Skin Immunity to *Candida albicans*

Sakeen W. Kashem\(^1\) and Daniel H. Kaplan\(^2\)*

*Candida albicans* is a dimorphic commensal fungus that colonizes healthy human skin, mucosa, and the reproductive tract. *C. albicans* is also a predominantly opportunistic fungal pathogen, leading to disease manifestations such as disseminated candidiasis and chronic mucocutaneous candidiasis (CMC). The differing host susceptibility for the sites of *C. albicans* infection have revealed tissue compartmentalization with tailoring of immune responses based on the site of infection. Furthermore, extensive studies of host genetics in rare cases of CMC have identified conserved genetic pathways involved in immune recognition and the response to the extracellular pathogen. We focus here on human and mouse skin as a site of *C. albicans* infection, and we review established and newly discovered insights into the cellular pathways that promote cutaneous antifungal immunity.

**Compartmentalization of Immunity Against C. albicans Skin Infection**

*C. albicans* is the most common and well-studied of the disease-causing *Candida* spp., and naturally colonizes the skin, genital, and/or intestinal mucosa in up to 70% of healthy individuals [1]. Under normal circumstances, the fungus does not cause disease but the absence of appropriate immune recognition and response mechanisms can lead to the inability to control *C. albicans* colonization and invasion. CMC is a rare non-life threatening condition that occurs in the setting of primary and acquired immunodeficiencies resulting in oropharyngeal candidiasis (OPC) or superficial mucosal and cutaneous lesions with thickening, hyperkeratosis, and erythema of the skin or the nailbeds. The genomic sequencing of HIV-negative CMC patients has identified many genes that are crucial for host defense against *Candida albicans*. Subsequent mechanistic studies have further defined the importance of specific pattern-recognition receptors, dendritic cells, cytokines, and T cell signaling events in immunity against *C. albicans* with the common theme of defects in innate and/or adaptive interleukin-17 (IL-17) pathways (referred to as type 3 immunity) (Table 1).

In addition to infections at barrier surfaces, *Candida albicans* is also the leading cause of fatal fungal bloodstream infections. The increased rate is thought to result from increased use of immunosuppressive agents, anticancer treatments, increased antimicrobial resistance, and the frequency of invasive surgeries [1]. The genetic susceptibilities associated with systemic candidiasis as well as infections of gastrointestinal and female reproductive organs differ significantly from those associated with CMC [2]. Unlike CMC patients, who have defects in type 3 immunity, genetic defects upstream or downstream of IL-17 have not been implicated in patients with disseminated candidiasis [3]. Instead, type I interferons (IFNs) have been demonstrated to play an important role in patients with systemic infections. In mice, IL-17 plays a role in systemic candidiasis, but IFN-γ from type 1 T helper (Th1) and natural killer (NK) cells have been recently appreciated as key players in the host response [4–7]. Susceptibility to gastrointestinal and vulvovaginal candidiasis is largely dictated by local environmental factors such as local nutrients, pH, bile acids, and local commensal flora [8,9]. The host response to *C. albicans* infection in tissues other than the skin has been recently reviewed in depth [8–10].

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Mouse models of OPC and cutaneous candidiasis demonstrate high fidelity to the human disease. Mice with genetic defects as those found in patients with CMC have greatly increased susceptibility to skin and mucosal *C. albicans* infections [10]. Unlike humans, *C. albicans* is not a commensal fungus of mice [11]. Thus, mice allow the examination of primary innate and adaptive immune responses against *C. albicans*. Cutaneous candidiasis models include either application of *C. albicans* onto stratum corneum-stripped epidermis or direct intradermal inoculation [12,13]. The well-characterized nature of the skin-resident and circulating leukocytes of the skin make the murine skin an ideal site to study both innate and adaptive antifungal immune responses. Specifically, the IL-17 cytokine family has been identified to be essential against host defense, driving neutrophil recruitment and antimicrobial peptide production [10]. It has been appreciated that IL-17 can be produced by leukocytes from both the innate [e.g., innate lymphoid cells (ILCs), γδ T cells] and adaptive immune systems (e.g., CD4+ T cells) [5,14]. This review focuses on recent advances in understanding the mechanisms by which the primary innate and the secondary adaptive type 3 immune response develop during *C. albicans* infection. Better understanding these mechanisms can assist in the development of vaccines against *C. albicans* and other extracellular pathogens as well as provide insight into type 3 autoimmune diseases of the skin.

**Innate Immune Response to *C. albicans***

**Pattern Recognition**

**C-Type Lectins**

C-type lectins encompass a large family of receptors that bind to glycans through their extracellular carbohydrate recognition domain and mediate intracellular signaling via various cytoplasmic domains. Dectin-1 is one of the most commonly studied and reviewed C-type lectins [2,15]. Dectin-1 recognizes β-glucan on the cell wall of most species of fungi including *C. albicans* [16]. Signaling by Dectin-1 activates cells by a Syk-dependent pathway, resulting in formation of the CARD9–BCL10–MALT1 trimer and activation of NF-κB, leading to transcription of proinflammatory cytokines such as IL-1β, IL-6, and IL-12 [15].

Humans with SNP variants of Dectin-1 and mutations of Card9 develop CMC [17,18]. These patients demonstrate impaired IL-1β, IL-6, IL-22, and IL-17 production alongside impaired

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**Table 1. Primary Immunodeficiencies Leading to CMC**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2RG, RAG1, RAG2, ADA</td>
<td>Loss of T and/or B cells</td>
<td>[30]</td>
</tr>
<tr>
<td>UNC119, MAGT1, RAG1</td>
<td>Idiopathic CD4 lymphopenia</td>
<td>[99,100]</td>
</tr>
<tr>
<td>STAT3</td>
<td>HIES due to defective IL-23R and IL-6R signaling and decreased Th17</td>
<td>[101,102]</td>
</tr>
<tr>
<td>DOCK8</td>
<td>HIES due to defective T cell synapse formation and dysregulated DC migration</td>
<td>[103]</td>
</tr>
<tr>
<td>IκBα</td>
<td>Impaired TCR and NF-κB signaling</td>
<td>[29]</td>
</tr>
<tr>
<td>IL-17F/IL-17RA/IL-17RC/Act1</td>
<td>Defective IL-17A/F signaling</td>
<td>[104–106]</td>
</tr>
<tr>
<td>RORC</td>
<td>Loss of IL-17A/F production, lymph nodes, and impaired IFN-γ response</td>
<td>[107]</td>
</tr>
<tr>
<td>Aire</td>
<td>Autoantibodies to IL-17A/F/IL-22</td>
<td>[108]</td>
</tr>
<tr>
<td>STAT1</td>
<td>Gain of function mutation leading to excessive type I and II IFN responses leading to decreased Th17</td>
<td>[104,109]</td>
</tr>
<tr>
<td>IL-12RB1</td>
<td>Abolished response to IL-23 and IL-12</td>
<td>[66]</td>
</tr>
<tr>
<td>Clec7A/Card9</td>
<td>Defective phagocytosis, IL-1β, and IL-6 production by PBMCs and IL-17-producing T cells</td>
<td>[17,18]</td>
</tr>
</tbody>
</table>
phagocytosis of \textit{C. albicans} yeasts\cite{18}. Work in mouse models has revealed that the role of Dectin-1 is more nuanced. Recognition by Dectin-1 varies by species, strain, and life form (i.e., yeast vs filamentous). Dectin-1 signaling has been shown to be required for protection from intravenous and oral candidiasis \textit{in vivo}, but has also been shown to be redundant\cite{19,20}. These initially discordant results resulted from the use of different strains of \textit{C. albicans}. Some strains of \textit{C. albicans} have increased cell wall chitin resulting in lower availability of cell wall \(\beta\)-glucans for recognition by Dectin-1\cite{21}. In addition, Dectin-1 specifically recognizes \textit{C. albicans} yeast and not filamentous forms owing to a difference in \(\beta\)-glucan availability (covered below)\cite{22}. Recognition of fungi by other C-type lectin receptors, including the important concept of trained immunity, has been reviewed in depth elsewhere\cite{2,15}.

**Toll-Like Receptors (TLRs)**

Several TLRs recognize \textit{C. albicans} cell-wall polysaccharides including TLR-2, which recognizes phospholipomannans, and TLR-4, which recognizes O-linked mannans\cite{23}. Activation of TLRs by their ligands leads to triggering of intracellular signaling pathways, such as MAPK (mitogen-activated protein kinase) and NF-\(\kappa\)B (nuclear factor \(\kappa\) light-chain enhancer of activated B cells) pathways, leading to transcription and secretion of TNF-\(\alpha\), IL-6, and/or type I IFNs\cite{24}. TLRs are expressed differentially on numerous cell types including KCs, melanocytes, dendritic cells, and macrophages and can also cooperate with C-type lectins or the inflammasome to drive IL-1\(\beta\), TNF-\(\alpha\), and IL-12 production\cite{25,26}.

Deficiency for TLRs or for the adapter protein Myd88 significantly alters the survival of mice to intravenous \textit{C. albicans} infection \textit{in vivo}, and Myd88 deficiency in Langerhans cells (LCs) renders mice unable to mount a Th17 response to \textit{C. albicans} skin infection\cite{27,28}. However, deficiencies for IRAK-4 or Myd88 lead to recurrent pyogenic bacterial infections and cold abscesses but do not lead to CMC in humans\cite{29,30}. Mutations of I\(\kappa\)Ba, which acts downstream of TLRs and of the T cell receptor (TCR), lead to CMC. Given the disparity of CMC susceptibility in I\(\kappa\)Ba variant patients compared to those with Myd88/IRAK4 deficiency, it is likely that the role of T cells trumps that of pattern recognition through TLRs in human resistance against CMC\cite{29}.

**Nod-Like Receptors (NLRs)**

NLRs generally interact with ASC (apoptosis-associated speck-like protein containing a CARD) and procaspase-1 to form the inflammasome to convert procaspase-1 into active caspase-1, which in turn converts pro-IL-1\(\beta\) and pro-IL-18 into mature IL-1\(\beta\) and IL-18\cite{31}. In humans, NLR mutations and polymorphisms have not been identified with CMC but a defective NLRP3 activation increases \textit{C. albicans} colonization of the gut and NLRP3 polymorphism predisposes patients to recurrent vulvovaginal candidiasis (RVVC)\cite{32,33}. In mice, macrophage-derived Nlrp3 recognizes filamentous forms of \textit{C. albicans}, and deficiencies for Asc, Nlrp3, or IL-1R1 lead to decreased \textit{C. albicans} resistance in intravenous and oral routes of \textit{C. albicans} infection\cite{34,35}. Nlrp10 has also been implicated in host defense against \textit{C. albicans} by the induction of dendritic cell migration and differentiation of T helper cells\cite{36,37}. However, subsequent studies demonstrated that Nlrp10-deficient mice also possessed functional mutations of Dock8. Dock8, but not Nlrp10, was found to be responsible for DC migration\cite{38}. This supports the clinical association between hyper IgE syndrome (HIES) caused by Dock8 mutations and CMC\cite{39}. Finally, stromal cell-derived NLRC4 has also been demonstrated to the crucial for mediating immunity against oral candidiasis\cite{40}. While there has been some preliminary characterization of NLRs in immunity against \textit{C. albicans} disseminated and oral infections, the role of the inflammasome in mediating immunity against \textit{C. albicans} skin infection is currently unknown.

**Stromal Cells**

The uppermost layer of the avascular epidermis is the cornified envelope that consists of dead keratinocytes (KCs), keratin, and various hydrophobic lipids; this provides a physical barrier
against the environment and potential pathogens. In addition, the corneal envelope contains antimicrobial and anti-
*Candida* peptides, such as β-defensins and cathelicidins, which are produced by KCs in response to infection or colonization [41]. Notably, mice deficient for a key component of the corneal layer – ceramide synthase 3 – are susceptible to *C. albicans* skin infections [42].

Beneath the corneal envelope are the granular, spinous, and basal layers that are composed of KCs that express PRRs. These KCs initiate the early cutaneous immune responses. *C. albicans* has been shown to adhere to human KCs and induce proinflammatory cytokine secretion *in vitro* but their role in directly activating KCs *in vivo* is unknown [43]. KCs constitutively express receptors for TNF-α, IL-17A, and IL-22. TNF-α and IL-17 act on KCs and epithelial cells to drive production of antimicrobial peptides, such as β-defensins and S100 proteins, and chemokines to drive the recruitment of neutrophils and inflammatory cells [44]. IL-22 acts on KCs to drive their proliferation by downregulating genes involved in terminal differentiation [45]. Recent studies have also identified the role of KCs in initiating immune responses through control of dendritic cell migration and recruitment of memory T cells into the skin [46-48]. Thus, the interaction between *C. albicans* and epithelial cells of tissues is a crucial topic of investigation going forward.

In addition to KCs, melanocytes can also respond to *C. albicans*. Melanocytes are located in the basal layer of the epidermis and synthesize melanin to provide skin pigmentation. In invertebrates, melanocytes modulate melanin production during infection, and inflammation can lead to hypo- or hyperpigmentation in humans [49]. Melanin has also been demonstrated to have antimicrobial properties [50]. While early studies demonstrated that *C. albicans* negatively regulates the transcription of melanogenesis genes, more recent studies have shown that melanocytes may recognize *C. albicans* via TLR4 to increase melanization and inhibit infection (Figure 1) [51,52].

**Cutaneous Nerves**

The skin is also a sensory organ that is highly innervated by terminal nerve fibers. Neuro-immune interactions have been appreciated in human and in mouse inflammatory and infectious disease models [53]. Myeloid cells in the dermis and epidermis have been shown to localize closely with cutaneous nerve fibers, specifically fibers expressing calcitonin gene related peptide (CGRP) [54,55]. CGRP is a neuropeptide produced and released by sensory neurons that mediate pain signaling, as well as other functions. In the context of *C. albicans* vulvovaginal infection, *C. albicans* has been shown to stimulate pain, allodynia, and the development of CGRP* nerve fibers [56]. In addition, zymosan, a derivative of yeast cell walls, has been used as an experimental trigger of pain in rodent models [57]. Recently, pathogens such as *C. albicans* and *S. aureus* have been shown to directly activate sensory neurons taken from murine dorsal root ganglions [14,58]. Zymosan can activate sensory neurons directly, while *Staphylococcus aureus* can activate neurons both directly and by causing membrane permeability in nerves through its secreted toxins [14,58]. Thus, it is possible that neurons may be activated by recognition of cell-wall products through neuronal PRRs as well as through secreted microbial products.*C. albicans* can also metabolize host arachnoid acid to byproducts that can directly activate nociceptor transient receptor potential cation channel subfamily V member 1 (TRPV1), suggesting that multiple pathways of activation may exist [59].

The activation of neurons by *C. albicans* leads to increased secretion of the neuropeptide CGRP [14]. CGRP has been demonstrated to have antifungal properties *in vitro*, to act on KCs to drive proliferation *in vitro*, to skew LCs towards type 2 responses *in vitro*, and to induce IL-23 secretion by dermal DCs *in vivo* [14,60-62]. In the mouse model of *C. albicans* epicutaneous infection, mechanical ablation of all cutaneous nerves or chemical denervation of TRPV1* nociceptors (i.e., pain sensing nerves) with resiniferatoxin (RTX) rendered mice less able to resist *C. albicans* skin infection as a result of diminished IL-23/IL-17 production (Figure 1).
Addition of CGRP in RTX-treated mice reversed the increased fungal burden [14]. Thus, pain sensation via TRPV1 channels and CGRP secretion by sensory nerves is crucial for cutaneous host defense against *C. albicans*.

**IL-23 and Antigen-Presenting Cells**

IL-23 is a heterodimeric protein composed of IL-12p40 and IL-23p19 subunits that signals through heterodimeric IL-12Rβ1 and IL-23R [63]. IL-23 has crucial roles in protection from pathogens and in the pathogenesis of autoimmunity by inducing a unique inflammatory gene signature that includes *Il17a*, *Il17f*, *Csf2*, *Tnfa*, and others [64]. Mutation of IL-12Rβ1 or of downstream STAT3 leads to reduced numbers of Th17 cells and CMC in humans [65,66]. In mice, IL-23, but not IL-12, deficiency leads to increased susceptibility to intravenous, oral, epidermal, and intradermal primary and secondary infection with *C. albicans* due to decreased IL-17, as well as reduced neutrophil infiltrates and epithelial hyperplasia [13,14,67,68].

IL-23 has been demonstrated to be produced by dendritic cells after *C. albicans* infection in mice and humans [14,69]. The skin harbors three major subtypes of dendritic cells. LCs are the only MHC-II positive cells in the epidermis, while CD11b+ dermal DCs (dDCs) and CD103+ dDCs make up the majority and minority of the DC subsets in the dermis, respectively [70]. The requirement of skin DC subsets for imiquimod-induced psoriatic inflammation is unclear, with reports showing both LCs and CD11b+ dDCs are nonredundant producers of IL-23 in vivo [71,72]. In response to *C. albicans* skin infection, LCs are not required for IL-23 production or...
innate immune resistance against the fungus. Mice deficient for LCs, however, have exaggerated NK cell-mediated inflammation in response to heat-killed *C. albicans* application to the footpad (Figure 1) [14,73]. In addition, ablation of LCs in mice induces exaggerated contact hypersensitivity (CHS) and delayed-type hypersensitivity (DTH) responses, suggesting that LCs are immune-suppressive in these contexts [74–76].

Furthermore, mice deficient for both LCs and CD103+ dDCs have intact immunity against *C. albicans*. Mgl2-DTR mice that can be depleted of CD11b+ dDCs and tissue-resident macrophages have decreased IL-23 transcription, IL-17 production, and increased fungal burden in skin after infection with *C. albicans* [14]. Mixed bone-marrow chimeric mice in which CD11b+ dDCs lack IL-23 production have a defective immune response to primary *C. albicans* skin infection, particularly owing to decreased IL-17 production by dermal γδ T cells (see below) [14]. Thus, CD11b+ dDCs are both necessary and sufficient for IL-23-driven anti-*C. albicans* responses. Interestingly, CD11b+ dDC reside alongside dermal nerve fibers and also express the receptor for CGRP [14,55]. CGRP released by sensory nerves after *C. albicans* infection acts on the CD11b+ dermal DCs to stimulate IL-23 production. Thus, the sensory nervous system and CD11b+ dermal DCs participate in a crucial cutaneous inflammatory circuit that drives host resistance to *C. albicans*.

**IL-17 and γδ T cells**

The IL-17 family consists of six cytokines (IL-17A–IL-17F) that signal through five receptors (IL-17RA–IL-17RE). IL-17A and IL-17F form homo- and heterodimers and signal through a dimer of IL-17RA and IL-17RC. Mutations in IL-17F, IL-17RA, IL-17RC, and a downstream signaling molecule Act1 all lead to CMC in humans [10,64]. IL-17RA expression is found in both hematopoietic and non-hematopoietic cells. In hematopoietic cells, IL-17 can signal on neutrophils and NK cells to drive antifungal immunity [6,77]. In non-hematopoietic cells such as KCs, IL-17 induces the transcription of proinflammatory cytokines such as IL-6, G-CSF, chemokines such as CCL20, and the antimicrobial peptides β-defensins and S100A proteins [44,78]. These KC signals are important for neutrophil trafficking and function, as well as for host defense against *C. albicans* and other extracellular pathogens. Unlike IL-17A/F, IL-17C is produced by epithelial KCs, but not by hematopoietic cells, and signals through IL-17RA and IL-17RC [64]. IL-17C induces a gene profile strikingly similar to that induced by IL-17A, and plays an important role in psoriasis pathogenesis, but plays no detectable role in protection against oral, dermal, or disseminated candidiasis in *vivo* [79,80]. Similarly, IL-17RE was dispensable for protection against candidiasis, further demonstrating the specific necessity for IL-17A/F signaling [80].

Th17 cells have been long considered the predominant source of IL-17 during *C. albicans* mucocutaneous infections (see below). Recently, tissue-resident type 3 innate lymphoid cells (ILC3s) and γδ T cells have been appreciated as primary producers of effector cytokines at the site of *C. albicans* infection in mouse models [81,82]. In humans, loss of function STAT3 mutations lead to decreased number and function of IL-17-producing unconventional mucosa-associated invariant T cells [83]. Unlike CD4+ T cells, which are primed by DC antigen presentation and signals in secondary lymphoid organs to become IL-17 producers, innate lymphoid cells and γδ T cells are pre-programmed into the IL-17-secreting lineage in the bone marrow and thymus, respectively [84]. In humans, γδ T cells have been shown to make IL-17 in response to IL-23 produced by DCs after *C. albicans* stimulation [69]. Thus, these cells may serve as primary responders in patients who have not yet developed *C. albicans*-specific effector or memory T cells and may augment early immunity. In mouse models of OPC, some groups have found that γδ T cells and innate-like CD4+ T cells in tissues are both crucial for resistance while other groups have demonstrated the need of ILCs for protection [81,82]. In the skin, dermal γδ T cells are the obligate source of IL-17 after epicutaneous *C. albicans* [14]. Most IL-17-secreting dermal γδ T cells have a Vγ4 TCR [85]. These embryonically derived γδ T cells with
constitutive expression of IL-23R can produce IL-17 and proliferate rapidly in response to IL-23 from CD301b+ dermal DC [14,55]. Thus, IL-17 production is not restricted to CD4+ T cells after infection, and tissue-resident cells are important mediators of antifungal immunity.

Neutrophils
It has long been appreciated that IL-17 is a crucial cytokine that drives the recruitment and activation of neutrophils [86]. Neutrophils have been demonstrated to be required for protection against mucosal and systemic C. albicans infections [77]. Recently, neutrophils have also been shown to constitutively express RORgt and to produce and respond to IL-17 in a mouse model of Aspergillus fumigatus [86]. Neutrophils are also crucial for phagocytosis of C. albicans because they sense pathogen size via Dectin-1 and release neutrophil extracellular traps in response to Candida albicans filaments but not to yeast [87]. In addition, adoptive transfer of neutrophilic myeloid-derived suppressor cells have been shown to improve mice survival following invasive C. albicans infection [88]. Neutrophils in response to C. albicans infection have been studied extensively and are reviewed elsewhere, but their role in cutaneous host defense against C. albicans skin infections remains an open area of investigation [2,23,89].

Adaptive Immunity Against C. albicans Skin Infection
The importance of adaptive IL-17 producing CD4+ T cells in protection against C. albicans has been demonstrated in mice and humans. In humans, Th17 cells are the crucial mediators of antifungal barrier immunity. Patients with Th17 deficiencies in the context of STAT3-deficiency/ HIES have increased susceptibility to mucocutaneous candidiasis [65]. Stimulation of naïve human CD4+ T cells with C. albicans can induce the expansion of T cell clones and induce the production of IL-17 and IFN-γ that depended on IL-1β [90]. Interestingly, memory T cell responses to C. albicans demonstrated functional heterogeneity, with distinct Th1/Th2/Th17 cell subsets sharing the same T cell clone, suggesting that polarized T cell responses might result from preferential expansion rather than T cell priming [91]. However, in mouse models of cutaneous candidiasis, both fungal morphology and DC subsets have been demonstrated to be important for the differentiation of specific T helper subsets that lead to a compartmentalized, tissue-specific response against secondary exposure of C. albicans (Figure 2) [5].

Th17 Cell Differentiation
During infection or inflammation, DCs migrate to the lymph node, upregulate co-stimulatory molecules, and secrete cytokines that induce the proliferation and differentiation of effector and cytotoxic T cells [70]. Dock8 mutations in humans lead to defective T cell responses and dendritic cell migration that cause HiES and CMC [39,92]. In mice, skin DCs prime distinct T helper responses that have differing functions in protective immunity against subsequent C. albicans infections [12]. LCs migrate to the lymph node 3–4 days after infection, where they express high amounts of the Th17-differentiating cytokines IL-1β, IL-6, and TGF-β. Mice deficient for LCs have intact C. albicans-specific T cell expansion but have significantly decreased Th17 cells [12]. In the epidermis, C. albicans colonizes as budding yeasts. C. albicans strains that are genetically locked into yeast, but not filaments, are capable of inducing Th17 differentiation through LCs [5]. The yeast morphology of C. albicans provides accessibility ligands for the β-glucan receptor Dectin-1 in its bud scars [22]. In mice, LCs express the pattern recognition receptor Dectin-1 [5]. Humans with Dectin-1 polymorphisms and mice with Dectin-1 deficiency display a decreased C. albicans-specific Th17 response [18]. Binding of Dectin-1 by C. albicans induces the secretion of the proinflammatory cytokine IL-6 by human peripheral blood mononuclear cells (PBMC) and mouse LCs [5,18]. Production of IL-6, but not IL-1β, IL-23, or TGF-β, from LC is necessary for Th17 cell differentiation, while IL-6 from other sources was dispensable. Finally, LCs deficient for Myd88 have defective Th17 cell generation while LC migration is unaffected [28]. Thus, pattern recognition of C. albicans via Dectin-1 and TLRs by LCs allows the elaboration of IL-6 that is required for Th17 cell differentiation.
As discussed previously, CD11b+ dermal DC are required for innate immunity against C. albicans and for Th17 generation against bacterial and fungal pathogens in other tissues [93]. CD11b+ dermal DCs also express Dectin-1 but are not required for Th17 generation after C. albicans infection because of the inaccessibility of pseudohyphal Dectin-1 ligands in the dermis [5,12]. Unlike LCs and CD11b+ dermal DCs, CD103+ dermal DCs do not express Dectin-1 and suppress Th17 cell differentiation presumably through anti-Th17 cytokines such as IL-27 and IL-12 [5]. While CD103+ dDCs and CD11b+ dDCs are not required for Th17 differentiation, they do play a role in activating and differentiating bystander IL-17-secreting CD8+ T cell responses that can protect against C. albicans [12,94].

Th1 Cell Differentiation and Compartmentalization of the Effector Response
Unlike the yeast form of C. albicans, filamentous C. albicans invade past the stratum corneum and the dermis and disseminate to systemic tissues. Epicutaneous and intravenous infection with a strain of C. albicans that expresses model antigens under a filament-specific promoter induces Th1 but not Th17 responses [5]. Given that Batf3-deficient mice have defective Th1 cell differentiation in response to epicutaneous and disseminated C. albicans infection, CD103+ dermal DC likely induce Th1 cells through the secretion of IL-12 or IL-27 [12]. In the oral mucosa, CD103+ and CD11b+ migratory DCs collaborate to induce C. albicans-specific T cell expansion and Th1 cell differentiation, while oral LCs were dispensable [95]. Thus, different DCs in distinct tissues appear to play diverse roles. Interestingly, a patient with an IRF8 mutation and lacking both conventional and plasmacytoid dendritic cells was recently found to be infected with oral candidiasis [96].
Similarly to humans, mice infected with *C. albicans* demonstrate heterogeneous T helper profiles that include both Th17 and Th1 cells. Mice lacking Th17 cells have impaired protection against secondary cutaneous, but not systemic, *C. albicans* infection, while mice with exaggerated Th17 cells have greater protection against cutaneous, but not systemic, reinfection [5]. In addition, adoptive transfer of Th17 cells from *C. albicans*-primed mice into naïve animal afforded host protection against oral and cutaneous, but not systemic, *C. albicans* infection [5,97]. Conversely, mice lacking Th1 cells have impaired protection against secondary systemic, but not cutaneous, *C. albicans* infection, while mice with exaggerated Th1 cells have increased resistance against systemic but not cutaneous reinfection. Finally, adoptive transfer of Th1 cells from *C. albicans*-primed mice into naïve animals afforded host protection against systemic but not cutaneous *C. albicans* infection [5]. Thus, specific T helper subsets have compartmentalized immunity against distinct routes of *C. albicans* reinfection. While differential priming of T helper subsets to distinct routes of infection has been appreciated in other models, the mechanism of compartmentalized protection is still unknown [88]. It remains to be determined whether distinct T helper subsets have different tissue homing, persistence, and/or function.

### Concluding Remarks

In this review we highlight the mechanisms underlying innate and adaptive immunity in response to *C. albicans* skin infections. Innate immunity against *C. albicans* skin infections is driven by recognition of the pathogen by the cutaneous stromal and nervous system that alarm DCs to adoptive transfer of Th17 cells from secondary cutaneous, but not systemic, areas to prime cutaneous Th17 responses to these species of *Candida* differ from skin immunity against *C. albicans*?

How is *C. albicans* recognized by sensory neurons? Understanding whether neurons express pattern-recognition receptors, and what specific *C. albicans* element is being sensed, will be crucial for deciphering the interaction between the pathogen and the nervous system in the skin innate immune response. What are the roles of innate lymphoid cells, neutrophils, and recruited myeloid cells in *C. albicans* skin infection? While much is known about the function of these leukocytes in other systems of *C. albicans* infection or in *Candida* skin resident murine dendritic cell subsets promote distinct and opposing antigen-specific T helper cell responses. Immunity 35, 260–272

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### Outstanding Questions

Major disease-causing *Candida* species include *C. dubliniensis*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and *C. krusei*. How do the immune responses to these species of *Candida* differ from skin immunity against *C. albicans*?

How is *C. albicans* recognized by sensory neurons? Understanding whether neurons express pattern-recognition receptors, and what specific *C. albicans* element is being sensed, will be crucial for deciphering the interaction between the pathogen and the nervous system in the skin innate immune response. What are the roles of innate lymphoid cells, neutrophils, and recruited myeloid cells in *C. albicans* skin infection? While much is known about the function of these leukocytes in other systems of *C. albicans* infection or in vivo, very little is known about their specific contributions to immunity in the context of *C. albicans* infection. Why and how is T cell immunity against *C. albicans* compartmentalized to the morphology of the pathogen? Do distinct T helper subsets have divergent tissue migration? What is the role of IFN-γ in protective immunity against skin and invasive *C. albicans* infections? How is *T* cell memory generated and maintained in the skin in response to *C. albicans*? Are there *C. albicans*-specific tissue-resident Th17 cells in the skin? What stromal signals, cytokines, and antigen-presenting cells contribute to the maintenance of these cells?

How does the immune response to other common skin pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes* differ from skin immunity against *C. albicans*?
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