis factor (TNF)α,

IL-10, transforming growth factor (TGF)β and dendritic cell maturation [125–127].

Given that β-1,3 glucan polymers are major constituents of fungal cell walls and strongly immune activatory, dectin-1 also plays a role in inducing host antifungal activity. This could also possibly explain why some fungi have developed surface structures to "mask" β-1,3 glucan from the immune system. For instance, *Histoplasma capsulatum* masks its β-1,3 glucan with a layer α-1,3 glucan [128] and it seems that *C. albicans* hyphae β-1,3 glucan is masked by layers of *N*- and *O*-linked mannoproteins to prevent detection by dectin-1. However, in the yeast form of *C. albicans*, although *N*- and *O*-linked mannoproteins are present, the underlying β-glucan layer can become exposed at the budding scar, allowing recognition by dectin-1. Thus, it could be postulated that the primary role of dectin-1 is in the recognition of yeast forms of *Candida*. In addition, the β-glucan that is present in *C. albicans* hyphal cell walls appears to be structurally different to yeast β-glucan [129] and, thus, may not be as immune activatory or recognisable by dectin-1.

Although some studies have failed to demonstrate dectin-1 expression in epithelial cells from the gastrointestinal tract [130] and the lung [131, 132], oral epithelial cells do express dectin-1 [133, 134]. Interestingly, dectin-1 expression appears to be downregulated in the presence of viable *C. albicans* cells [134] and is unaffected by dectin-1 ligands [133, 135]. This suggests that dectin-1 probably plays a minor role in epithelial cell detection of *C. albicans*.

Studies using dectin-1 knockout mice have provided mixed data sets with regard to systemic *C. albicans* infection models, showing both no difference [136] and increased mortality [137] depending on the study and the *C. albicans* strain used. On the one hand, a role for dectin-1 is supported given that CARD9 knockout mice are susceptible to systemic fungal infection [138] and that patients with CARD9 primary immunodeficiency are susceptible to both mucosal and systemic candidiasis [139]. On the other hand, another study investigating the role of the common genetic polymorphism in CARD9 (S12N) showed no role for CADR9 in systemic candidiasis, suggesting that the β-glucan recognition pathway might be redundant in systemic immunity to *C. albicans* [140]. Nevertheless, a recent study has identified a potential role for dectin-1 in the maintenance of mucosal health. Dectin-1$^{-/-}$ mice showed increased severity of disease during induced colitis but this severity could be reversed by the application of fluconazole to remove the fungal microbiota [141]. Histologically, extensive invasion by fungi of the underlying tissue was observed that was not evident in wild-type mice. Clinical data showed that a subgroup of ulcerative colitis patients with particularly aggressive disease shows a common single nucleotide polymorphism (rs2078178) in dectin-1, potentially suggesting a requirement for a functional dectin-1 receptor to maintain the mycobiota in a commensal state [141]. However, the role of dectin-1 in mucosal infections is far from clear as a recent study in mice indicated that dectin-1 did not play a role in controlling gastrointestinal colonisation of *C. albicans* [142]. Notably, in humans, a stop codon mutation (Tyr238X) in dectin-1 is known to be associated with an increased risk of developing mucocutaneous fungal infections with increased oral and gastrointestinal colonisation and recurrent vulvovaginal *Candida* (RVVC) infection [143, 144]. Another dectin-1 polymorphism (I223S) has also been associated with susceptibility to oropharyngeal candidiasis (OPC) in a West African cohort of HIV positive patients [145]. Therefore, although important, the precise role of dectin-1 in the susceptibility to *Candida* infection is still unclear and requires further investigation.

3.1.6. Dectin-2. Dectin-2 (also known as CLEC6a) is a type II transmembrane protein but is activated differently to dectin-1. Dectin-2 lacks an intracellular signalling domain [146] and needs to dimerise with FcRγ, which does possess an intracellular signalling domain, to transmit a signal [87]. In myeloid cells and inflammatory monocytes, dectin-2 recognises high mannose structures that are common to many fungi and binds to hyphae with higher affinity than to yeast [147, 148]. This may explain why dectin-2 deficient mice are susceptible to *C. albicans* infection but, interestingly, not *C. neoformans* [148, 149]. Dectin-2 may also detect α-mannosyl linkages [150]. Dectin-2 can induce several cytokines and chemokines through multiple signalling pathways, including NF-κB, MAPK, SYK, CARD9-Bcl10-Malt1, and PKCδ, and can activate the NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome and respiratory burst [87, 151]. Recently, dectin-2 was shown to potentially play a role in host defense against *C. glabrata* infections as dectin-2$^{-/-}$ deficient mice were more susceptible to *C. glabrata* infections, showing a defective fungal clearance in kidneys [152].

3.1.7. Dectin-3. Dectin-3 (also called CLECsf8, MCL, or CLEC4d) was recently identified and appears to form heterodimers with dectin-2 to recognise α-mannans on the surface of *C. albicans* hyphae, leading to NF-κB activation [153]. Notably, dectin-3$^{-/-}$ mice were highly susceptible to *C. albicans* infection. Compared with their respective homodimers, dectin-2/3 heterodimers bound α-mannans more effectively, leading to potent inflammatory responses. This suggests that different CLRs may form a variety of hetero- and homodimers that may provide different sensitivity and diversity for host cells to detect various fungal infections.

3.1.8. Mannose Receptor. The MR (also known as CD206) is a prototypical type I (group VI) transmembrane protein that is predominantly expressed on macrophage and dendritic cells. MR receptor binds several carbohydrate molecules, including branched *N*-linked mannans, N-acetylglucosamine, glucose, and fucose [154]. Thus, MR can recognise many fungal, bacterial, and viral pathogens. MR lacks conventional intracellular signalling domains although ligation still induces a variety of cellular responses, including signal pathway induction, phagocytosis, promotion of antigen presentation to T cells, and cytokine secretion [81, 154–158]. For example, the MR is recruited to the phagosome after *C. albicans* ingestion and activates intracellular signalling and cytokine production [159]. MR may also be required for the induction of protective

Th17 responses in *C. albicans* infection [158] but may inhibit cytokine production in response to other fungi, for example, *Pneumocystis carinii* [160]. Notably, MR deficiency does not appear to confer susceptibility to *C. albicans* systemic infection [161] like it does to *C. neoformans* [162], although minor changes in fungal burdens can be observed [161]. In oral epithelial cells, MR blocking does not alter the secretion of IL-6, IL-8, and GM-CSF upon stimulation with *Candida* cell wall components [135]. Currently, there is no definitive role for MR in mucosal antifungal host defences.

3.1.9. Mincle. Mincle (also known as CLEC4e or CLECsf9) is also a type II transmembrane protein that transmits its signal after dimerisation with the FcRγ adaptor protein [146]. Mincle is usually expressed in macrophages, monocytes, neutrophils, myeloid dendritic cells, and some B cell subsets, but not in plasmacytoid dendritic cells, T cells, and NK cells [151]. Mincle predominantly binds carbohydrate structures containing α-mannans [161, 163] and recognises *C. albicans* [88, 164, 165], *Malassezia* spp. [163], and *Fonsecaea pedrosoi*, the causative agent of chromoblastomycosis [166]. As with dectin-2, mincle is not thought to be required for phagocytosis [88] but does contribute to the induction of cytokines and chemokines via NF-κB, MAPK, SYK, CARD9-Bcl10-Mat1t, and PKCδ [151, 163]. Although mincle-induced responses appear to be MyD88 independent, mincle may synergise with TLRs to induce inflammatory cytokines and the respiratory burst [167].

3.1.10. DC-SIGN. DC-SIGN (also known as CD209) is another type II transmembrane receptor that is expressed predominantly on dendritic cells and macrophages. However, the role of DC-SIGN in antifungal immunity is unclear [119], although DC-SIGN does appear to recognise high (*N*-linked) mannose containing glycoproteins and induce IL-6 production [89, 156]. Although the role of DC-SIGN in the endocytosis and uptake of pathogens to promote antigen presentation is well documented [155, 156], its role in phagocytosis is questionable [89, 156].

3.1.11. Nod-Like Receptors (NLRs) and Inflammasomes. NLRs are a family of intracellular PRRs characterized by leucine-rich repeats and a nucleotide-binding domain that detect PAMPs present in the cell cytoplasm. Like TLRs and CTLs, NLRs recognise microbial products but they also recognise host-derived danger signals or alarmins [168]. Currently, 23 human and 34 mouse NLRs have been identified [169]. NLRs usually associate with two other proteins, ASC (apoptosis-associated speck-like protein containing a CARD) and procaspase-1 (procysteine-dependent aspartate-directed protease 1) to form large multimeric protein complexes called the inflammasome. The main function of the inflammasome is to convert procaspase-1 into active caspase-1, which leads to the processing of immature pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18 [170]. Although *C. albicans* is not recognized by NLRC1 (NLR family CARD domain containing protein 1) or NLRC2 [171], *C. albicans* is known to activate inflammasomes incorporating NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) [172] and NLRC4 [173], resulting in IL-1β production. Notably, NLRP3 is strongly expressed in nonkeratinizing epithelia such as the oral cavity and oesophagus [174] suggesting a potential role of NLRP3 in fungal recognition in oral epithelial cells, which is supported by studies showing increased IL-1β and IL-18 levels upon stimulation with *C. albicans* [133, 175–178]. Mice lacking NLRP3 appear susceptible to candidiasis [179] whereas mice lacking IL-1 receptor type 1 (IL-1RI), IL-18, or caspase-1 have contrasting susceptibility profiles to fungal infections [180]. Notably, IL-1β (and IL-1α) deficient mice demonstrate increased mortality during disseminated candidiasis [181]. Recent reports have also identified a crucial role for NLRP3 together with TLR2 and dectin-1 in preventing dissemination of *C. albicans* in a murine model of oral infection [182]. Consistent with a role for NLRP3 in mucosal protection [183], defective NLRP3 activation increases *C. albicans* colonisation in the gut and exacerbates Crohn's disease [184], and a length polymorphism in intron 4 of the gene (CIAS1) that codes for NLRP3 predisposes patients to RVVC [185]. Nevertheless, the full extent of the functional roles for NLRs and inflammasomes in antifungal host defences is still not fully understood.

3.2. Soluble Molecules in Candida Recognition. The complement cascade plays an important role in host defence against fungal pathogens and is rapidly activated in response to host invasion by *Candida* [186–188]. *Candida* activates all three known pathways (classical, alternative, and mannose-binding lectin (MBL)) with no one obvious pathway dominating the response [189]. Given that the *Candida* cell surface is covered with an abundance of mannoproteins, it is not surprising that *Candida* pathogens are effective at activating the MBL pathway, which appears important for opsonisation, phagocytosis, and other complement functions [190, 191]. The interaction between activated C3b and the complement receptor CR3 is usually required for the uptake of *Candida* cells by phagocytes [192]. *C. albicans* cell wall proteins (e.g., Gpm1, Pra1, and Gpd2) have the potential to bind complement components such as Factor H, FHL-1, C4BP and plasminogen from human plasma that interfere with phagocytic opsonisation and uptake [186, 188, 193–198]. For instance, binding of Pra1 to factor H and FHL-1 probably comprises an evasion strategy involving the inhibition of C3 cleavage into opsonic and anaphylatoxic components, thereby preventing recognition and uptake by phagocytes [199].

C5 is also important in *Candida* infections since mice that lack functional C5 gene copies are susceptible to invasive systemic infections [200–203]. C5 deficiency is associated with increased production of proinflammatory cytokines (TNFα and IL-6) and rapid fungal replication in organs that can lead to cardiac failure [204, 205]. Activation of C5 leads to the formation of C5b, which subsequently triggers the formation of the membrane attack complex (MAC). Although deposition of MAC on the surface of *C. albicans* does not result in fungicidal activity, probably as a result of the thickness of the fungal cell wall, it may facilitate the stimulation of phagocytes and subsequent release of terminal complement components from these cells. Interestingly, as

no effect on inflammation is detected in C3 deficient mice, this may suggest a largely C3-independent processing of C5 in systemic *C. albicans* infection [206].

After phagocytosis, the oxidative burst is triggered which leads to fungal killing, a process that can be blocked with monoclonal antibodies to prevent C3b-CR3 interactions. C3b-CR3 interactions also appear necessary for the inhibition of hyphal growth and cytokine production by lymphocytes [207]. MBL has also been reported to directly inhibit *Candida* growth [208] and enhancing TNFα release from *Candida*-infected monocytes [209]. The anaphylatoxin C3a released from C3 during complement activation may also have direct antifungal activity, independent of its chemotactic activity [210]. Together, these data indicate the importance of complement activation in host defence against *C. albicans* infections. However, for more in-depth information regarding the role of complement in *Candida* infections, the reader is guided to the following reviews [186, 188].

3.3. Cellular Responses to Candida

3.3.1. Neutrophils. Neutrophils are the major effector cell of innate immunity and possess a dual role in antifungal responses. First, they phagocytose and kill infecting *Candida* cells (below) and, second, they indirectly mediate mucosal protection via cross talk with epithelial cells (addressed above). Neutrophils predominantly phagocytose nonopsonised *Candida* via TLRs and CTLs and opsonised *Candida* via CR3 and Fc receptor (FcR) [211]. Once phagocytosed, this leads to both intra- and extracellular killing of *Candida* via oxidative and nitrosative mechanisms, although fungicidal activity varies against different *Candida* spp. [45, 212, 213]. Intracellularly, preformed cytoplasmic granules fuse with the phagosome but, unlike in macrophages, no major pH modifications occur [214]. Neutrophil granules contain antimicrobial proteins including defensins, lactoferrin, lysozyme, myeloperoxidase, and elastase amongst others [215], which can also be released into the extracellular environment.

Oxidative mechanisms are crucial for phagocytic killing of *Candida*. Upon activation, neutrophils produce reactive oxygen species (ROS) during the oxidative burst, which requires assembly of the NADPH oxidase enzyme complex in the cytoplasmic and phagosomal membrane [216]. First, the superoxide radical is generated, which is then dismutated to hydrogen peroxide, a strongly oxidative and damaging molecule [217]. Next, myeloperoxidase utilises hydrogen peroxide to generate hypochlorous acid, which is also a highly oxidative molecule that reacts with organic amines to form chloramines that have further antimicrobial properties [211, 218]. Reactive nitrogen species (RNS) are also utilised in the phagocytic killing of *Candida* [211]. Upon activation, neutrophils express inducible nitric oxide synthase (iNOS), which generates nitric oxide (NO) from arginine and oxygen. NO is highly reactive and is transformed into peroxynitrite, which in turn is reduced to nitrogen dioxide and a hydroxyl radical. Since iNOS is localised intracellularly, the production of RNS is restricted to the intracellular compartment [217]. Another more recently discovered mechanism of *Candida* killing is the production of neutrophil extracellular traps (NETs) [219, 220], which are formed during a unique process of neutrophil cell death termed NETosis. In this process, the neutrophil "explodes," releasing a web of chromatin fibrils coated with the contents of the neutrophil, such as serine proteases, antimicrobial peptides (e.g., calprotectin), and other microbicidal compounds.

Candida spp. are well adapted to survive the oxidative, nitrosative, osmotic, and nutritional stresses encountered during interactions with neutrophils. Multiple processes, genes, and proteins are altered within the fungus in response to the stresses. These include activation of signalling pathways (e.g., the stress-activated protein kinase Hog1), utilisation of alternative carbon and nitrogen sources and metabolic cycles (e.g., glycolysis, glyoxylate, fatty acid, and amino acid), upregulation of transporters (e.g., oligopeptide, ammonium, and iron), and detoxification of neutrophil oxidative/nitrosative killing mechanisms (e.g., catalase, superoxide dismutases, and nitric oxide dioxygenase). However, these details are outside the scope of this review and the reader is guided to recent reviews that focus on the *Candida* response to neutrophils [211, 221].

3.3.2. Macrophages. Macrophages are able to act as phagocytic cells and also as antigen presenting cells capable of activating T cells. Upon activation, macrophages differentiate into two phenotypically and functionally diverse subsets, M1 and M2 [222–224], which depends on the cytokine milieu in which they are activated. The classical M1 phenotype is derived from exposure the T helper (Th)1 cytokine IFNγ, whereas the alternatively activated M2 phenotype is derived from exposure to Th2 cytokines, IL-4 and IL-13. M1 macrophages are microbicidal and proinflammatory, whilst M2 macrophages are involved in wound healing and extracellular matrix remodelling.

Like neutrophils, macrophages predominantly recognise and phagocytose nonopsonised *Candida* via TLRs and CTLs and opsonised *Candida* via CR3 and FcR [211, 225]. However, phagosome maturation in the macrophage is different to that of neutrophils, in that macrophage phagosomes follow the endocytic maturation pathway and develop into phagolysosomes with a characteristic acidic pH that promotes enzyme activity, for example, cathepsin D [226]. M1 macrophages utilise both oxidative and nitrosative killing mechanisms (as described above for neutrophils) but predominantly synthesise the RNS, NO, through the action of iNOS to directly kill phagocytosed *Candida*. M1 macrophages also secrete TNFα and the chemokines CXCL9 and CXCL10 [227]. These chemokines are ligands for the CXCR3 receptor expressed on Th1 cells and NK cells, thereby attracting these immune cells to infection sites. M2 macrophages, on the other hand, promote fungal persistence within the macrophage, providing a mechanism for immune evasion. M2 macrophages also express higher levels of MR (CD206) resulting in increased phagocytosis of *Candida* [228]. Concomitantly, the arginase-1 (Arg1) gene is also increased in expression, which competes with iNOS for the same substrate (arginine), thereby reducing

NO levels [229]. This is further exacerbated by reduced levels of TNFα production in M2 macrophages. As such, macrophages play a critical role in host resistance to *Candida* but this depends on the *Candida* strain interacting with the macrophage [230].

Candida spp. likely utilise similar adaptions to survive in macrophages as they do in neutrophils. *C. albicans* and *C. glabrata* are known to alter metabolic requirements by utilising alternative carbon sources and upregulating enzymes required for gluconeogenesis, glyoxylate cycle, and β-oxidation of fatty acids and downregulating protein synthesis and glycolysis [211, 225]. This includes production of catalase and superoxide dismutases to detoxify extracellular ROS [231] and secretion of flavohemoglobin enzymes to combat intracellular RNS killing [232]. With regard to *C. albicans*, intracellular trafficking also appears aberrant and the fungus may inhibit both lysosomal acidification and NO release [233]. For further details the reader is guided to recent reviews that focus on the *Candida* response to macrophages [225].

4. Nonimmune Responses to *Candida*

Candida spp. and *C. albicans,* in particular, are highly versatile pathogens and have the ability to infect any site of the body. Therefore, it will come as no surprise that several different host cell types in multiple body compartments are capable of recognising and responding to *Candida*. Also, given the many different environmental conditions and circumstances under which these host cells and tissues might encounter *Candida*, they will mount an array of immune responses. The host cells that recognise *Candida* broadly fall into two categories: haemopoietic and nonhaemopoietic cells. Haemopoietic cells include myeloid and lymphoid cells and these play a central role in host defence against microbial infections. Thus, they are key players in removing fungal pathogens from multiple sites. Foremost are the neutrophils, which play a dominant role in fungal clearance. However, both macrophages and dendritic cells also have key roles, not just in directly combating fungi but also in activating and informing subsequent adaptive immune responses. Adaptive responses are predominantly coordinated by $CD4^+$ T helper cells and with the recent discovery of new T helper phenotypes, our understanding of how fungal infections are controlled has expanded enormously (see Section 5). In addition, the role of nonhaemopoietic cells and particularly epithelial cells has also expanded rapidly in recent years. Apart from maintaining barrier function at mucosal surfaces, the key roles that epithelial cells appear to play in identifying fungal pathogens and orchestrating protective immune responses are now being elucidated.

4.1. Epithelial Cells and Immunity. Epithelial cells comprise mucosal surfaces and are usually the first line of defence against *Candida* pathogens. In the vast majority of cases *Candida* infections are superficial and restricted to mucosal surfaces, and it is only when mucosal surfaces are breached (as in the case of disseminated infections) that systemic immunity comes in to play. Until recently, though, it was thought that the main role of epithelial cells was limited to providing an anchorage point for colonisation and a food source for *Candida*. However, recent studies have dramatically changed our view of the importance of epithelial cells in host-fungal interactions. Specifically, it has emerged that one of the fundamental roles of epithelial cells appears to be in targeted responses to *C. albicans* hyphae and the subsequent discrimination between commensal/colonising and invasive/pathogenic *C. albicans* [133, 134, 234, 235].

4.1.1. Epithelial Cell Detection of Candida. Being a commensal eukaryotic microbe, the interactions between *Candida* spp. and epithelial cells are likely to be numerous and complex. Although several innate receptors for fungi have been identified (above), there is debate as to how influential these receptors are in epithelial recognition of and innate responses to *Candida* and to microbes in general. TLRs are known to be expressed by epithelial cells but their expression profile depends on anatomical and cellular location [67, 177, 236–248]. However, epithelial TLRs are functionally active and induce antimicrobial peptide responses [240, 243, 246, 249–251] and proinflammatory cytokines [241–243, 245, 251–260] when stimulated with different microbial ligands. Notably, the majority of these studies have been performed in intestinal, respiratory, or uterine epithelial cells. Less is known regarding TLR activation of oral and vaginal epithelial cells, with some studies demonstrating a lack of cytokine induction by bacterial [240, 261] or fungal [133] agonists, even though viable *C. albicans* cells are able to induce cytokines [63, 262, 263]. In oral epithelial cells the predominant TLR expressed *in vivo* are TLR1, TLR2, TLR4, and TLR8 [177, 246]; however, epithelial TLR4 does not appear to be activated by LPS [133]. Furthermore, whilst heat killed *C. albicans* has no apparent effect on epithelial TLR expression [177, 239], viable *C. albicans* appears to downregulate all TLRs apart from TLR2, which is marginally upregulated [134].

With regard to *C. albicans,* a role for epithelial TLRs is both supported and refuted. For example, in oral epithelial cells, recognition of yeast cells seems to be via conventional fungal PAMPs (TLRs, CTLs), whereas recognition of hyphae appears to be independent of these PAMPs (or at least TLR2, TLR4, or dectin-1) [133]. Other conflicting studies indicate a potential role for TLRs in recognition of several *Candida* species; however, it appears that TLR recognition (or involvement) is a secondary event that acts to induce a protective or inflammatory epithelial response [177, 264]. With regard to *A. fumigatus* conidia, lung epithelial cell recognition appears to require both TLR-dependent and independent pathways, in that IL-8 production appears TLR-independent [265]. Interestingly, recent studies indicate that non-PRRs may also be involved in *C. albicans* recognition, most notably Her2 (human epidermal growth factor receptor 2), a member of the epidermal growth factor receptor family (EGFR/ErbB) [58]. In this instance, rather than acting as a generic fungal PAMP, Her2 interacts with the hypha-associated protein, Als3 (agglutinin-like sequence 3), which then triggers the induced endocytosis of *C. albicans*.

4.1.2. Epithelial Identification of "Pathogenic" Candida. One of the most fundamental functions of the mucosal surfaces and epithelial cells in particular is the ability to identify when an opportunistic microbe such as *C. albicans* has become dangerous or pathogenic. This ability to discriminate between "commensal" and "pathogenic" states of any endogenous microbe is essential to health. During mucosal infections, *C. albicans* forms highly penetrative hyphae that invade and damage tissue as well as inducing strong mucosal inflammatory responses [133, 266]. These observations, together with the fact that *C. albicans* strains unable to produce hyphae or maintain hypha formation are noninvasive and avirulent in mucosal models [34, 42, 47, 48, 267, 268], strongly indicate that hypha formation plays key role in disease progression. Therefore, it stands to reason that epithelia cells must possess mechanisms that enable them to detect and respond strongly to hyphae when necessary.

Epithelial cells are capable of rapidly detecting different *Candida* species and *C. albicans* in its yeast or hyphal form [133, 235]. Initial detection is independent of fungal viability, indicating that activation of epithelial signalling is the result of specific recognition of the fungus and not a feature of invasion or damage induction. Transcript profiling experiments and targeted proteomics indicate that viable *Candida* strongly activates NF-κB, phosphatidylinositide 3-kinase (PI3K), and MAPK signalling pathways [133, 134] and appears tailored to the hyphal form of the fungus (Figure 2). In *C. albicans*, yeast cells activate NF-κB and PI3K signalling along with weak, transient activation of all three MAPK pathways (p38, JNK, and ERK1/2) [133]. This drives the early and brief activation of the transcription factor c-Jun via JNK and ERK1/2 pathways. However, the presence of *C. albicans* hyphae induces sustained NF-κB and PI3K signalling along with much stronger activation of MAPK signalling, resulting in the activation of the transcription factor c-Fos via the p38 pathway. Hyphal presence also activates the MAPK phosphatase, MKP1 [133], which stabilises and regulates MAPK-induced immune responses [269]. This combination of c-Fos activation and MKP1 regulation appears to be specifically associated with hypha formation and correlates with proinflammatory cytokine responses and cell damage [133, 235]. Interestingly, this MAPK-p38/c-Fos pathway is only activated by hypha-forming *Candida* species (*C. albicans* and *C. dubliniensis*), but not by non-hypha forming *Candida* species (*C. tropicalis, C. glabrata, C. parapsilosis,* and *C. krusei*) [235]. Also, although vaginal epithelial cells show different initial recognition characteristics and cytokine/chemokine profiles to oral epithelial cells, the key components of the hyphal response pathway are identical (p38/c-Fos), indicating a commonality in hypha-induced responses in different epithelial cell types [234]. Notably, this hyphal response is highly dependent on the fungal burden encountered by the epithelial cell, indicating that a threshold level needs to be reached prior to full activation [133]. Thus, this mechanism may represent a "danger response" mechanism allowing epithelial surfaces to remain quiescent in the presence of colonising *C. albicans* (low burdens of yeast and/or hyphae) but permitting a specific and strong response to potentially dangerous levels of invasive hyphae common in disease pathologies. If so, this mechanism may be critical to the host's ability to identify when this normally benign fungus has become pathogenic.

4.1.3. Epithelial Activation of Protective Innate Immunity. The terminal stage of epithelial activation is the induction of an effector immune response. Epithelial cells produce a variety of cytokines and chemokines, but the precise combination depends upon the *Candida* strain or species and the epithelial cell type involved [63, 67, 263, 270–273]. For example, infection of oral epithelial cells with *C. albicans* results in the induction of the cytokines G-CSF, GM-CSF, IL-1α, IL-1β, IL-6, and the chemokines RANTES and IL-8 [133, 175, 177, 263, 274–276]. For *C. albicans*, cytokine induction appears to be associated with hypha formation, since those species or strains that do not produce hyphae in culture conditions are unable to produce strong effector responses [34, 48, 133, 235, 276, 277].

The secretion of epithelial proinflammatory cytokines and chemokines in response to *C. albicans* will result in the recruitment and activation of a variety of immune cells including neutrophils. Interestingly, neutrophils appear to protect against *C. albicans* infection indirectly via immunological cross talk with the epithelium [278]. This intriguing mechanism was characterised in a reconstituted oral epithelial model system and showed that neutrophils could protect the epithelium from *C. albicans* induced cell injury *via* a process that was independent of phagocytosis, neutrophil transmigration, or physical neutrophil-epithelial cell contact [177]. Notably, the addition of neutrophils to the *C. albicans* infection model strongly upregulated epithelial TLR4 expression, which was directly responsible for protection since both *C. albicans* invasion and cell damage could be restored by TLR4 blockade (antibody) or "knockdown" of TLR4 using siRNA (short interfering RNA), even in the presence of PMNs. Importantly, this work demonstrated that although TLR4 was not required for the initial activation of epithelial cells, epithelial TLR4 was required to mediate antifungal protective responses in the presence of neutrophils. The most potent cytokines produced by neutrophils that induced this protective TLR4-mediated response was TNFα [177], which confirms the important role of this cytokine in host defence against opportunistic fungal infections [279]. Furthermore, in an *in vitro* model of esophageal candidiasis, coincubation of neutrophils with *C. albicans* led to a significant upregulation of β-defensin 2 and 3 in esophageal cells compared with effects of neutrophils or *C. albicans* alone [280]. Thus, increased PMN-dependent production of antimicrobial peptides by epithelial cells could contribute to the protective effect and further underlines the important role for PMNs in clearance of experimental oral candidiasis [67].

However, neutrophils may not play an obvious protective role in the vaginal lumen and, indeed, in humans, neutrophils might even exacerbate vaginal disease [281]. The reasons for this are as yet unknown but the triggers for epithelial and neutrophil activation may be different in the vaginal lumen, perhaps due to differences in the microenvironment and heightened responsiveness to oestrogen. As a result, neutrophils may not function as well in the vagina and thus

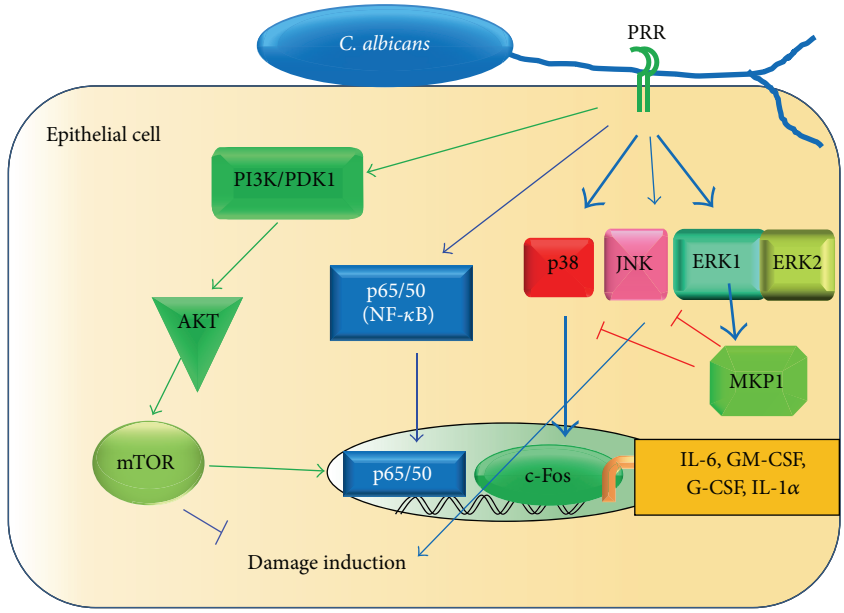

Figure 2: Signalling and damage pathways activated by *C. albicans* hyphae. *C. albicans* hyphal cells, when in sufficient quantities, are recognised by an unknown PRR mechanism that results in the activation of NF-κB, MAPK, and PI3K pathways. MAPK signalling via p38 and ERK1/2 appears to discriminate between yeast and hyphal cells. Activation of p38 by hyphae leads to activation of the c-Fos transcription factor, which, in conjunction with the p65/p50 NF-κB heterodimers and PI3K/AKT results in upregulation of cytokine and inflammatory mediator expression. Concurrently, activation of ERK1/2 signalling results in stabilisation of the MKP1 phosphatase, which deactivates p38 and JNK, hence acting as part of a negative feedback loop and preventing a potentially deleterious overreaction of the immune system. Damage induced by hyphae appears to be mediated via JNK activation and prevented via the PI3K/AKT/mTor pathway. Figure adapted from [262] and based on data from [48, 133, 134, 234, 235, 277].

cause more harm than good. In the oral cavity the triggers may not be so dynamic and the neutrophils function more efficiently and, as such, tend to be beneficial rather than immunopathogenic (Paul Fidel, personal communication).

Other key epithelial responses include the production of antimicrobial peptides such as β-defensins and cathelicidin (LL-37) in response to *C. albicans* infection [282]. These peptides have direct candidacidal activity and play a significant role in combating infections and invasion as well as initiating other immune responses [283, 284]. However, it is still somewhat unclear whether these peptides are induced after direct recognition of *C. albicans* or in response to damage caused by *C. albicans*. Other peptides, including S100A8/9 alarmins, are also produced, which act as key chemotactic mediators and appear critical in recruiting neutrophils to the vagina during *C. albicans* infections [285–287]. Matrix metalloproteases are also produced, which play a role in epithelium remodelling and barrier function [288]. Oral and vaginal epithelial cells also appear to possess direct innate antifungal activity via an annexin-A1 dependent mechanism [289]. This fungistatic effect does not require live epithelial cells and suggests that the uppermost surface epithelial layers are able to naturally inhibit the growth and proliferation of *C. albicans* at the mucosal surface [290, 291]. This may help maintain *C. albicans* in the commensal state during health.

It is apparent that there is a significant amount of cross talk between epithelial cells and other cells of the immune system during *Candida* infections. This cross talk fulfills two functions, acting to both maintain normal physiological conditions when *Candida* are recognised as commensal organisms and to initiate a protective immune response to clear the fungi when recognised as pathogenic. The production of cytokines and chemokines by epithelial cells in response to fungal infection results in the recruitment and activation of various different immune cells, including neutrophils, monocyte/macrophages, dendritic cells, and T cells. This leads to the generation of tailored immune responses with the aim of clearing fungal infections via both the innate and adaptive immune pathways (see below).

4.2. Endothelial Cells and Immunity. Systemic *Candida* infections pose a significant threat to health, particularly in immunocompromised hosts. In order to gain access to the host vasculature to facilitate dissemination, invading *Candida* pathogens must cross the endothelial lining of the blood vessels by passing from the abluminal to the luminal surface. Once *Candida* cells enter the bloodstream they are transported throughout the host where they accumulate in the major organs and contribute to increased morbidity. The endothelium is not merely a static physical barrier but functions as an integral component of the innate immune system that contributes to the host response to fungal pathogens. Endothelial cells induce proinflammatory and procoagulant

responses to *Candida* infection and are themselves targets for immune suppression by fungal invaders. Endothelial cells mount different responses to *Candida* pathogens depending upon morphology and species.

C. albicans hyphae are endocytosed by endothelial cells [292] via the interaction between host N-cadherin and fungal Als3 protein [56, 57], often resulting in endothelial cell injury or death [293, 294]. In response to *C. albicans* infection, endothelial cells express mRNAs encoding for E-selectin, ICAM-1, VCAM-1, IL-6, IL-8, MCP-1, and cox2 [295]. Expression was dependent upon endocytosis and fungal viability, since cytochalasin D blocked chemokine induction and heat killed *C. albicans* had no stimulatory effect. Infection with a mutant strain of *C. albicans* (V6) that was unable to germinate failed to induce the same response, as did infection with *C. tropicalis* or *C. glabrata*, suggesting that endothelial cells can distinguish between infecting *Candida* species as well as between morphological forms [295]. Other studies show that endothelial cells also produce TNFα, which stimulates the production of IL-8, E-selectin, ICAM-1, VCAM-1, IL-1α, and IL-1β [296]. These proinflammatory cytokines and adhesion molecules act to recruit leukocytes to the site of vascular invasion, which help clear the fungus. Notably, endothelial cells express ICAM-1 independently from TNFα, IL-1α, and IL-1β, indicating that the induction of distinct proinflammatory responses most likely occurs through different mechanisms [296].

Genome-wide responses to *C. albicans* infection are both varied and complex. Transcript profiling experiments of primary HUVEC (human umbilical vein endothelial cells) revealed that 56 genes were upregulated whilst 69 were downregulated following infection with *C. albicans* yeasts [297]. Upregulated genes included those involved in chemotaxis, cell death and proliferation, transcriptional regulation, and intercellular signalling. Particularly overrepresented were genes involved in neutrophil recruitment and signal transduction. Endothelial cells invoke a number of key signalling pathways in response to *Candida* infection including the proinflammatory NF-κB pathway and the stress-activated p38 MAPK pathway. Indeed, activation of NF-κB appears critical in the endothelial response, as attenuation of NF-κB signalling by a dominant negative (kinase-dead) IKK2 mutant (IKK2KD) abolished production of IL-8 and CCL20. Endothelial cells appear to recognise *C. albicans* through a receptor mediated process since depletion of IRAK1 and MyD88 in endothelial cells by RNA interference abolished *C. albicans* induced expression of NF-κB target genes [297]. The target genes of *C. albicans* transcription factors Cph1p and Efg1p are important for correct endothelial cell responses to infection since a *C. albicans cph1/efg1*Δ mutant strain induced fewer genes and a weaker transcriptional response overall when compared with a wild-type control [298]. Thus, the production of leukocyte adhesion molecules, proinflammatory cytokines, and procoagulant factors by endothelial cells contributes to the host innate immune response to infiltration by pathogenic *Candida* and may facilitate clearance through active recruitment of leukocytes to the site of invasion.

5. Adaptive Immune Responses and Therapeutic Targets

5.1. T Cell Responses to Candida. The adaptive arm of the anti-*Candida* response is initiated through the recruitment of dendritic cells (or Langerhans cells) and macrophages during innate immunity. During infection, epithelial cells initiate host defence via the production of multiple proinflammatory molecules, including CCL20 and β-defensin 2 which act as chemoattractants to recruit mucosal homing CCR6-expressing dendritic cells (Figure 3). Dendritic cells recognise *Candida* through PRRs including TLR2/4, dectin-1, dectin-2, DC-SIGN and MR, which results in fungal ingestion, dendritic cell activation and trafficking to the local lymph nodes. In the lymph node, dendritic cells will present processed fungal antigens to naïve and memory T cells, initiating adaptive immunity. However, following PRR recognition, different dendritic cell subsets can be activated via distinct signalling pathways to shape T cell responses against *Candida* infections [299, 300]. Myeloid (inflammatory) dendritic cells initiate Th17 and Th2 cell responses via TLR-MyD88 pathways, whereas plasmacytoid (tolerogenic) dendritic cells activate Th1 and T regulatory (Treg) cells via TRIF [93]. The nature of the T cell response is determined by the cytokine milieu the T cells encounter during activation: IL-12/IFNγ for Th1 cells, IL-4 for Th2 cells, IL-1β/IL-6/IL-23 for Th17 cells, and IL-2/TGF-β for Treg cells. In addition, signal transducer and activator of transcription 3 (STAT3) is involved in determining canonical or noncanonical activation of NF-κB and, therefore, the expression of indoleamine 2,3-dioxygenase (IDO), which is a key enzyme that controls dendritic cell function and plasticity. These functionally distinct pathways in dendritic cells ultimately affect the equilibrium between Th and Treg cells and may be exploited by *Candida* spp. to promote commensalism or infection [93].

Although there is ongoing debate as to the protective role of Th1 phenotypes in *Candida* infection, the role of Th2 cells is widely accepted as more deleterious, being associated with increased fungal growth and dissemination [93]. Murine and human clinical studies indicate a role for cell-mediated immunity and specifically the Th1 phenotype in combating oral and gastrointestinal *C. albicans* infections [278, 301–303]. Indeed, a high proportion of AIDS patients who have low $CD4^+$ T cell levels develop OPC [304], indicating the importance of $CD4^+$ T cells in host defence against oral infections [305]. In murine *Candida* gut infections, fungal clearance correlated with increased IFNγ levels and IL-5 producing T cells in Peyer's patches and mesenteric lymph nodes [306]. In this study, neutralisation of Th2 responses via IL-4 blocking resulted in improved *Candida* clearance and a concomitant enhancement of Th1 responses. Therefore, for a number of years, Th1 responses were regarded as protective against *Candida* infections [302, 307]. This viewpoint was supported by studies demonstrating that T cell deficient mice, although susceptible to OPC, could be protected using adoptive transfer of $CD4^+$ T cells [308]. However, as with epithelial cell responses, it is apparent that the role of the different Th phenotypes is location specific.

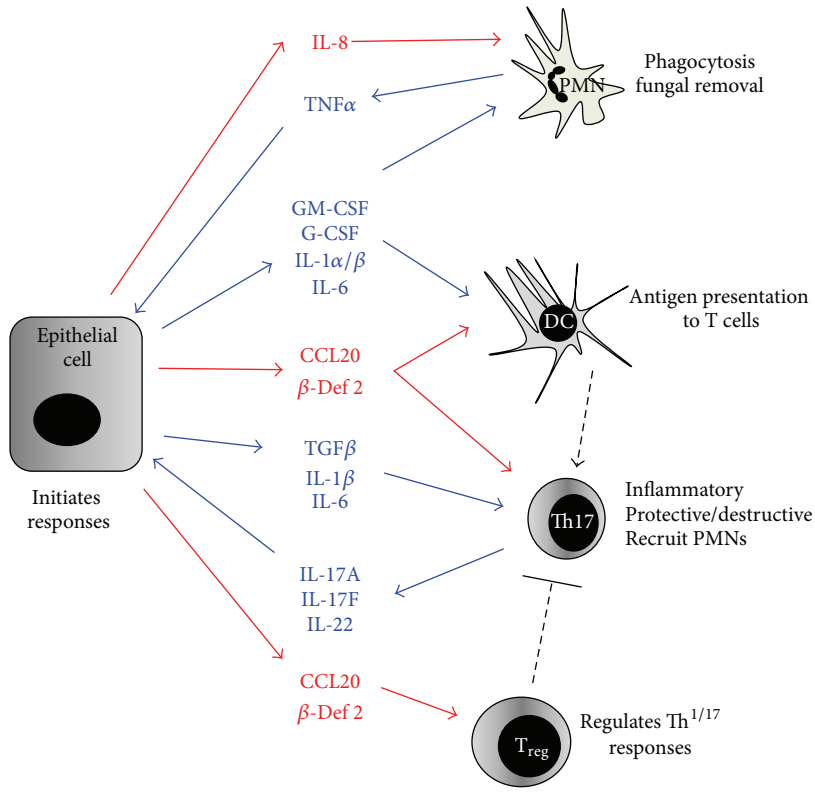

Figure 3: Initiation of innate and adaptive immunity during *C. albicans* infection. Infection of epithelial cells by *C. albicans* results in the production of cytokines (blue) and chemokines (red) which recruit and activate various other immune cells. IL-8 recruits circulating neutrophils (PMNs) that are in turn activated by a variety of cytokines including GM-CSF, G-CSF, and IL-1 family members. Activated PMNs produce TNFα among other cytokines, which affect epithelial gene transcription. TGFβ is produced constitutively by epithelial cells and will act with IL-1α and IL-6 to induce T cell differentiation to the Th17 phenotype. Mucosal homing cells including Th17 T cells and activating dendritic cells will also be recruited by the increased expression of CCL20 and β-defensin 2, acting through the CCR6 receptor. This will lead to the presence of active Th17 T cells at the site of infection. CCL20 and β-defensin 2 will also recruit in Treg cells which will act to suppress and control the Th17 response. Figure adapted from [262].

For example, although Th1 immunity is generated during vulvovaginal candidiasis it is not protective. Instead, local mucosal responses governed by $\gamma\delta$ T cells and DCs have been implicated as being the predominant mechanism for anti-*Candida* cellular immunity at this site [309]. In contrast to Th cells, Treg cells prevent expansion of Th17 subsets (see below) and minimise host damage [310] and suppress inflammatory responses in disseminated *C. albicans* resulting in higher susceptibility in mice [103, 311]. However, Tregs may also enhance Th17-mediated fungal clearance [312]. Notably, the tolerance-inducing effects of Tregs seem to be beneficial at mucosal sites [313, 314] and it is notable that mice lacking TLR2 have reduced numbers of Treg cells [103], indicating a possible role for TLR2 in maintaining peripheral tolerance.

5.2. T Helper 17 Cells. Recently, our view of the importance of different T cell phenotypes during fungal infections changed with the discovery of Th17 cells, so named as they secrete IL-17 [315]. It appears that dendritic cell recognition of *Candida* through dectin-1 and dectin-2 is instrumental in driving Th17 development [316]. Th17 cells are induced by a combination of IL-6, IL-1β, and TGFβ and further matured (or reactivated) upon stimulation with IL-23. Th17 cells secrete IL-17A, IL-17F, and IL-22 and are now accepted as playing a major role in preventing extracellular infections and autoimmunity [317, 318]. Furthermore, IL-17A and IL-17F are known to stimulate a variety of cells (e.g., epithelial cells and fibroblasts) to produce antimicrobial peptides, metalloproteases, and chemokines that promote neutrophil recruitment and activation [319], ultimately resulting in clearance of fungal infections [320]. Concomitantly, IL-22 plays a major role in limiting fungal cell growth and maintaining epithelial barrier function [321–323]. Indeed, recently it was shown that polymorphisms in the IL-22 gene associated with protection against RVVC correlated with high levels of vaginal IL-22 and decreased levels of IL-17A and TNFα [324].

There is now good evidence to suggest that IL-17 production is a key event in the protection against *C. albicans* infections [320, 325–328]. The first evidence for a role for Th17 cells and IL-17 in host defence against *C. albicans* demonstrated that IL-17 receptor knockout mice were more susceptible to systemic *C. albicans* infection than wild-type animals [329]. Since then, the majority of studies suggest

a protective role for IL-17 during both systemic and mucosal infections. For example, mice lacking Th1 cytokines (e.g., IFNγ) resist oral infections, whilst those lacking the Th17-driving IL-23 cytokine show increased susceptibility to oral infection [330]. In addition, IL-17RA$^{-/-}$ and IL-23p19$^{-/-}$ deficient mice have increased susceptibility to OPC [331], and patients with impaired IL-17 production suffer from mucosal *C. albicans* infections in hyper-IgE syndrome and CMC [332–334]. However, there are also reports suggesting that Th17 immunity may exacerbate *C. albicans* infections [313, 335] or that *C. albicans* may downregulate Th17 responses [336]. Thus, the Th17 pathway may also be involved in the immunopathogenesis of chronic fungal diseases, in which persistent fungal antigens may promote immune dysregulation [93]. Notably, a specific role for Th17 cells in vaginal candidiasis remains unclear in mouse models, as one study demonstrated a requirement for IL-17 and IL-23 to reduce fungal burdens [337], whereas another study showed that the acute neutrophil response mediated by S100 alarmins was independent of the Th17 pathway [286].

Recent studies investigating patients with autoimmune conditions (e.g., CMC) have also highlighted the importance of Th17 responses in protection against *C. albicans* [112, 332, 338, 339]. This link is supported by the increased incidence of CMC in cases of autoimmunity with neutralising antibodies to Th17 cytokines (IL-17A, IL-17F, and IL-22) [340]. Recently, two genetic aetiologies of CMC were identified: an autosomal recessive deficiency in the IL-17 cytokine receptor, IL-17RA, and autosomal dominant deficiency of IL-17F [139]. IL-17RA deficiency completely abolished cellular responses to IL-17A and IL-17F. By contrast, IL-17F deficiency was partial, with mutant IL-17F displaying impaired but not abolished activity. These data indicate that IL-17A and IL-17F are essential for mucocutaneous immunity against *C. albicans*. Other primary immunodeficiencies associated with an increased susceptibility to *Candida* infection through their effects on Th17/IL-17 signalling include mutations in STAT-1 [341–343], STAT-3 [344, 345], tyrosine kinase (TYK)-2 [346], dedicator of cytokinesis (DOCK)8 [347], IL-12Rβ1 [348], and autoimmune regulator (AIRE) [349]. It should be noted that although originally thought to be exclusively produced by Th17 T cells, it is now known that IL-17 is also produced by a variety of innate immune cell types, including $\gamma\delta$ T cells, NKT cells, innate lymphoid cells (ILCs), lymphoid tissue inducer (LTi) cells, and macrophages [350, 351]. However, the functional role of IL-17 produced by these cell types during *Candida* infections remains to be fully explored.

5.3. B Cells and Antibody Responses to Candida. Antibody production comprises the final part of the adaptive immune response. For many years the role of antibody-mediated immunity in antifungal defence was controversial, especially since hypogammaglobulinaemia (reduction or absence of immunoglobulins) is not thought to be associated with a predisposition to fungal disease [352]. However, recent advances and new experimental methods have indicated that antibody-mediated immunity constitutes an important arm of host antifungal defence [353, 354]. Antibodies are capable of mediating several different effects, ranging from protective to nonprotective, or even pathogenic (enhancing disease). Typically, the main mechanisms of antibody-mediated immunity include neutralisation (against viruses or toxins), opsonisation, complement activation, and antibody-dependent cellular cytotoxicity (ADCC). However, although neutralisation is not (currently) thought to play a significant role in antifungal immunity, the other three mechanisms appear to play some role [354, 355].

A number of studies have now demonstrated that antibodies can be protective against *Candida,* with a number of protective monoclonals or antibody fragments (Fabs) having been described for *C. albicans* [356–369]. These studies demonstrated that there are multiple targets for antibodies including polysaccharides, proteins, and glycolipids. Since many of these targets are present in the *Candida* cell wall, the antibodies probably act by disrupting or interfering with fungal cell wall processes, dynamics, or remodelling [370]. As such, a number of these antibodies are able to directly affect the host-fungal interaction via the inhibition of *Candida* biofilm formation [371], growth [362], hypha formation [361], and metabolic processes such as nutrient (iron) acquisition [372]. Antibody binding may also inhibit fungal replication and even induce cell death [361], although the mechanisms by which this occurs are unclear. Notably, some monoclonals (e.g., MAb 2G8) possess cross protective properties against multiple fungal pathogens (*C. albicans*, *A. fumigatus,* and *C. neoformans*) by targeting commonly shared fungal moieties such as β-glucan [362, 373]. This latter finding is of significant importance conceptually and economically as it suggests that a single therapeutic (or vaccine) could provide protection against multiple fungal pathogens.

With respect to *C. albicans* vaccine candidates, one monoclonal (MycoGrab/efungumab) targeting the heat shock protein 90 progressed through to Phase III clinical evaluation against invasive systemic infection [374]. However, despite promising results, MycoGrab/efungumab was nevertheless not pursued into a marketable product. Another vaccine targeting recombinant *C. albicans* Sap2 using influenza virosomes (PEV7) to protect against RVVC is also currently in clinical evaluation by Pevion Biotech AG (Bern, Switzerland). Rodent studies indicated that PEV7 generated potent serum and vaginal IgG and IgA antibody responses following intramuscular or intravaginal immunization. This appeared to establish long-lasting, antibody-mediated protection in the rat model [375]. Finally, a vaccine targeting the recombinant N-terminal region of the hyphal protein Als3 (rAls3p-N) formulated with alum adjuvant (NDV-3) was also recently tested in a Phase 1 clinical trial, inducing robust humoral and cellular immune responses [376, 377]. Recently, NDV-3 was evaluated in a murine model of vulvovaginal candidiasis and induced high anti-rAls3p-N serum IgG and vaginal IgA titers, as well as reducing fungal burdens [378]. Furthermore, anti-rAls3p-N antibodies enhanced the *ex vivo* killing of *C. albicans* by neutrophils primed with IFNγ. This suggests that NDV-3 may protect by priming both humoral and adaptive immune responses [378].

Although antibody-based therapies against *Candida* infections are still somewhat of a controversial topic, there are

no conceptual limitations for the development of such therapies. Antibodies remain an attractive therapeutic option for fungal diseases, especially with regard to enhancing immune function in susceptible patients with impaired immunity. However, given the efficacy of current antifungal drugs, antibody-based therapies will need to be developed as an adjunctive combination therapy that is superior to conventional therapy. This would require large clinical trials and would have cost implications. Irrespective, antibody-based therapies provide new and versatile options for developing new antifungal therapeutics in the future [379–382].

6. Summary

Host responses to *Candida* are highly diverse due to the variety of fungal PAMPs and antigens recognised by different immune cells at multiple infection sites. As such, a variety of detection mechanisms are utilised by host cells, some of which enable the host to discriminate between the morphological status and potentially the commensal and pathogenic state of *Candida*. Furthermore, the importance of nonhaemopoietic cells in host defence has begun to be elucidated, which provides a more complete picture of the complex network of immune interactions between host and *Candida*. We have come a long way in deciphering the key proteins, cells, and mechanisms that contribute to host immunity against *Candida*, but the next few decades should provide a seismic leap forward in clinical and translational applications with regard to how *Candida* infections can be managed and controlled.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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