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Organ-Specific Mechanisms Linking Innate and Adaptive Antifungal Immunity

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Abstract

Fungal infections remain a significant global health problem in humans. Fungi infect millions of people worldwide and cause from acute superficial infections to life-threatening systemic disease to chronic illnesses. Trying to decipher the complex innate and adaptive immune mechanisms that protect humans from pathogenic fungi is therefore a key research goal that may lead to immune-based therapeutic strategies and improved patient outcomes. In this review, we summarize how the cells and molecules of the innate immune system activate the adaptive immune system to elicit long-term immunity to fungi. We present current knowledge and exciting new advances in the context of organ-specific immunity, outlining the tissue-specific tropisms for the major pathogenic fungi of humans, the antifungal functions of tissue-resident myeloid cells, and the adaptive immune responses required to protect specific organs from fungal challenge.

Every organ is endowed with resident immune cells that are specially equipped for immune surveillance and homeostatic maintenance of organ functions [1]. Many of these resident immune cell populations are macrophages or close relations, including alveolar macrophages in the lung and microglia in the brain. Organs such as the skin, gastrointestinal (GI) tract and other mucosal barriers are also rich in other innate cells that provide additional homeostatic control, and include dendritic cells (DCs) and non-conventional lymphoid cells such as innate lymphoid cells (ILCs), mucosal-associated invariant T-cells (MAIT) cells and gamma-delta T-cells. Based on their close association with the tissue parenchyma and vasculature, these innate cells are often the first responders to tissue damage and infection and thus they have a remarkable influence over the resulting immune response. For example, their production of chemokines drives accumulation of inflammatory cells [2], while expression of MHC molecules by these cells can regulate adaptive immune responses [3]. Therefore, resident immune cells can act as a bridge between innate and adaptive immunity and shape organ-specific immune responses.

Human fungal diseases continue to represent a significant global health problem [4]. Despite antifungal therapy being widely available, mortality and morbidity rates associated with

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fungal infections remain unacceptably high. Moreover, there are worrying recent reports of emerging fungal pathogens with inherent resistance to our arsenal of available antifungal drugs [5]. Vaccines and immunotherapies to treat fungal diseases are therefore a priority. In the last few decades, we have significantly enhanced our understanding of the molecular pathways controlling innate fungal recognition and the antifungal responses elicited by myeloid cells. However, we understand less with regard to the generation and regulation of the adaptive immune response to many of these pathogens, and even less about the organ-specific pathways controlling fungal growth. Yet, the goal of antifungal immunotherapies will be to elicit long-term memory and protection, thus it will be important to determine the signals required to generate effective antifungal memory responses. Moreover, the specificity of these immunotherapeutic approaches will also need to be fine-tuned to reduce the potential side effects, thus delineating antifungal immune mechanisms in an organ-specific context will also be important.

In this review, we will cover how cells and molecules considered part of the innate immune system regulate the adaptive immune response during fungal infections, presenting these exciting new advances in the context of organ-specific immunity (Figure 1). Finally, we will highlight gaps in knowledge and indicate at major new developments in other fields that may help to bridge these gaps in the fungal immunology field.

The Central Nervous System (CNS)

Fungal CNS infections are rare and most often associate with acquired immunodeficiency caused by HIV infection [6]. Less often, inborn errors in immunity predispose to fungal CNS disease [2]. The majority of fungal meningitis cases are caused by *Cryptococcus neoformans*, an infection that is critically dependent on $CD4^+$ T-cells since HIV infection is the predominant risk factor for developing infections with this species [7; 8]. Cerebral infection by dematiaceous fungi (e.g. *Exophiala* species, *Curvularia* species) is the most common form of systemic disease for this group of pathogenic fungi, and primarily affects “putatively” immunocompetent people who become traumatically inoculated through the skin or mucous membranes, although cerebral cases without apparent mucocutaneous inoculation are not uncommon [9]. Other fungi that cause meningitis include *Candida albicans* and *Aspergillus fumigatus*, both rare causes of brain infection that most commonly occur following complications after neurosurgery or with iatrogenic immunosuppression, but have also been associated with some anti-cancer treatments [10] and mutations in the signaling molecule, *CARD9* [2; 11].

Microglia are the most numerous innate immune cells in the CNS and are important for neuronal function, immune surveillance and synaptic pruning [12]. The ontogeny of microglia, along with several other tissue-resident macrophage populations, has recently been revealed to be dependent on embryonic precursors deriving from the fetal yolk sac that seed the developing brain and give rise to long-lived cells that divide *in situ* [1; 12; 13]. Microglia exhibit strong responses to various species of fungi, including *C. albicans* and *C. neoformans* [14; 15], utilizing the receptor GPR43 [16], PI3 kinase signaling [17], and inducible nitric oxide synthase (iNOS) [18] for *C. neoformans* phagocytosis and killing. Using bone-marrow derived macrophages, several studies have shown that classically-

activated macrophages (M1) are required for protection against *C. neoformans*, since these cells elicit IFNγ-producing Th1 cells which control cryptococcal infections in the lung and brain whereas alternatively-activated macrophages (M2) and Th2 cells do not [6; 19]. Microglia may also polarize towards 'M1' and 'M2'-like activation states, however it is not yet clear if the M1/M2 paradigm is accurately applicable to microglia [20] and if the same clear protective phenotypes are generated in the brain as observed with bone-marrow derived M1 macrophages. Likewise, our understanding of how the protective antifungal Th1 response is generated in the brain is not well understood. Microglia express MHC Class II and produce inflammatory cytokines such as IL-12 during brain inflammation [21; 22], and are therefore capable of activating $CD4^+$ T-cells and driving Th1 differentiation; this has never formally been shown for fungal-induced meningitis although it has been demonstrated for parasitic meningitis [23]. Moreover, there are other antigen-presenting cells (APCs) in the brain, such as astrocytes and recruited DCs, that may also be involved in the induction of antifungal T-cell immunity, but are as yet not explored.

Lastly, human CARD9 deficiency is a primary immunodeficiency disorder associated with the spontaneous development of fungal brain infections caused by *C. albicans* and *A. fumigatus*, as well as dermatophytes and dematiaceous yeast-like fungi [24]. CARD9 is a signaling adaptor protein expressed mainly by myeloid cells, including high expression by microglia [2], and is critical for the activation for antifungal immune responses to a variety of fungal pathogens in mice and humans [24]. We recently showed that CARD9 deficiency predisposes to fungal brain infections because of defects in neutrophil chemoattractant production by glial cells in the brain, resulting in absent recruitment of neutrophils during *C. albicans* infection and uncontrolled fungal growth (Figure 2); these mechanisms were specific to both the brain and fungal infection [2]. Whether CARD9 promotes the generation of adaptive immune responses in the brain, and to which fungal species, remains unexplored. In other organs, however, CARD9 has been indicated to play key roles in the induction of T-cell responses in a variety of settings (discussed in detail below).

The Liver

Fungal infections of the liver are usually a complication of disseminated infections, such as those caused by *Candida albicans* and *Histoplasma capsulatum* [25; 26]. The tissue-resident macrophages of the liver are called Kupffer cells, and they make up the largest population of tissue-resident macrophages in the body. Kupffer cells are found along the sinusoidal endothelium and closely interact with these cells and hepatocytes. Kupffer cells are required for hepatocyte health and liver function, as well as clearing microbial products and toxins from the blood that filter through the liver via the portal vein [27].

The role of Kupffer cells in sensing and responding to fungi is very poorly understood. Liver macrophages vastly increase in number following systemic *C. albicans* infection and the liver clears yeast cells quickly in immunocompetent mice [28], suggesting that Kupffer cells are proficient at fungal phagocytosis and killing. Indeed, early work showed that Kupffer cells were able to phagocytose *C. albicans* yeast with similar kinetics to peritoneal macrophages, although killing of phagocytosed yeasts by Kupffer cells was not as efficient [29]. Other studies have shown a dependency on integrin αxβ2 and tyrosine kinases for

antifungal defense by Kupffer cells [30; 31]. In terms of stimulating adaptive antifungal immunity, Kupffer cells are highly tolerogenic and preferentially induce regulatory T-cells (T_{reg}) rather than effector cells [3]. Instead, activation of effector T-cells falls onto the shoulders of liver-resident DCs, a highly heterogeneous population which separates into several subsets characteristic of those found in both lymphoid and non-lymphoid organs, each with distinct functions [32]. For example, human $CD141^+$ liver DCs (equivalent to $CD103^+$ DCs in the mouse) are abundant in healthy liver and preferentially expand Th1 and Th17 effector cells [33], as well as activating anti-viral $CD8^+$ T-cells [32]. Whether these functions are activated during a systemic fungal infection, and the mechanisms controlling such a response, have yet to be defined.

The Kidneys

Systemic candidiasis is associated with profound kidney invasion and renal failure in mice [28; 34]. As such, the majority of studies analyzing disseminated *C. albicans* infections in mice have focused on the kidney as the primary target organ. Multiple studies have shown a strong induction of the innate immune response in the kidney during *C. albicans* infection [35; 36], associated with a large influx of neutrophils and $Ly6C^{hi}$ monocytes [28] (Figure 3). This innate inflammatory response is required to control infection early on [37; 38], yet also drives immunopathology through the action of CCR1-expressing neutrophils late in the course of infection [39].

The kidneys have an extensive network of CX_3CR1^+ phagocytes that interact with renal endothelial cells and actively probe their environment to provide immune surveillance [40; 41]. However, determining the difference between a kidney-resident macrophage versus a kidney-resident DC has proven difficult and is a key issue in the renal immunology field [42; 43]. Kidney-resident macrophages and DCs express similar surface markers, such as CX_3CR1, CD11b and CD11c, and share developmental pathways [43; 44]. These cells also share functional qualities such as phagocytosis and antigen presentation, whereas splenic macrophages and DCs preferentially perform either phagocytosis or antigen presentation, respectively [45; 46]. As a result, many studies indicate that their results are due to the action of either kidney macrophages or DCs, when their methods do not allow for this distinction. The use of microscopy to define morphology and spatial localization, combined with surface marker expression, has proven more useful to distinguish between these renal mononuclear cell types [36; 42]. Moreover, the advent of sophisticated sequencing-based technologies has recently been used to separate complex subtypes of immune cells in non-lymphoid organs [47], and may provide further clarity on the different subpopulations of phagocytes in the kidney in the near future. Nomenclature issues aside, most studies agree that there is a large population of CX_3CR1^+ macrophages found throughout the healthy kidney cortex and medulla regions [40]. The majority of kidney-resident DCs are also CX_3CR1^+, and their function appears to be closely related to their spatial localization within the kidney [48; 49]. CX_3CR1^+ DCs in the kidney cortex, for example, are the main conductors of adaptive immunity, while DCs in the kidney medulla are more involved in the induction of innate immune responses through chemokine production [50]. Finally, there is a small population of $CD103^+CD11b^-$ DCs, no $CD103^+CD11b^+$ DCs, and small numbers of lymphocytes resident in the healthy kidney [42; 43].

The role of kidney-resident phagocytes in control of fungal infection has been explored in a small number of studies (Figure 3). Early on in a *C. albicans* infection, there are significant fluctuations in the myeloid cell pool in the kidney [51], including a large expansion of macrophages [28; 36] and accumulation of $CD103^+CD11b^-$ DCs [52]. CX_3CR1^+ macrophages are the main phagocytic cells for *C. albicans* during infection and as a result, decreased accumulation of CX_3CR1^+ macrophages *in vivo* results in significantly increased kidney fungal burdens associated with poor survival of CX_3CR1-deficient macrophages. In line with this, humans with the dysfunctional *CX3CR1-M280* allele are more likely to develop systemic candidiasis [36] and human *CX3CR1-M280* mononuclear phagocytes exhibit impaired survival [53]. Thus, kidney-resident macrophages are critical for early innate control of *C. albicans* infection.

Kidney-resident DCs are also required for control of renal fungal infections. $CD11c^+$ DCs recruit GM-CSF-producing NK cells, which enhance the antifungal activity of accumulating neutrophils in the kidney [51] (Figure 3). Similarly, IL-15-producing $Ly6C^{hi}$ monocytes in the spleen have also been shown to drive $GM\text{-}CSF^+$ NK cell activation and neutrophil function during systemic *C. albicans* infection [54]. In addition to their role in innate immunity, kidney-resident DCs are also critical for the activation of adaptive immune responses [43]. However, the induction and control of antifungal lymphocyte responses in the kidney is far less well studied. Early studies demonstrated that IL-4 was detrimental to systemic *C. albicans* control, and that $IFN\gamma^+$ Th1 cells were protective [37; 55]. $CD103^+CD11b^-$ DCs in the kidney are required for the production of the Th1-polarizing cytokine, IL-12, during *C. albicans* infection [52] and thus may be important for inducing these T-cell populations. $CD103^+$ DCs in the kidney have also been shown to mediate T_{reg} recruitment and activation of cytotoxic T-cells in models of kidney injury [56; 57], indicating that this population has diverse functions that are context-dependent. However, mice lacking T-cells do not show an increased susceptibility to systemic *C. albicans* infections [58] and thus the relevance of these DC functions in the context of a fungal infection is uncertain. Mice lacking $CD103^+$ DCs do not have increased kidney fungal burdens and exhibit normal survival rates when challenged with *C. albicans* [52], supporting the lack of a role for T-cell-activating DCs. However, while T-cells do accumulate within infected kidneys [28], these cells do not carry the appropriate fungal-specific T-cell receptors [59]. This suggests that there is a defect in the ability to recruit the relevant antigen-specific T-cell populations to the *C. albicans*-infected kidney. Indeed, restoration of this defect leads to a significant reduction in kidney fungal burdens [59], indicating that antigen-specific T-cells can play protective roles in the kidney, but their recruitment becomes disrupted during fungal infection.

The Lungs

Pulmonary fungal infections are among the most common, partly because fungal spores are ubiquitous in the environment and it is estimated that we inhale hundreds of fungal spores daily. As a result, immunosuppressed patients are highly susceptible to pulmonary infections caused by *A. fumigatus, C. neoformans, H. capsulatum, Blastomyces dermatitidis* and *Pneumocystis jirovecii*. Some of these species along with several others (for example, *Alternaria* species) have also been shown to exacerbate underlying lung diseases including

asthma and cystic fibrosis [60; 61; 62; 63]. As such, fungi cause a wide range of pulmonary disorders that are challenging to diagnose and treat.

Alveolar macrophages (AMs) are, like microglia and Kupffer cells, long-lived resident immune cells that derive from fetal precursors and self-renew [64]. AMs are found in the alveolar airspaces, and are distinct from interstitial macrophage subpopulations in the lung, which are found in the lung parenchyma. AMs have been shown to phagocytose *Pneumocystis carinii* yeasts through a GM-CSF-dependent pathway and innate recognition by the C-type lectin receptor Dectin-1, leading to fungal killing and protection [65; 66]. AMs are also adept at phagocytosis and killing of *A. fumigatus* conidia [67], which again is predominantly dependent on expression of Dectin-1 by AMs [68] (Figure 4A). In contrast, some fungi can readily survive inside AMs, using these host cells as a means of escaping immune recognition and causing latent infection (Figure 4B). For example, *B. dermatitidis*, *H. capsulatum* and *C. neoformans* have all been shown to subvert AM oxidative killing mechanisms through inhibition of iNOS [69].

How AMs affect antifungal T-cell responses is not well understood. AMs express low levels of co-stimulatory molecules and MHC Class II, and are thus considered poor conductors of adaptive immunity [64]. Like Kupffer cells in the liver, the poor ability of AMs to activate T-effector cells could be to help maintain a tolerogenic environment, especially since the lung is constantly dealing with microbial and environmental insults. Instead, antifungal T-cell responses are most likely activated by lung-resident DCs. There are at least 3 subsets of DCs resident in the lung (reviewed extensively in [70]), which have been shown to mediate distinct and overlapping functions. For example, $CD103^+$ DCs are superior at cross-presentation and activation of anti-viral $CD8^+$ T-cells, while $CD11b^+$ DCs promote Th2 and Th17 responses, depending on the initial insult [70; 71]. In the *A. fumigatus*-infected lung, $CD11b^+CD24^+$ DCs are required to drive protective Th17 responses [72], while $CD103^+$ DCs have been shown to activate Th1 responses in the *H. capsulatum*-infected lung via Type 1 IFN production and Toll-like receptor (TLR) 7 and 9 signaling [73]. $CCR2^+$ monocyte-derived DCs are also recruited to the lung upon fungal infection to provide additional protection [74] and prime $CD4^+$ T-cells [75] (Figure 4A). Their recruitment has been found to depend on the scavenger receptor MARCO during *C. neoformans* infections, since deletion of this receptor in mice leads to uncontrolled lung infection with reduced recruitment of monocyte-derived DCs [76], similar to what has been described for mycobacterial infections [77]. Recruitment of $CCR2^+$ monocytes to the lung has also been found to be targeted by some fungi to subvert and evade clearance. For example, *B. dermatitidis* produces a proteolytic enzyme, DppIVA, which cleaves monocyte-recruiting chemokines, such as CCL7, rendering them inactive leading to reduced monocyte recruitment and differentiation [78] (Figure 4B). Moreover, *B. dermatitidis* can also induce host metalloproteinase MMP-2, which additionally cleaves CCL7 and disrupts the $CCR2^+$ monocyte response and subsequent T-cell responses [79].

The molecular control of IL-17-dependent responses, which appear to be generally non-redundant for protection against pulmonary fungal infections [80; 81; 82], are only partially understood. During *A. fumigatus* infection, Dectin-1 is required for Th17 polarization (Figure 4A), since genetic deficiency of Dectin-1 or depletion of Dectin-1^+ monocyte-

derived DCs leads to enhanced Th1 polarization of *A. fumigatus*-specific T-cells due to aberrant T-bet expression [83]. On the other hand, Dectin-1 is redundant for Th17 immunity during infection with *H. capsulatum* and *B. dermatitidis,* which requires the TLRs instead [80]. Indeed, while Dectin-1 is certainly capable of driving Th17 immunity, other receptors have been shown to be superior at this function, such as the related receptor, Dectin-2 [84] and the Mannose Receptor (MR; CD206) [85]. The role of Dectin-2 and MR in pulmonary antifungal immunity has only been analyzed in a small number of studies, which have shown that Dectin-2 plays species-specific roles in antifungal defense in the lung [86], and MR signaling is required for $CD4^+$ T-cell proliferation in the *C. neoformans*-infected lung [87]. Both Dectin-1 and Dectin-2 signal using CARD9 [88], which has also been indicated to drive Th17 immunity [24]. In the lung, deletion of Card9 causes a reduction in Th17 polarization during pulmonary infection with *C. neoformans* [89], *H. capsulatum* and *B. dermatitidis* [86]. However, while the C-type lectin-CARD9 signaling axis appears to be critical for the induction of protective T-cell immunity in the murine lung, it is important to note that mutations in these molecules in humans have thus far not been found to enhance susceptibility to pulmonary fungal infections. Similarly, patients with mutations in *IL-17F, IL-17RA, IL-17RC* and *ACT1* that lack IL-17 receptor signaling have not been reported to develop pulmonary fungal disease to date [90; 91].

Lastly, lung epithelial cells can also significantly contribute to control of pulmonary infection and intimately associate with the lung-resident myeloid cells discussed above. Epithelial cells produce inflammatory cytokines and neutrophil chemoattractants using a MyD88-dependent pathway during acute *A. fumigatus* pulmonary challenge, which is critical for inducing protective neutrophil recruitment and fungal clearance [92] (Figure 4A). How epithelial cells influence antifungal T-cells in the lung remains to be determined, although their interaction with lung-resident DCs and indirect effects on T-cell polarization are well characterized in other models. For example, epithelial production of TSLP has been shown to profoundly affect DC responses, resulting in the production of Th2-polarising cytokines such as IL-5 and IL-13 through a pathway dependent on OX40L [93], which in turn drives pathogenic Th2 responses and contributes towards the severity of asthma [94].

The Skin and Subcutaneous Tissues

The human skin is readily colonized by fungi, particularly *Malassezia* species and, to a lesser degree, *Candida* species [95]. These fungi, while considered commensals, have been suggested to influence and exacerbate underlying skin disorders such as alopecia and psoriasis. Significant improvements in psoriatic symptoms have been reported in some patients treated with antifungal drugs, although the underlying reasons for this are not well understood since no clear correlations between *Malassezia* and *Candida* colonization and severity of psoriasis have been found [96]. Superficial fungal infections of the skin are relatively common and are most often caused by the dermatophytes, such as *Trichophyton*. However, some fungal species can cause extreme, sometimes deforming, chronic infections of the skin and subcutaneous tissue. These tropical diseases include chromoblastomycosis (most often caused by *Fonsecaea pedrosoi*), phaeohyphomycosis (caused by a variety of dematiaceous fungi) and eumycetoma (most often caused by *Madurella* species). In all

cases, the immune responses and resident immune cells in the skin controlling fungal growth and clearance are not well understood.

Langerhans cells (LC) are the best-defined DC population resident in the skin, found in the epidermal layer. They express large amounts of the C-type lectin Langerin, which is the major antifungal receptor in human LC by binding to both mannose and β-glucan within *Candida* and *Malassezia* cell walls [97]. In the deeper dermis layer, dermal DCs are found and can be split into several subsets based on expression of Langerin and CD103 [98]. The role of skin DC subsets in antifungal immunity has been investigated extensively by the Kaplan laboratory, in which an epicutaneous *C. albicans* infection model has been used to probe the relative contributions of different skin DC subsets to driving IL-17-mediated immune responses [99]. IL-17 is required to protect against *C. albicans* skin infections by recruiting neutrophils which phagocytose and kill the fungus [100] (Figure 5). Using this model, the authors demonstrated that LC drove Th17 differentiation through Dectin-1-mediated IL-6 production [101] (Figure 5), whereas Th1 and $CD8^+$ T-cell responses predominantly relied on $Langerin^+$ dermal DCs [99]. In addition to controlling antifungal T-cell responses, LC have also been shown to modulate the behavior of NK cells. Using an intradermal model of fungal-induced sensitization, Kaplan and colleagues showed that LC were required to dampen inappropriate inflammatory responses mediated by $CXCR6^+$ NK cells recruited from the liver [102], which have also been shown to mediate contact hypersensitivity reactions and memory-like responses to these allergic insults [103].

In addition to Th17 cells, gamma-delta T-cells and $CD8^+$ T-cells can also contribute towards protection through IL-17 production. Gamma-delta T-cells are activated by a subset of dermal DCs expressing CD301b, which produce IL-23 to activate gamma-delta T-cells in response to neuropeptides produced by nociceptive neurons in the skin [104] (Figure 5). $IL\text{-}17^+$ $CD8^+$ T-cells also protect against *C. albicans* invasion of the skin, and are activated by $CD103^+$ resident DCs which become activated by specific bacterial commensals living on the skin [105]. Thus, skin-resident DCs exquisitely tailor multiple lymphoid populations for protection against fungal skin infections. These responses can also be further fine-tuned by keratinocytes, specialized epithelial cells which make the uppermost layer of the skin. Keratinocytes are responsible for maintaining epidermal localization of LC and memory T-cells through TGFβ signaling [106] (Figure 5), and have also been shown to produce antimicrobial peptides and chemokines that affect developing immune responses in the skin [107].

The roles of CARD9 in skin immunity have been emerging in recent years; several clinical cases of human CARD9-deficiency associating with the development of rare, debilitating fungal skin diseases have now been described [24]. In particular, CARD9 deficiency predisposes to phaeohyphomycosis and deep dermatophytosis which appears to be linked to severe defects in the generation of Th17 responses, since these CARD9-deficient patients were reported to have reduced numbers of circulating Th17 cells [108; 109]. However, not all CARD9-deficient patients have decreased peripheral Th17 cells, and a direct role for IL-17 signaling in controlling these diseases has not been shown, thus the relevance of these defects in CARD9-deficient patients remains to be determined. CARD9 has also been indicated to play critical roles in sterile skin inflammation. For example, during atopic

dermatitis, CARD9-signaling in dermal DCs was shown to drive IL-1α/β production following application of the hapten TNCB, which in turn activated T-cells through the IL-1R/MyD88 pathway to make IFNγ and IL-17 [110]. Similarly, the CARD9-coupled receptor Mincle was shown to have natural ligands in the skin, which bound and activated Mincle following chemical-induced skin damage leading to activation of skin-resident myeloid cells and the subsequent production of multiple pro-inflammatory cytokines [111]. Mincle is also a key receptor for *F. pedrosoi*, the causative agent of chromoblastomycosis. Recognition of *F. pedrosoi* by Mincle and signaling through the Syk-CARD9 pathway is required for sterilizing immunity, but also depends on co-operation with the TLRs [112]. However, TLR-mediated recognition of *F. pedrosoi* by macrophages was found to be defective [112]. Application of the TLR7 agonist, Imiquimod, was shown to help control infection in both mice and humans, by restoring these recognition defects [112; 113].

The Oral Mucosa

Fungal infections of the oral mucosa are most often caused by *C. albicans*, usually occurring as a result of HIV infection [114], inborn errors in IL-17 immunity [115] and mutations in *AIRE* resulting in APECED [116]. Most of these risk factors affect T-cell responses and thus these cells are critical for antifungal immunity at this site, particularly Th17 cells [117] which are naturally abundant in the oral mucosa and develop independently of microbial signals [118]. Mice deficient in IL-17 or T-cells are highly susceptible to oropharyngeal candidiasis (OPC), whereas deficiencies in IFNγ signaling do not affect susceptibility [119]. IL-17 is predominantly produced by natural Th17 cells and gamma-delta T-cells in the oral mucosa in response to *C. albicans* [120; 121], with lesser contributions by ILC type 3 cells [122], which is required for the production of antimicrobial peptides and fungal clearance [123] (Figure 6). Activation of conventional Th17 cells after re-infection at this site depends on CARD9 signaling [124] and monocyte-derived DCs and Flt3-dependent resident DCs, which traffic fungal antigens to draining cervical lymph nodes in a CCR7-dependent manner [125], while CARD9 is dispensable for innate natural Th17 dependent immunity [124]. Another crucial factor for protection against OPC is the IL-1R. Damaged keratinocytes, caused by the action of the *C. albicans* mycotoxin Candidalysin [121; 126], release IL-1α which stimulates G-CSF production from endothelial cells, this in turn promotes neutrophil development and recruitment to the oral mucosa [127], independently of IL-17 [128] (Figure 6).

While the protective capacity of Th17, IL-17$^+$ gamma-delta T-cells and neutrophils in antifungal defense at the oral barrier is relatively well established, the functional contributions of other resident cells at this site are not well understood and are currently understudied. For example, most mucosal barriers are also heavily populated with non-conventional lymphoid cells such as ILCs and MAIT cells. ILCs are grouped by their expression of key cytokines and master transcription factors; ILC1 express T-bet and IFNγ (these include NK cells), ILC2 express GATA-3 and IL-5/13, and ILC3 express RORγt and IL-17/IL-22 [129]. The role for ILCs at the oral mucosa in antifungal immunity is somewhat controversial, with some studies demonstrating a role for ILC3 [122] and others showing no role for ILCs [120]. This is likely in part due to the experimental intractability of studying ILCs, which has since massively evolved and led to multiple key developments in our

understanding of the behavior and function of these cells in the GI tract (see below). Like ILCs, MAIT cells are also innate-like lymphocytes whose function is not well understood in the context of fungal infections. MAIT cells express an invariant T-cell receptor that recognizes microbial vitamin B2 metabolites in the context of MHC-related molecule, MR1. MAIT cells are particularly enriched in mucosal barriers and have been shown to strongly respond to bacteria and fungi, including *C. albicans* [130]. Whether MAIT cells protect against *C. albicans* infections *in vivo* is not known, although they have been shown to be critically involved in protection against disseminated bacterial infections [130]. Interestingly, human mutations in *STAT3*, which predispose to oral *C. albicans* infections, have recently been shown to cause MAIT cell dysfunction and reduced circulating numbers [131; 132]. Thus, it will be important to determine whether these MAIT cell disturbances have any functional relevance for the development of *C. albicans* infections in these patients.

The Gastrointestinal (GI) Tract

Commensal fungi in the GI tract are very poorly understood, in part because they have not received the same degree of attention as bacterial commensals and also because sequencing databases and methodologies for studying the ‘mycobiome’ are in their infancy relative to sequencing bacteria [133]. Yeast belonging to the *Saccharomyces* and *Candida* genera appear to be the dominant species found in the human GI tract [134], however other studies have suggested that *Candida* colonization of the human gut may be related to Western diets and antibiotic usage, since *Candida* colonization is less common in non-Western communities [135]. In germ-free mice, *C. albicans* is able to colonize the entire length of the GI tract equally well [136], where it exists in a specialized cell-type called the ‘GUT’ cell, characterized by enhanced expression of *WOR1* transcription factor and cell wall changes [137]. Mice are useful animal models to study *C. albicans* colonization of the mammalian GI tract, since they are naturally resistant to colonization with this fungus and can be rendered susceptible with short-courses of antibiotics. These models have allowed for the identification of key host signaling pathways and bacterial commensals which mediate *C. albicans* colonization resistance [138; 139]. Understanding the interaction between commensal fungi and the GI mucosal immune system is important, since it is often thought that these commensal populations act as reservoirs for life-threatening disseminated infections [140; 141], and dysbiosis of the mycobiome has been repeatedly linked with inflammatory bowel diseases (IBD) [142; 143]. Yet, we understand very little about how intestinal fungi are recognized and how their potential invasion of gut tissues is handled by the immune system.

Identification and characterization of intestinal myeloid cells is an intense area of investigation and there are many excellent reviews on the subject [144; 145]. In brief, mononuclear phagocytes in the gut can be broadly divided by CD103 expression. $CD103^+$ cells are generally accepted as migratory DCs, and can be further divided based on CD11b expression. $CD103^+CD11b^+$ DCs depend on IRF4 for their development and are essential for the induction of Th17 immunity in the GI tract [146], but not Th1, T_{reg} or the stability of bacterial commensal communities [147]. $CD103^-$ cells contain both macrophages and DCs; a subset of these cells are $CD103^-$ DCs that migrate in the lymphatics to the mesenteric lymph nodes [148], and there is also a rare population of $CCR2^+$ monocyte-derived DCs that

selectively induce Th17 cells [149]. The antifungal activities of intestinal DCs and macrophages is not well understood. Thus far, Dectin-1 is the only antifungal receptor to be studied in detail in this tissue. All populations of DCs in the GI tract express Dectin-1, with the highest expression on $CD103^+$ populations [150]. Dectin-1 is not required to control colonization of the GI tract by *C. albicans* [151], but is required to prevent invasion of intestinal tissues in mice on a variety of genetic backgrounds [151; 152]. During intestinal infection with *C. albicans*, Dectin-1 promotes $CD4^+$ T-cell survival specifically in the mesenteric lymph nodes and lamina propia, since genetic deletion of Dectin-1 results in mass $CD4^+$ T-cell apoptosis and disruption of fungal-specific $CD4^+$ T-cell proliferation and activation within these tissues [150]. In line with a critical role for Dectin-1 in controlling fungal-induced inflammation of the intestine, human polymorphisms in *CLEC7A* (encoding Dectin-1) have been shown to associate with ulcerative colitis [153]. In animal models, mice deficient in either Dectin-1 or Dectin-3 develop worse DSS-induced colitis when first colonized with *Candida tropicalis* [150; 153; 154] indicating that fungi in the gut can have a profound influence over IBD, especially when combined with dysregulation of host immunity. Indeed, other work has shown that antifungal treatment in mice enhances their susceptibility to colitis by causing an expansion of antifungal-resistant fungi [155]. Moreover, human polymorphisms in *CARD9* have also been repeatedly linked to IBD [156; 157]. Using $Card9^{-/-}$ mice and models of DSS-induced colitis, Card9 has been shown to be critical for the recovery phase of colitis by promoting IL-22 production and epithelial cell health [158]. However, the role of fungi in CARD9-dependent control of colitis appears marginal. Although $Card9^{-/-}$ animals have increased levels of commensal fungi [158], the relative proportions of different fungal genera are not significantly different compared to $Card9^{+/+}$ mice and antifungal treatment does not alleviate colitis symptoms in $Card9^{-/-}$ animals [159]. In humans, however, CARD9-deficiency has been linked to the development of fungal colitis associated with enhanced *Candida* colonization of the gut [160]. Thus, while it is clear that Dectin-1/CARD9 signaling has a major influence in mucosal immunity of the GI tract, many questions remain as to their molecular control and how fungal commensals feature into these roles.

Finally, ILCs form a large, highly heterogeneous resident population in the GI tract [47] and have been shown to provide homeostatic control of the GI immune system. For example, ILC3 are critical for preventing dissemination of commensal bacteria through a pathway dependent on IL-22 [161], control intestinal T_{reg} numbers through GM-CSF production [162], and have also been shown to mediate deletion of bacteria-specific $CD4^+$ T-cells in the lamina propia through MHC Class II-TCR interactions, thus preventing unwarranted inflammation in response to commensals [163]. How ILC3 recognize and uptake bacterial antigens is unclear, although some work has shown a synergistic response of a specific subset of human ILC3 to TLR2 ligands and IL-2 [164], suggesting that these cells could sense bacteria and fungi via TLR2. Whether ILC3 in the gut respond to commensal fungi is unknown. ILC3 produce IL-22 and IL-17, cytokines that are thought to promote antifungal resistance at mucosal barriers. Thus, these cells could potentially be required to control fungal overgrowth in the GI tract and be important for controlling infection in this tissue as they are for the oral mucosa [122]. However, the function of ILCs in the context of fungal colonization and infection of the GI tract remains to be fully explored.

The Ocular Mucosa

Fungal keratitis is a leading cause of vision loss, and is predominantly caused by *Aspergillus* and *Fusarium* species. These infections typically occur following traumatic inoculation, have also been associated with the use of contaminated contact lenses, and can also occur in the setting of disseminated infections in profoundly immunosuppressed individuals [165]. The ocular mucosa includes the tear ducts and conjunctiva, which are associated lymphoid tissues that harbor lymphocytes and macrophages [166]. We recently showed that γδ T-cells in the conjunctiva are important sources of IL-17, which is made in response to commensal bacteria living on the eye surface [166]. As in the oral mucosa, IL-17 is an important component of antifungal defense by driving production of antimicrobial peptides, which are shed in the tears and promote protection against invasive *C. albicans* infection of the cornea [166].

Future Perspectives

The majority of studies analyzing antifungal immunity have utilized generic macrophage and DC populations to better understand mechanisms of myeloid cell control of fungal growth. These studies have provided seminal insights into the critical receptors and molecules needed to prevent fungal overgrowth and activate the appropriate T-cell responses. However, it is clear that our immune system exhibits organ-specific restrictions. For example, mutations in key antifungal molecules like *CLEC7A* and *CARD9* do not affect susceptibility to all fungal diseases equally, indicating that there are species- and organ-specific roles for these molecules. Many recent studies have demonstrated the sheer complexity of tissue-resident cells, with their diverse functions and phenotypes, and have indicated that rare subpopulations can have profound effects in health and disease. The powerful new technologies used to make these advances have not yet been strongly utilized in the context of fungal disease, yet there is great opportunity to better understand organ-specific antifungal immune responses. Improving our knowledge of antifungal immunity and the cells required to implement protection is critical for the development of sorely-needed adjunctive immune-based therapies, to help tackle the global burden of human fungal disease.

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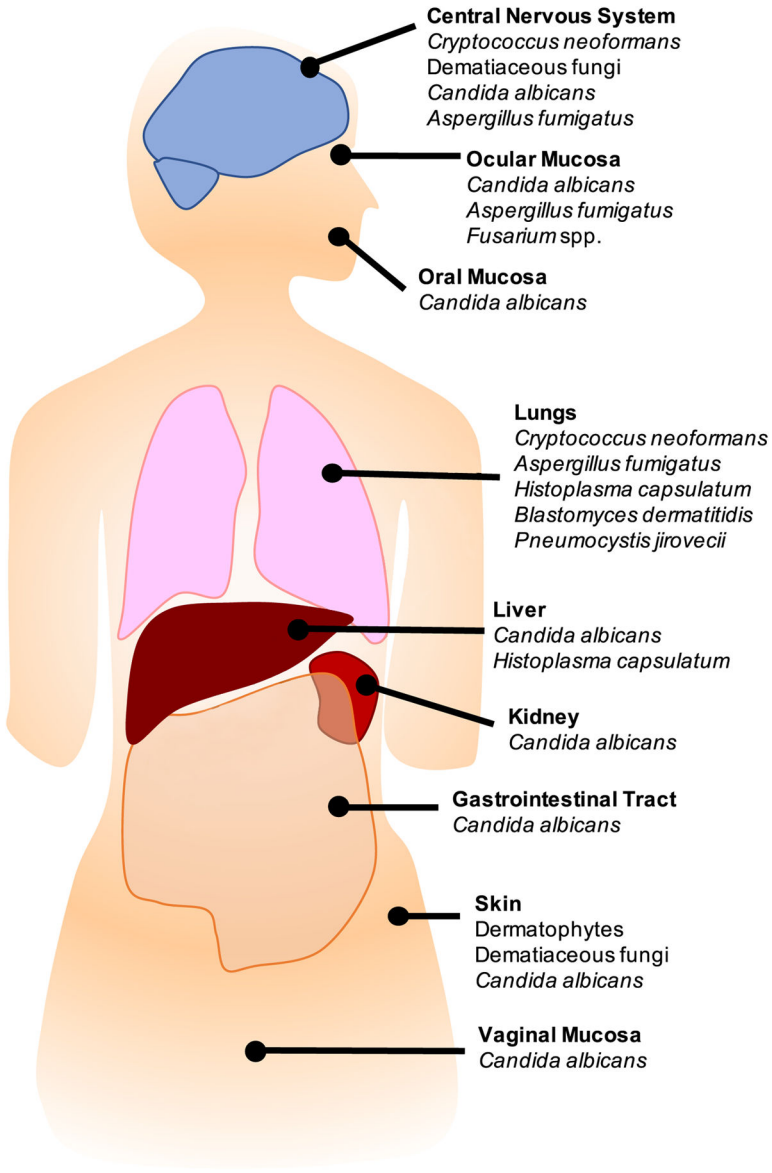

Figure 1.

Overview of the predominant fungal species causing clinical infections of the labelled organs in humans.

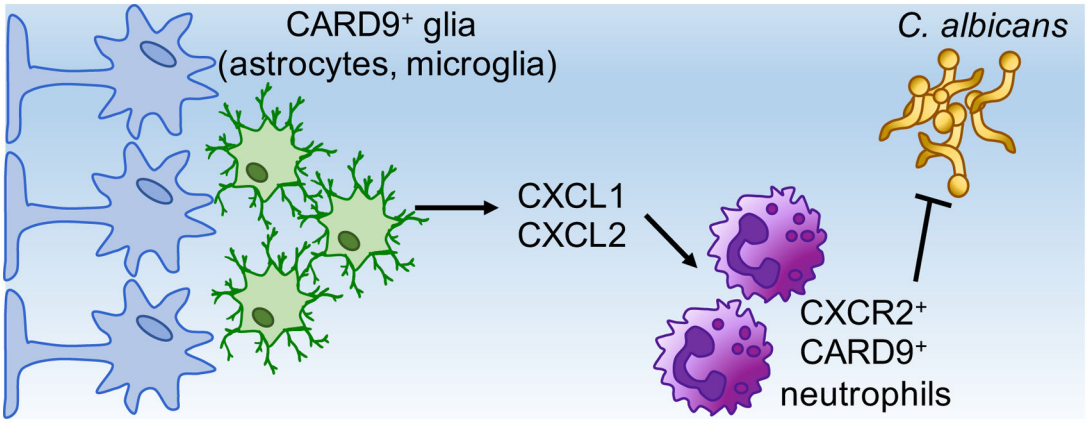

Figure 2. CARD9-Dependent Control of *C. albicans* Infection of the Brain

Glial cells in the brain, including astrocytes (shown in blue) and microglia (shown in green), produce CXCL1 and CXCL2 upon *C. albicans* infection in a CARD9-dependent manner. This in turn recruits $CXCR2^+$ neutrophils, which are required to control *C. albicans* infection in this tissue.

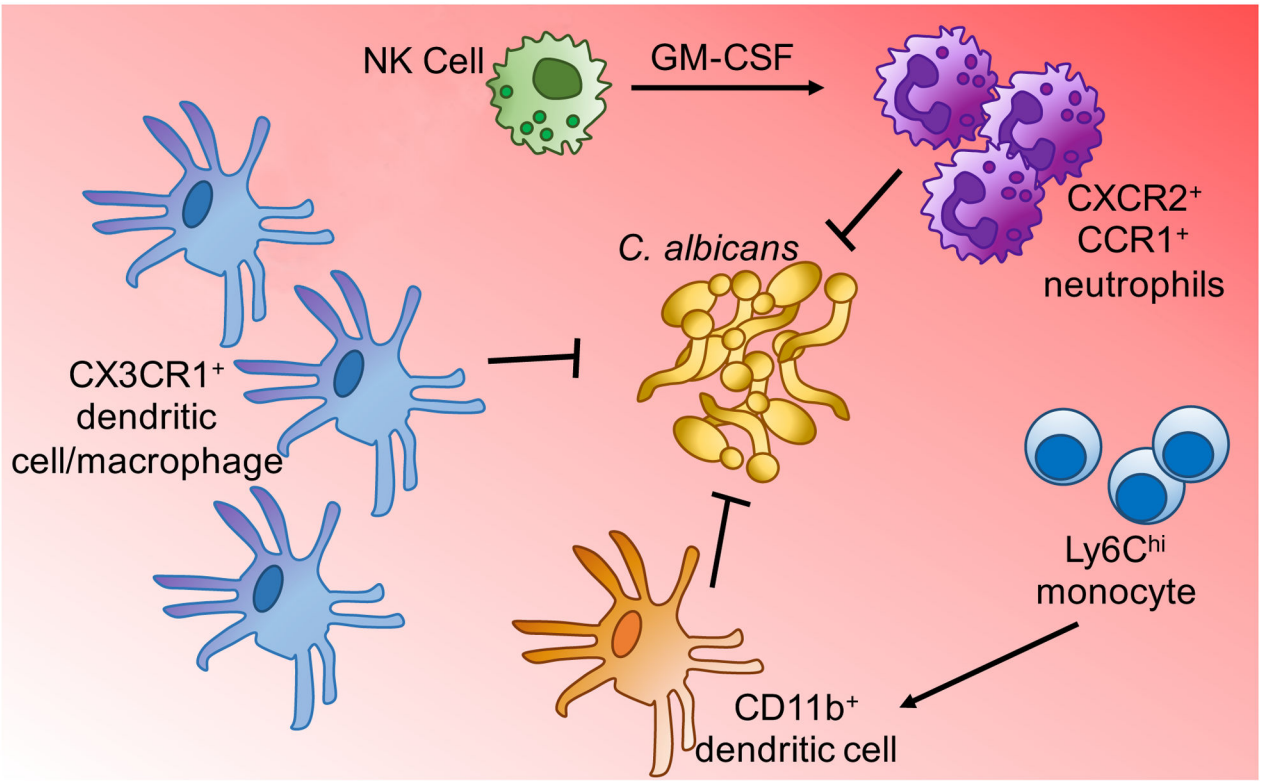

Figure 3. Myeloid Cell Mediated Protection Against Renal *C. albicans* Infections

Control of *C. albicans* growth in the kidney requires multiple populations of myeloid cells, including resident CX3CR1-expressing macrophages and dendritic cells, and recruitment of inflammatory monocytes and neutrophils. The antifungal functions of neutrophils are further enhanced by GM-CSF, produced by recruited NK cells.

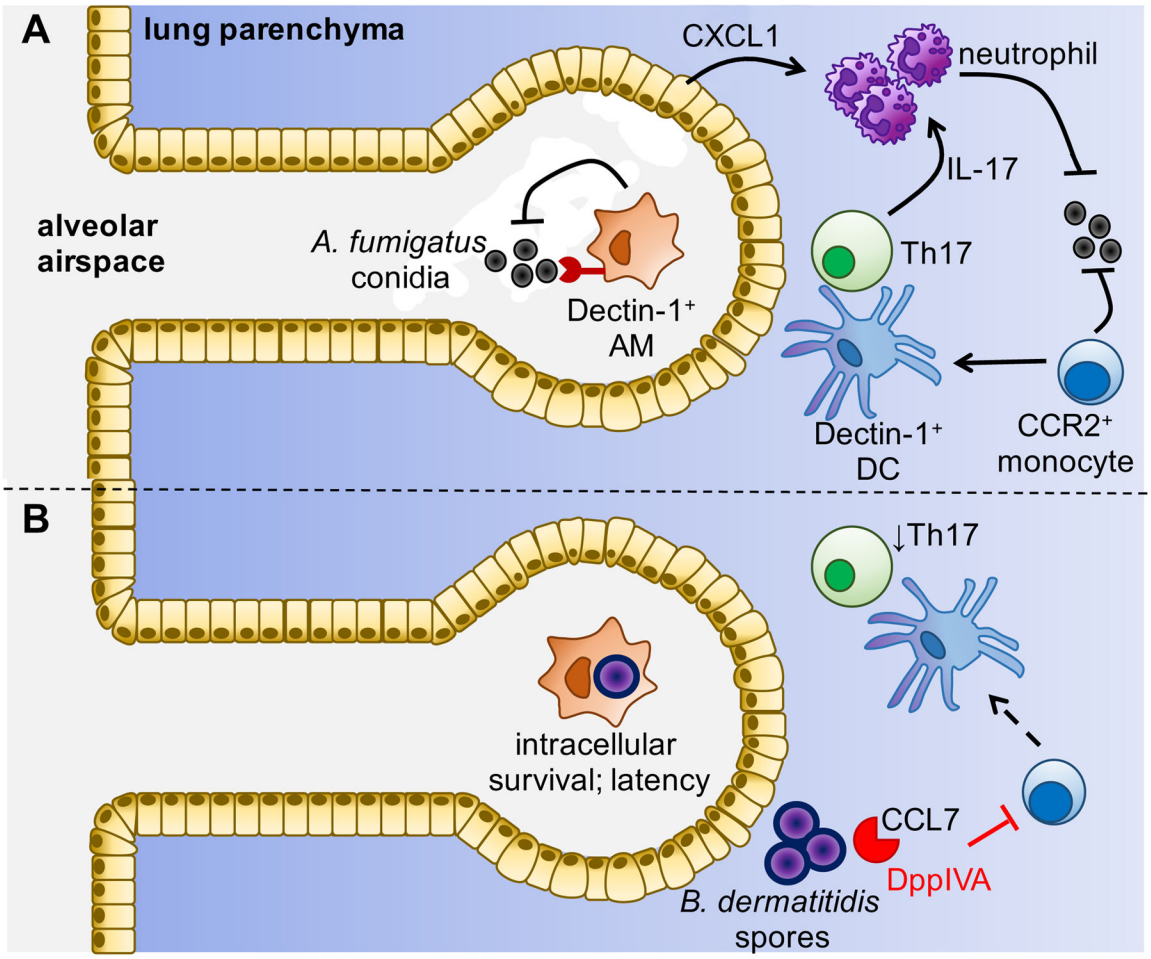

Figure 4. Mechanisms Controlling Immunity to Pulmonary Fungal Pathogens

(**A**) *A. fumigatus* conidia are inhaled and phagocytosed by resident alveolar macrophages (AMs) via Dectin-1. Escape into the lung parenchyma activates epithelial cells to produce CXCL1, which recruits neutrophils that help fight infection. *A. fumigatus* infection also stimulates the recruitment of $CCR2^+$ monocytes, which differentiate into Dectin-1-expressing DCs that elicit protective Th17 cells. (**B**) In contrast, other fungi such as *B. dermatitidis* are able to survive intracellularly within AMs, and can further subvert immunity via the production of proteases (e.g. dipeptidylpeptidase IVA; DppIVA) that cleave chemokines to prevent monocyte/DC recruitment and function.

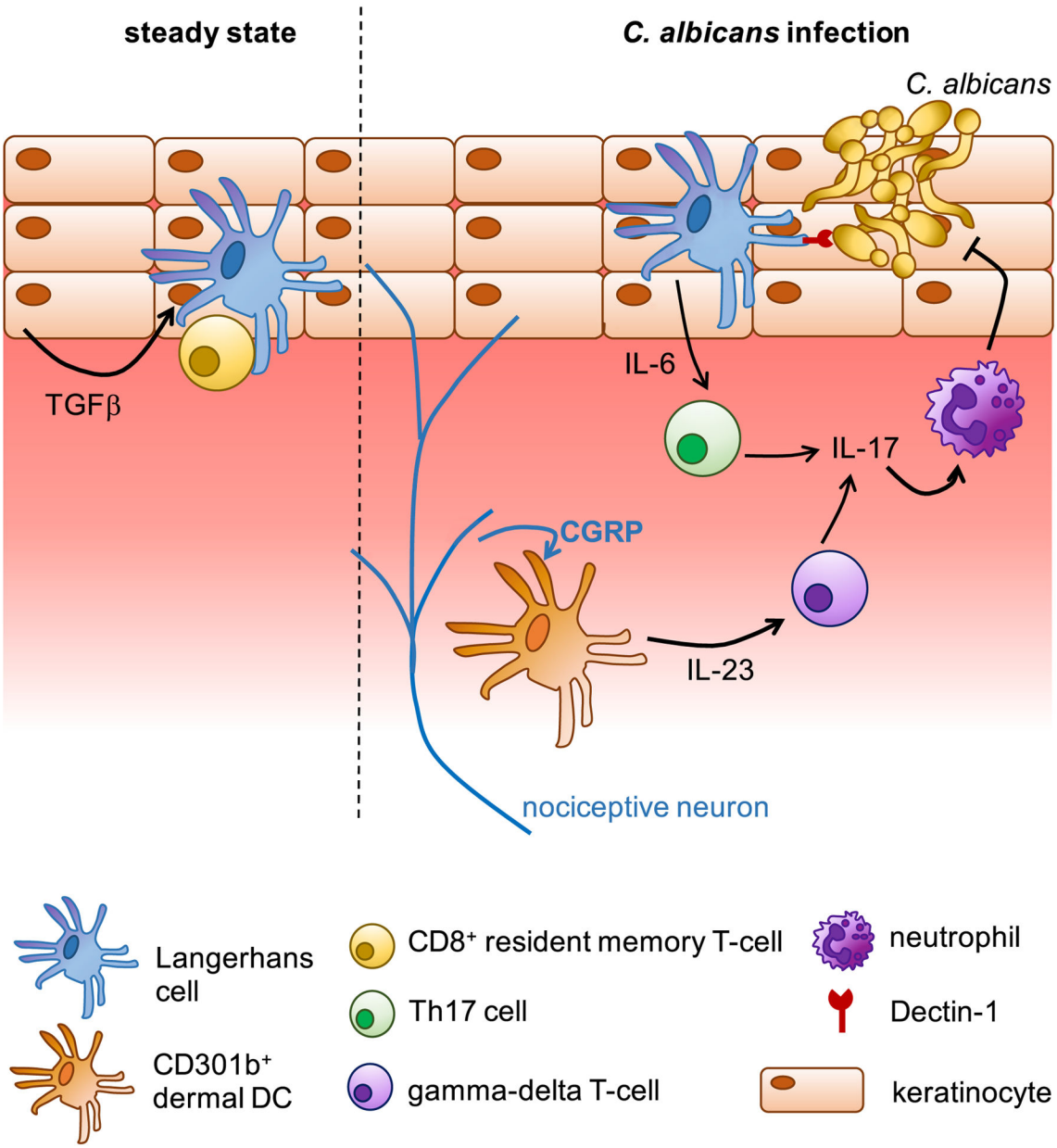

Figure 5. Protection Against *Candida albicans* Infection of the Skin

In the steady-state, TGFβ production by keratinocytes promotes localization of resident DC and T-cell populations to the epidermal layer. Upon infection, neurons in the skin release neuropeptides such as calcitonin gene-related peptide (CGRP) which activates Langerhans cells and dermal DCs to secrete cytokines that activate IL-17-producing lymphoid cells, which in turn recruits and promotes neutrophil effector function.

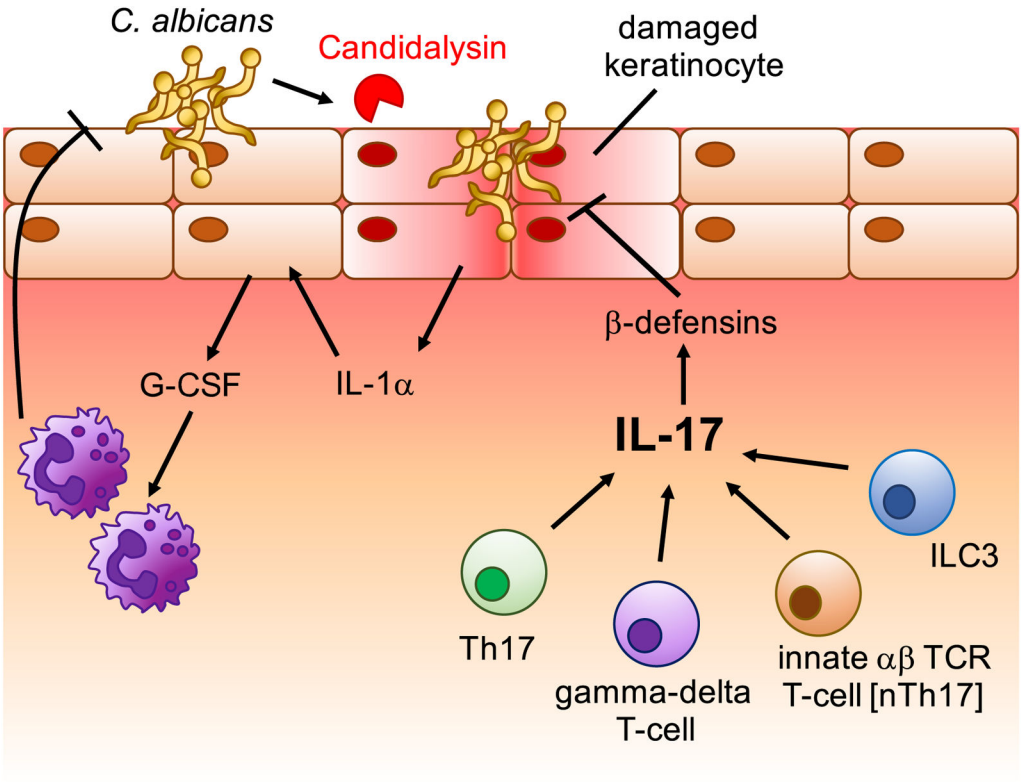

Figure 6. IL-17-Dependent and Independent Mechanisms Controlling Immunity to *C. albicans* at the Oral Mucosa

C. albicans hyphae produce the mycotoxin Candidalysin, which causes damage to keratinocytes and allows invasion of the oral mucosa. Damaged keratinocytes release IL-1α, which in turn stimulates G-CSF from neighboring cells to recruit neutrophils that act to control *C. albicans* infection. IL-17 is the predominant protective cytokine at the oral mucosa and has multiple cellular sources, including Th17 cells and a variety of innate-like lymphocytes (gamma-delta, innate αβ T-cells [nTh17], ILC3). IL-17 production stimulates the production of antimicrobial peptides, such as b-defensins, which protects against *C. albicans* growth and invasion of oral epithelium.