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Skin Immunity to *Candida albicans*

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Abstract

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

Compartmentalization of immunity against *C. albicans* skin infection

C. albicans is the most common and well-studied of the disease-causing *Candida spp.* that 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. Chronic mucocutaneous candidiasis (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 critical for host defense against *Candida albicans*. Subsequent mechanistic studies have furthered 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).

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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, anti-cancer treatments, increased anti-microbial 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 that have defects with type 3 immunity, genetic defects upstream or downstream of IL-17 have not been implicated in patients with disseminated candidiasis[3]. Rather, type I Interferons have been demonstrated to play an important role in patients with systemic infections. In mice, IL-17 plays a role in systemic candidiasis but IFNγ from Th1 and 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 micro-environmental factors such as local nutrients, pH, bile acids and local commensal flora[8,9]. The host response to *C. albicans* infections in tissues other than the skin has been recently reviewed in depth[8–10].

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 for 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 leukocyte of the skin make the murine skin an ideal site of study of both innate and adaptive anti-fungal immune responses. Specifically, the IL-17 cytokine family has been identified to be essential against host defense, driving neutrophil recruitment and anti-microbial peptide production[10]. It has been appreciated that IL-17 can be produced by leukocytes from both the innate (e.g. ILCs, γδ T cells) and adaptive immune system (e.g. CD4+ T cells)[5,14]. This review focuses on recent advances in understanding the mechanisms by which the primary innate and secondary adaptive type 3 immune response develop during *C. albicans* infection. Better understanding these mechanisms can assist with 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 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 of 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 pro-inflammatory 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 phagocytosis of *C. albicans* yeasts[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 *in vivo*, but has also been shown to be redundant[19,20]. These initially discordant results resulted from the use of different strains of *C. albicans*. Some strains of *C. albicans* have increased cell wall chitin resulting in lower availability of cell wall β-glucans for recognition by Dectin-1[21].

In addition, Dectin-1 specifically recognizes *C. albicans* yeast and not filamentous forms due to a difference in β-glucan availability (covered below) [22]. Recognition of fungi by other C-type lectin receptors, including the important concept of trained immunity, has been reviewed in depth elsewhere[2,15].

Toll like receptors—Several Toll-like Receptors (TLRs) recognize *C. albicans* cell wall polysaccharides including TLR-2, which recognizes phospholipomannans, and TLR-4, which recognizes O-linked mannans[23]. Activation of TLRs by their ligands leads to triggering of intracellular signaling pathways, such as MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathways, leading to transcription and secretion of TNFα, IL-6 and/or type I interferons[24]. TLRs are expressed differentially on numerous cell types including keratinocytes, melanocytes, dendritic cells and macrophages and can also cooperate with C-type lectins or the inflammasome to drive IL-1β, TNFα and IL12 production[25,26].

Deficiency of TLRs or adapter protein Myd88 significantly alters the survival of mice to intravenous *C. albicans* infection *in vivo* and Myd88 deficiency in Langerhans cells renders mice unable to mount Th17 response to *C. albicans* skin infection[27,28]. However, deficiency of IRAK-4 or Myd88 lead to recurrent pyogenic bacterial infections and cold abscesses but do not lead to CMC in humans[29,30]. Mutations of IκBa, which acts downstream of TLRs and of the T cell receptor (TCR) lead to CMC. Given the disparity of CMC susceptibility in IκBa 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[29].

Nod-like receptors—Nod-like receptors (NLRs) generally interact with apoptosis-associated speck-like protein containing a CARD (ASC) and procaspase-1 to form the inflammasome to convert procaspase-1 into active caspase-1, which in turn converts pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18[31] In humans, NLR mutations and polymorphisms have not been identified with CMC but a defective NLRP3 activation increases *C. albicans* colonization of the gut and NLRP3 polymorphism predisposes patients to recurrent vulvovaginal candidiasis (RVVC)[32,33]. In mice, macrophage derived Nlrp3 recognizes filamentous forms of *C. albicans*, and deficiency of Asc and Nlrp3 and IL-1R1 leads to decreased *C. albicans* resistance in intravenous and oral routes of *C. albicans* infection[34,35]. Nlrp10 has also been implicated in host defense against *C. albicans* by the induction of dendritic cell migration and differentiation of T helper cells[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[38]. This supports the clinical association between Hyper IgE Syndrome (HIES) from Dock8 mutations and CMC[39]. Finally, stromal cell derived NLRC4 has also been demonstrated to the critical for mediating immunity against oral candidiasis[40]. While there has been some preliminary characterizations of NLRs in immunity against *C. albicans* disseminated and oral infections, the role of the inflammasome in mediating immunity against *C. albicans* skin infection is currently unknown.

Stromal cells

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

Beneath the cornefied envelope are the granular, spinous and basal layers that are composed of KC that expresses PRRs. These KC initiate the early cutaneous immune responses. *C. albicans* has been shown to adhere to human keratinocytes and induce pro-inflammatory cytokine secretion *in vitro* but their role in directly activating KCs *in vivo* is unknown[43]. Keratinocytes constitutively express the receptors for TNFα, IL-17A and IL-22. TNFα and IL-17 acts on keratinocytes 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 keratinocyte to drive their proliferation by down-regulating genes involved in terminal differentiation[45]. Recent studies have also identified the role of keratinocytes 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 critical topic of investigation going forward.

In addition to keratinocytes, 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 hyper-pigmentation in humans[49]. Melanin has also been demonstrated to have antimicrobial properties[50]. While early studies demonstrated that *C. albicans* negatively regulates transcription of melanogenesis genes, more recent study has shown that melanocytes may recognize *C. albicans* via Toll Like Receptor 4 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 infection 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 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 permiability in nerves through its secreted toxins[14,58]. Thus, 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 bi-products 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* lead to the 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 resineferatoxin (RTX) rendered mice less able to resist *C. albicans* skin infection due to diminished IL-23/IL-17 production (Figure 1). Addition of CGRP in RTX treated mice ameliorated the increased fungal burden[14]. Thus, pain sensation via TRPV1 channels and CGRP secretion by sensory nerves is critical for cutaneous host defense against *C. albicans*.

IL-23 and Antigen Presenting Cells

IL-23 is a heterodimeric protein of IL-12p40 and IL-23p19 subunit that signals through hetrodimeric IL-12Rb1 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-12Rb1 and the downstream STAT3 lead reduced numbers of Th17 cells and CMC in humans[65,66]. In mice, IL-23, but not IL-12, deficiency leads to increases susceptibility to intravenous, oral, epidermal and intradermal primary and secondary infection of *C. albicans* infections due to decreased IL-17, reduced neutrophilic 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. Langerhans cells are the only MHC-II positive cells in the epidermis while CD11b+ dermal DCs (dDCs) and CD103+ dDCs remake up for 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 of LCs, however, have exaggerated NK cell mediated inflammation in response to heat killed *C. albicans* application to the footpad (Figure 1)[14,73]. Additionally, ablation of LCs in mice induces exaggerated CHS and DTH responses, suggesting that LCs are immune-suppressive in these contexts[74–76].

Furthermore, mice deficient in 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 defective immune response to primary *C. albicans* skin infection, particularly due 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 critical 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 anti-fungal immunity[6,77]. In non-hematopoietic cells such as keratinocytes, IL-17 induces transcription of pro-inflammatory cytokines such as IL-6, G-CSF, chemokines such as Ccl20, and antimicrobial peptides S100A proteins and β-defensins[44,78]. These keratinocyte signals are important for neutrophil trafficking and function and for host defense against *C. albicans* and other extracellular pathogens. Unlike IL-17A/F, IL-17C is produced by epithelial keratinocytes but not hematopoietic cells and signals through IL-17RA and IL-17RE[64]. IL-17C induces a gene profile strikingly similar to 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 of 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 in 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 mucosal associated invariant T cells[83]. Unlike CD4+ T cells, which are primed by dendritic cell antigen presentation and signals in the secondary lymphoid organs to become IL-17 producers, innate lymphoid cells and γδ T cells are pre-programmed into 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 immunity early. In mouse models of OPC, some groups have found that γδ T cells and innate-like CD4+ T cells in tissues are both critical 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 of the 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 been long appreciated that IL-17 is a critical cytokine that drives 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 Rorγt, produce and respond to IL-17 in a mouse model of *Aspergillus fumigatus*[86]. Neutrophils are also critical for phagocytosis of *C. albicans* as they sense pathogen size via Dectin-1 and release neutrophil extracellular traps in response to *Candida albicans* filaments but not yeast[87]. In addition, adoptive transfer of neutrophilic myeloid derived suppressor cells have been shown to improve mice survival of 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 critical mediators of anti-fungal barrier immunity. Patients with Th17 deficiencies in the context of STAT3 deficiency/HIES has increased susceptibility to mucocutaneous candidiasis[65]. Stimulation of naïve human CD4+ T cells with *C. albicans* can induce the expansion of T cell clones that can induce the production of IL-17 and IFNγ 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 dendritic cell subsets have been demonstrated to be important for differentiation of specific T helper subsets that lead to 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 induces the proliferation and differentiation of effector and cytotoxic T cells[70]. Dock8 mutations in

humans lead to defective T cell response and dendritic cell migration that causes 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]. Langerhans cells migrate to the lymph node 3 to 4 days after infection, where they express high amount of Th17 differentiating cytokines IL-1β, IL-6 and TGF-β. Mice deficient in Langerhans cells 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 Langerhans cells[5]. The yeast morphology of *C. albicans* provides accessibility ligands for the β-glucan receptor Dectin-1 in its bud scars[22]. In mice, Langerhans cells express the pattern recognition receptors Dectin-1[5]. Humans with Dectin-1 polymorphisms and mice with Dectin-1 deficiency lead to decreased *C. albicans* specific Th17 response[18]. Binding of Dectin-1 by *C. albicans* induces the secretion of the pro-inflammatory cytokine IL-6 by human PBMC and mouse Langerhans cells[5,18]. 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 were dispensable. Finally, Langerhans cell deficiency of 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 for 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 due to the inaccessibility to Dectin-1 ligands of psuedohyphae in the dermis[5,12]. Unlike Langerhans cells 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+ dDC 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 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 response but not Th17 response[5]. Given that Batf3 deficient mice have defective Th1 cell differentiation to epicutaneous and disseminated *C. albicans* infection, CD103+ dermal DC likely induces Th1 cells through the secretion of IL-12 or IL-27[12]. In the oral mucosa, CD103+ and CD11b+ migratory DCs collaborate together to induce *C. albicans* specific T cell expansion and Th17 cell differentiation while oral LCs were dispensable[95]. Thus, there seems to be varied functions by different DCs in distinct tissues. Interestingly, a patient with IRF8 mutation lacking both conventional and plasmacytoid dendritic cells was recently found to be infected with oral candidiasis[96].

Like humans, mice infected with *C. albicans* demonstrate heterogeneous T helper profiles that includes both Th17 and Th1 cells. Mice lacking Th17 cells have impaired protection against a secondary cutaneous, but not systemic, *C. albicans* infection while mice with

exaggerated Th17 cells have greater protection against cutaneous, but not systemic, re-infection[5]. In addition, adoptive transfer of Th17 specific cells from *C. albicans* primed mice into naïve animal afforded the 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 re-infection. Finally, adoptive transfer of Th1 specific cells from *C. albicans* primed mice into naïve animal afforded the 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* re-infection. 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[98]. 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 mechanism of innate and adaptive immunity generation 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 dendritic cell to activate tissue resident IL-17 secreting γδ T cells. Adaptive immunity is dependent on recognition of specific morphologies of *C. albicans* by distinct dendritic cell subsets leading to compartmentalized T helper responses. In conclusion, *C. albicans* infection skin and mucosal infections have been a fruitful model of investigation of how IL-17 responses are developed. Findings addressed in this review provide a mechanistic insight into skin immunity that may have implications for both vaccination strategies and treatment autoimmunity. Investigation into fungal recognition, stromal-immune interaction and development of memory CD4+ response to *C. albicans* are important areas for future research.

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Highlights

- Primary immuodeficiencies reveal conserved IL-17 stimulating/signaling pathways involved in mucocutaneous defense against *C. albicans*
- Mouse models have demonstrated both innate and adaptive sources of IL-17 in response to *C. albicans*
- Immunity against *C. albicans* is compartmentalized towards sites of infection
- Non-hematopoietic cells provide antifungal immunity in the skin

Outstanding Questions

1. Major disease-causing *Candida* species include *C. dubliniensis, C. parapsilosis, C. glabrata, C. tropicalis*, and *C. krusei*. How does the immune response to these species of *Candida* vary from skin immunity against *C. albicans*?
2. 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 critical for deciphering the interaction between the pathogen and the nervous system in the skin innate immune response.
3. 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.
4. 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?
5. How does the immune response to other common skin pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes* vary from skin immunity against *C. albicans*?

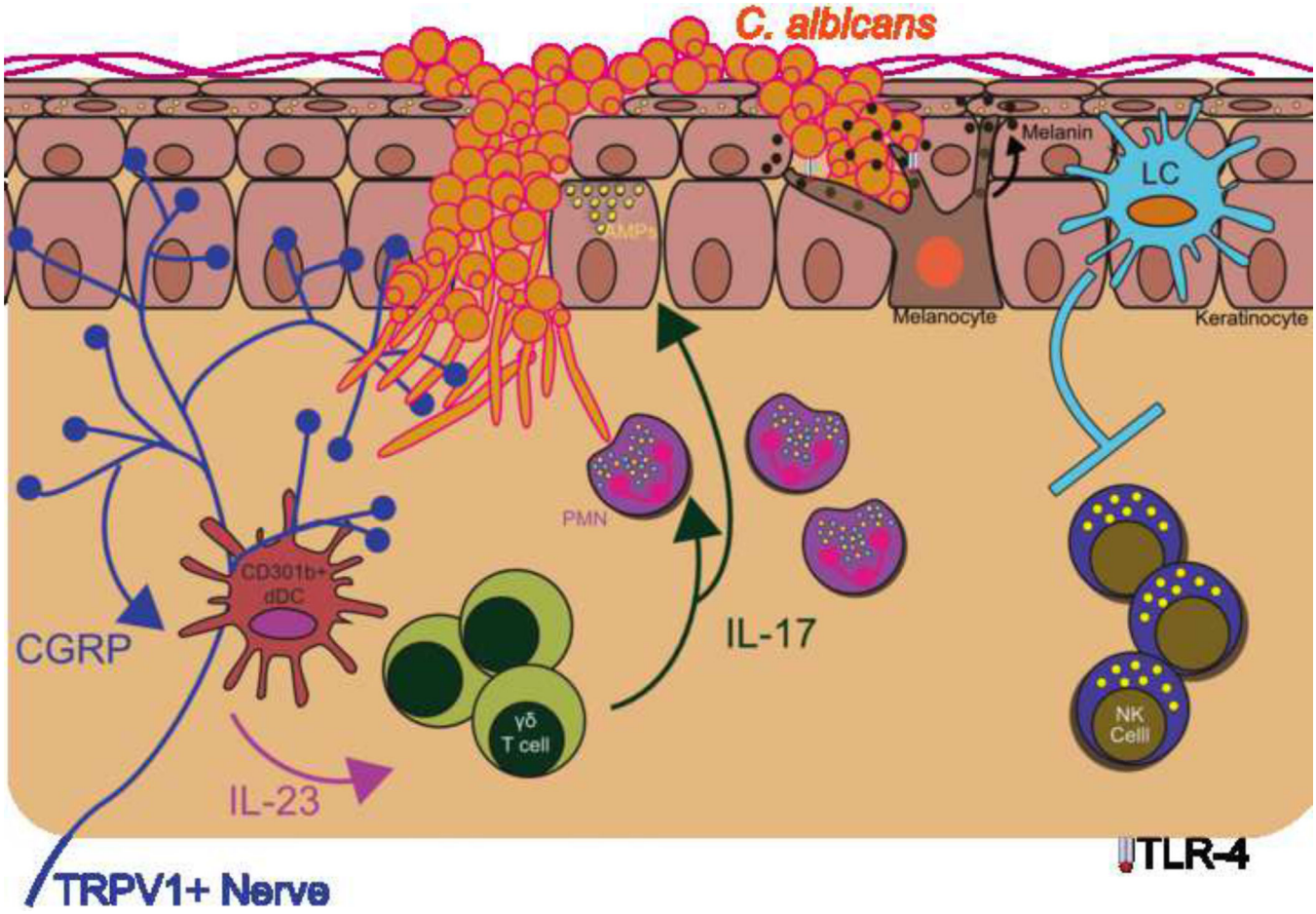

Figure 1. Innate immunity against *C. albicans* skin infection

The skin has a layered innate immune system. *C. albicans* directly activates cutaneous sensory nerves to induce the release of calcitonin gene related peptide (CGRP). CGRP acts on CD301b+ dermal dendritic cells (dDC), which subsequently release IL-23. IL-23 acts on dermal γδ T cells to drive IL-17 production in the skin, leading to anti-*C. albicans* resistance through the presumed activation of neutrophils and antimicrobial peptides such as β-defensins[14]. In addition, melanocytes in the basal epidermis can also recognize *C. albicans* via TLR-4 to drive production and release of melanin granules, which are antimicrobial in nature[52]. Finally, Langerhans cells of the epidermis can suppress liver derived CD49a+ NK cells in response to *C. albicans* through unknown mechanisms[73].

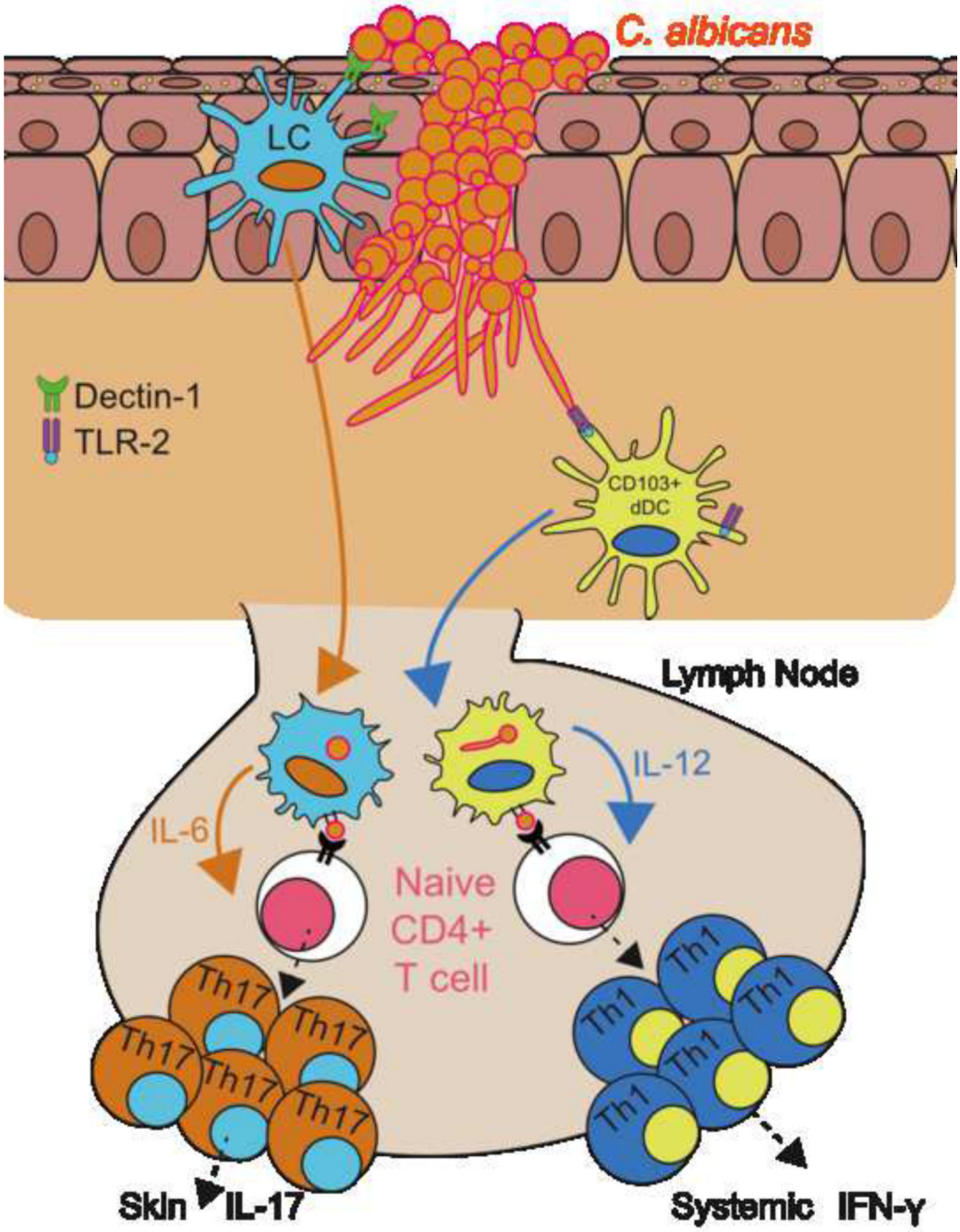

Figure 2. Adaptive immunity against *C. albicans* skin infection

The skin generates heterogeneous T helper response that provides compartmentalized immunity against *C. albicans*. In the epidermis, *C. albicans* exists as yeasts. *C. albicans* yeasts are recognized by Dectin-1 on Langerhans cells (LCs). Dectin-1 engagement on LCs lead to production of IL-6 in the secondary lymphoid organs that differentiate naïve CD4+ T cells to the Th17 cell lineage. These Th17 cells provide protection against secondary cutaneous infections but not against secondary systemic infections. Conversely, *C. albicans* invades as filamentous pseudohyphae in the dermis. Recognition of *C. albicans* filaments by

CD103+ dDCs, presumably through TLR-2, lead to Th1 cell differentiation in the secondary lymphoid organs. These Th1 cells provide protection against secondary systemic infections but not secondary skin infection[5,12]. Thus, recognition of distinct morphology of *C. albicans* via different dendritic cell subsets lead to tailored immune response that provide protect against specific subsequent routes of infections.

Table 1

Primary Immunodeficiencies leading to CMC

Gene	Phenotype	Reference
IL2RG, RAG1, RAG2, ADA	Loss of T and/or B Cells	[30]
UNC119, MAGT1, RAG1	Idiopathic CD4 Lymphopenia	[99,100]
STAT3	HIES due to defective IL-23R and IL-6R signaling and decreased Th17	[101,102]
DOCK8	HIES due to defective T cell synapse formation and dis-regulated DC migration	[103]
IκBA	Impaired TCR and NFkB signaling	[29]
IL-17F/IL-17RA/IL-17RC/Act1	Defective IL-17A/F signaling	[104–106]
RORC	Loss of IL-17A/F production, lymph nodes and impaired IFNγ response	[107]
Aire	Autoantibodies to IL-17A/F/IL-22	[108]
STAT1	Gain of function mutation leading to excessive type I and II IFN responses leading to decreased Th17	[104,109]
IL-12RB1	Abolished response to IL-23 and IL-12	[66]
Clec7A/Card9	Defective phagocytosis, IL-1β, IL-6 production by PBMC and IL-17 producing T cells	[17,18]