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IL-17-mediated immunity to the opportunistic fungal pathogen *Candida albicans*

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Abstract

IL-17 (IL-17A) has emerged as a key mediator of protection against extracellular microbes, but this cytokine also drives pathology in various autoimmune diseases. Overwhelming data in both humans and mice reveal a clear and surprisingly specific role for IL-17 in protection against the fungus *Candida albicans*, a commensal of the human oral cavity, gastrointestinal tract and reproductive mucosa. The IL-17 pathway regulates antifungal immunity through upregulation of pro-inflammatory cytokines including IL-6, neutrophil-recruiting chemokines such as CXCL1 and CXCL5 and antimicrobial peptides such as the defensins, which act in concert to limit fungal overgrowth. This review will focus on diseases caused by *C. albicans*, the role of IL-17-mediated immunity in candidiasis, and the implications for clinical therapies for both autoimmune conditions and fungal infections.

Introduction

Extensive research effort has centered on the role of the bacterial flora in human health and disease. Less well understood is the pathogenesis of the fungal species that inhabit our bodies. Fungi of the species *Candida*, dominantly *C. albicans*, are commensal microbes of the mouth, gastrointestinal tract, skin and vagina of healthy individuals (1). When host immunity is compromised, either through antibiotic use, barrier breach or immunodeficiency, pathogenic infection by *C. albicans* is a frequent consequence (2). There are no effective vaccines for *C. albicans*, or indeed for any fungi, and the development of *Candida* strains resistant to antifungal therapy is an increasing problem (3). In recent years the identification of genetic defects in mice and humans that impact the Th17/IL-17 axis has revealed the central importance of this pathway in controlling *C. albicans* infections, which is the subject of this review.

1. Infections caused by C. albicans

Several species of *Candida* cause candidiasis, though *C. albicans* is the most frequently isolated and is by far the best characterized. The other major disease-causing non-*albicans* species include *C. glabrata, C. tropicalis, C. krusei, C. dubliniensis* and *C. parapsilosis* (4). Most pathogenic *Candida* species are dimorphic, existing as yeast or pseudohyphal and

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hyphal forms. For these species, dimorphism is a key feature of virulence, and the tissue-invasive hyphal form is generally the most pathogenic (5). The recognition of different morphotypes by the host permits discrimination between commensal and pathogenic disease-causing forms of *C. albicans* (6–9) (see section 2 below).

1A. Mucocutaneous Candidiasis—There are multiple manifestations of candidiasis, differing in the immune response invoked. Mucocutaneous candidiasis broadly encompasses infections of the mucosae, nail and skin surfaces. *C. albicans* infection in the oral cavity is termed oropharyngeal candidiasis (OPC) or thrush, and is often mild and self-limiting. OPC is one of the first clinical signs of HIV, and OPC is common in neonates, the elderly, patients with xerostomia (dry-mouth) and individuals undergoing chemotherapy and radiotherapy for head-neck cancers. Severe cases in infants can lead to malnutrition and a failure to thrive. OPC is also a risk factor for esophageal cancer (10).

Chronic mucocutaneous candidiasis (CMC) presents as OPC and superficial lesions on the mucosa or thickened skin and nails, and is typically refractory to treatment. CMC occurs in patients with underlying genetic defects in IL-17-related immunity (10, 11). Although not life threatening, significant morbidity is associated with OPC and CMC due to pain, weight loss and decreased nutritional intake.

1B. Vaginal Candidiasis—*C. albicans* colonizes the reproductive tract in most women without pathological consequence, but at least one episode of vulvovaginal candidiasis (VVC) is diagnosed in 75% of women of reproductive age (12). Recurrent VVC, though infrequent, is associated with significant treatment costs and decreased quality of life. Consequently, experimental vaccines against *Candida* are being evaluated in the context of chronic VVC (13, 14).

1C. Disseminated Candidiasis—Systemic candidiasis is the most severe form of *Candida* infection. *Candida* species represent the fourth most common cause of bloodstream infections in U.S. hospitals, with a mortality rate of 40–60% (10). Systemic candidiasis is typically caused by medical intervention, including indwelling catheters, antibiotics or abdominal surgery. Notably, mucocutaneous overgrowth of *C. albicans* is not usually associated with invasive disease, indicating tissue-specific compartmentalization of responses to *Candida* (15, 16).

1D. Candida in the intestinal tract—Although *C. albicans* does not usually invade intestinal tissue to cause disease, *Candida* species colonize the GI tract and can translocate to the bloodstream during intestinal barrier breaches (10, 17). While GI translocation of *C. albicans* into circulation is not common, systemic invasion resulting from damage to the GI tract, as during abdominal surgery, is a significant problem (18).

As will be described throughout this review, there are numerous immune mechanisms that participate in anti-*Candida* immunity, the dominance of which varies among tissues. Oral and dermal candidiasis are strongly IL-17-dependent, whereas immunity to vaginal candidiasis relies more on extrinsic factors such as microbial flora and changes in pH (14, 19). Although systemic candidiasis has an IL-17 component, IFNγ from Th1 and NK cells

seems to play a relatively more important role (1, 20). Studies using an intragastric colonization model indicated that Th1 cells and IL-22 were the dominant protective factors, whereas Th17 cells and IL-17 promote tissue destruction in this setting (21, 22). Murine models of disseminated, OPC, vaginal and cutaneous candidiasis are established that recapitulate human candidiasis with reasonable fidelity (23–26), and thus offer a cost-effective platform to study the immune response to *Candida* and to facilitate development of new therapeutics.

2. Pattern Recognition of Candida albicans

Although excellent reviews of the pattern recognition receptors (PRRs) involved in recognition of *C. albicans* are available (27–29), a brief discussion of this topic is in order. C-type lectin receptors (CLRs), particularly Dectin-1, are the main sensors of *Candida* species, although there are also significant contributions from TLRs and Nod-like receptors. The *Candida* cell wall consists of an outer mannoprotein layer that conceals an inner layer composed of β-glucan derivatives and chitin. CLRs recognize carbohydrate moieties found in the fungal cell wall, including mannans (Dectin-2, −3, Mincle, the mannose receptor, among others), chitin (receptor unknown), and β-glucan (Dectin-1). Activation of these PRRs triggers NF-κB and other downstream signals, triggering an inflammatory response. The dimorphic nature of *C. albicans* is part of its immune evasion strategy, as mannans in the external cell wall largely shield the β-glucans from exposure and thereby limit Dectin-1 signaling (30). The host response is activated during budding or transition to hyphae, when mannan reconfiguration exposes the glucan layer. Interestingly, anti-fungal drugs such as caspofungin may act by unmasking β-glucans and activating the immune system (31). Activation of certain TLRs is also anti-inflammatory, which helps to maintain homeostasis in the face of commensalism (30).

3. IL-17 in candidiasis

In 2005, the discovery of the “Th17” cell population fundamentally altered how CD4-dependent immunity was understood (32). Th17 cells arise from naïve precursors through signals from IL-1β, IL-6, TGFβ and IL-23. These cells express IL-17 (IL-17A) as well as IL-17F, IL-21 IL-22 and GM-CSF, and express characteristic factors including CCR6 and RORγt. Historically, one of the first indications that CD4+ T cells were vital in protection against *C. albicans* infection came from HIV/AIDS patients, nearly all of whom exhibited OPC (33, 34). Subsequently, human T cells with reactivity to *C. albicans* were found to be predominantly of the Th17 subset (35). In this regard, studies of human T cells ex vivo showed that *C. albicans* primes Th17 cells that produce IL-17 and IFN-γ, but not IL-10. Interestingly, this property was not generalizable, as *Staphylococcus aureus*-primed Th17 cells produce IL-10, which may constrain immune pathology. The differences in the response induced by distinct pathogens at the priming and effector stage is due to the different cytokine environments induced by each microbe, with IL-1β and IL-2 being important for the pro- and anti-inflammatory effects of *C. albicans*-specific Th17 cells respectively (36).

Studies conducted prior to the recognition of Th17 cells reported that IL-12 and Th1 cells were protective in mucosal candidiasis. This conclusion was based partly on the

susceptibility of IL-12p40−/− mice to OPC (2, 37) and was reasonable given the Th1-Th2 paradigm that prevailed at the time (38). Studies in a GI candidiasis model also indicated that Th1 cells were protective, whereas IL-17 activity was detrimental (22). However, mice lacking IFN-γ were resistant to OPC (39) and IL-17RA-deficient mice were susceptible to systemic candidiasis (20). Moreover, mice deficient in IL-17RA or IL-23p19, but not IL-12p35, are susceptible to oral infection (40). Consistently, defects anywhere along the IL-17 signaling pathway predispose to oral candidiasis, including IL-17RA, IL-17RC and Act1 (40–42). Strikingly, parallel defects are also seen in humans (see section 6) (43). Correlating with susceptibility in these settings is defective neutrophil recruitment and impaired antimicrobial peptide (AMP) production (40–42).

In VVC the role of IL-17-mediated immune responses is especially controversial. In this setting, neutrophils are more damaging than host-protective. Rather, resistance to VVC centers on maintenance of the epithelial layer and a balanced vaginal microbial flora (44). Whereas one report demonstrated a protective role for IL-17 cells in an estrogen-induced model of VVC, another concluded that the neutrophil response was not linked to Th17 cells (14, 45). Notably, humans with mutations in the IL-17 axis are not particularly susceptible to VVC (46). Thus, additional studies to elucidate the role of IL-17 in VVC are needed.

In systemic candidiasis, IL-17 is also important, as IL-17A$^{-/-}$ and IL-17RA$^{-/-}$ mice are more susceptible to infection than WT mice (20, 47, 48). In addition, there are key roles for IFNγ and TNFα in driving neutrophil recruitment to affected organs as well as enhancing the fungicidal activity of phagocytes (49–54). Experimental vaccines targeting *C. albicans* that are protective in systemic candidiasis, and notably generate both Th1 and Th17 responses; probably probably both cell subsets are needed for effective immunity (55). A recent report suggests that IL-17-dependent signaling in candidiasis does not occur locally, but instead targets bone marrow to stimulate NK cell production of GM-CSF; this cytokine in turn induces the candidacidal activity of neutrophils in the kidney (56).

Surprisingly little is known about IL-17-dependent immunity to non-albicans *Candida* species. Bar *et al*. identified an epitope from the *C. albicans* ALS1/3 adhesin molecule that is recognized by Th17 cells. This epitope is conserved among *Candida* species, including *C. dubliniensis, C. tropicalis, C. krusei* and *C. glabrata* (57). In addition, a patient with *C. dubliniensis* meningitis as a result of CARD9 deficiency exhibited a reduced Th17 cell frequency (58). *C. tropicalis* is part of the commensal mycobiome in the mouse intestine, and its proportion increases in colitis-prone Dectin-1−/− mice, correlating with increased levels of IL-17 as well as IFNγ and TNFα (59). Our recent analysis of *C. tropicalis* systemic infection in mice revealed, unexpectedly, that IL-17R/Act1 signaling does not contribute to immunity, whereas CARD9 and TNFα in neutrophils are essential (60). Clearly more analysis will be essential to understand immune responses to other fungi.

4. Sources of IL-17 in Candidiasis

Conventional CD4+ Th17 cells differentiate upon exposure to IL-6, TGF-β and IL-1β and the transcription factors (TFs) RORγt and STAT3 (Figure 1). IL-23, though not required for Th17 development, promotes the maintenance and function of Th17 cells in a STAT3-dependent manner. In addition, various innate cell types express IL-17 in an IL-23- and

RORγt-dependent manner, referred to broadly as 'Type 17' cells (61). Type 17 lymphoid subsets include iNKT, LTi γδ-T and natural Th17 (nTh17) cells. IL-17-expressing cells lacking an antigen receptor are classified as Group 3 innate lymphoid cells (ILC3s) (62). In some settings, neutrophils have been reported to express IL-17, though so far this does not seem to be the case in candidiasis (63–65). Innate Type 17 cells tend to reside in non-lymphoid tissues, where they are poised to be activated rapidly in an antigen-independent manner (61).

The awareness that IL-17 is produced by innate cell types as well as conventional Th17 cells stimulated studies to define the cellular sources of IL-17 during *Candida* infections (61). Newborns are highly prone to thrush, yet the disease is generally self-limiting, indicating that innate mechanisms effectively control oral *C. albicans* (2). Unlike humans, mice do not harbor *C. albicans* as a commensal microbe, and studies in a re-challenge model of OPC demonstrated that there is no pre-existing cross-reactive immunity to components in commensal microbiota or food (57, 66). Consistently, CD4-deficient mice are resistant to acute OPC (66), and the standard model of OPC used in the field (where clearance occurs 5 days) (23) reflects the innate response (59, 67) (Figure 1). Consistently, IL-17 mRNA is detected within 24 hours of infection (40, 66), pointing to an innate rather than adaptive origin of IL-17. Using a fate tracking reporter mouse system (68), we identified oral-resident IL-17^{+} γδ-T cells and nTh17 cells following encounter with *C. lbicans* (65). Work by Gladiator *et al*. alternatively suggested a role for ILC3s in OPC (69), though the concept is inconsistent with the high susceptibility of Rag1−/− mice (which have ILCs) to OPC (66, 70). An innate source of IL-17 in OPC agrees with data in dermal candidiasis demonstrating IL-17 production by γδ-T cells (68, 71, 72).

In adults, defects in conventional Th17 cells are consistently associated with CMC (73, 74), indicating that the adaptive response is dominant in anti-*Candida* immunity in humans. While innate responses to mucosal candidiasis apparently predominate in infants and naïve mice (Figure 1), generation of adaptive Th17 cells in murine OPC does confer additional protection (66, 75). The relative importance of the innate response in mice compared to humans may reflect important species differences. It is plausible, for example, that mice may require more robust oral innate immunity, since they are coprophagic.

Specific morphologies of *C. albicans* direct Th17 differentiation. The Kaplan group recently reported that the yeast form of *C. albicans* promotes development of a protective Th17 response through Dectin-1. Filamentous hyphae, independently of dectin-1, induce a Th1 response that is protective in a subsequent systemic challenge (6). Mucosal surfaces provide the interface where the transition from health to pathogenic state occurs, so understanding what provokes immune defenses at this intersection is essential. The switch between commensal and pathogenic *C. albicans* has been attributed to signaling differences between yeast and hyphae in oral epithelial cells, with distinct differences in downstream MAPK signaling seen between morphotypes (76).

5. IL-17-mediated Mechanisms of fungal immunity

How does IL-17 mediate antifungal immunity? The IL-17 family consists of 6 cytokines (IL-17A–IL-17F) and 5 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 (77–79). Upon engagement of ligand, IL-17RA/RC recruits Act1 and TRAF6, E3 ubiquitin ligases that trigger activation of downstream NF-κB, C/EBP and MAPK pathways (43). IL-17 signaling occurs primarily in nonhematopoietic cells, due to restricted expression of the IL-17RC subunit (80). However, exceptions to this paradigm have been observed in studies of fungal infection. Specifically, IL-17RC is reported to be expressed in human neutrophils during *Aspergillus fumigatus* infections, and PMNs were reported to both produce and respond to IL-17 (81). Additionally, IL-17 was shown to act on bone marrow to drive NK-dependent functions such as GM-CSF production during systemic candidiasis (56).

Because most nonhematopoietic cells respond to IL-17, the majority of characteristic IL-17 signature genes are upregulated in cells of mesenchymal, epithelial and endothelial origin. The profile of IL-17 target genes is illuminating regarding its function. Genes regulated by IL-17 encode proinflammatory cytokines such as IL-6 and factors important for neutrophil function and trafficking, such as G-CSF, CXC chemokines (CXCL1, CXCL2, CXCL5) and calprotectin (S100A8/9) (82). IL-17 also induces CCL20, the ligand for CCR6, a chemokine receptor characteristic of Type 17 cells. Upregulation of CCL20 may function to recruit more IL-17 producing immune cells to the infected tissue during ongoing fungal overgrowth (Figure 1). Some target genes, however, have a more restricted expression pattern. Of particular relevance to fungal immunity, IL-17 stimulation of epithelial cells or keratinocytes induces β-defensins (BDs), AMPs with potent candidacidal activity. In mice, BD3 is a dominant IL-17-dependent gene induced during acute OPC (40). Intriguingly, BD3 and its human orthologue, BD2 are ligands for CCR6, though it is not clear whether BD2 and BD3 actually function as chemoattractants for CCR6+ cells in situ (83). BD1 also plays an important protective role in murine OPC (84). Another class of AMPs with candidacidal activity are histatins, which are highly expressed in human salivary gland (85). Patients with Hyper-IgE/Job's syndrome exhibit reduced Th17 frequencies due to mutations in STAT3 (section 6), and exhibit reduced levels of salivary β-defensins and histatins. Moreover, IL-17 can directly induce histatin expression in human salivary gland cells in vitro (86). Thus, immunity to OPC is a function of cumulative IL-17-dependent gene regulation.

IL-17 is part of a family of related cytokines with overlapping activities (87). IL-17F is the most conserved, but does not appear to participate in anti-*Candida* immunity based on knockout mouse or antibody blocking studies (47, 88). IL-17C signals through a receptor consisting of IL-17RA paired with IL-17RE, and has considerable functional overlap with IL-17A (89). Epithelial cells, not hematopoietic cells, produce IL-17C, inducing a gene profile strikingly similar to IL-17A (89–93). Unlike IL-17A, however, IL-17C plays no detectable role in protection to oral, dermal or disseminated candidiasis in mouse models (94). Since IL-17C is pathogenic in psoriasis, this cytokine may prove to be another effective therapeutic target that could avoid potentially adverse side effects in fungal susceptibility.

Th17 cells produce IL-22 as another key signature cytokine. Although not part of the IL-17 family based on sequence homology, IL-22 promotes immunity to OPC as well as to gastric candidiasis (22, 40, 95). Like IL-17, IL-22 exerts its primary activities on non-hematopoietic cells, particularly epithelial cells. However, the signaling mechanisms induced by IL-22 are

strikingly different from those activated by IL-17; whereas IL-17 activates TRAF/NF-κB signaling, IL-22 activates the JAK-STAT pathway, primarily STAT3 (43). The sensitivity of certain human populations to candidiasis implicates IL-22 (section 6). For example, patients with autoimmune polyendocrinopathy syndrome-1 (APS-1) exhibit neutralizing Abs against both IL-17 family members as well as IL-22, and Job's syndrome patients have mutations in STAT3 (10).

The microbiome has generated much interest of late, and certainly contributes to antifungal immunity. Antibiotics are a risk factor for candidiasis, and administration of antibacterial agents concomitantly increases the abundance of fungi in the intestine (96). In a related subject, fungi constitute a significant but often overlooked part of the microbiome, sometimes termed the "mycobiome" (17). A seminal study in 2012 showed that there is a complex community of fungal species in the murine intestine that influences host immunity, in part through Dectin-1 (59). This is relevant to human autoimmune diseases, as SNPs in the genes encoding Dectin-1 (CLEC7A) and CARD9 are associated with risk for inflammatory bowel disease (59, 97). Although less well studied for other autoimmune conditions, fungal components such as zymosan can exacerbate pathology, at least in autoimmune models (98).

6. Defects in the IL-17 pathway in humans

'Experiments of nature' have been remarkably enlightening in validating the correlates of immunity to candidiasis in humans. Genetic defects underlying CMC have been defined through candidate gene or whole exome sequencing approaches, and nearly all link directly to the IL-17/Th17 pathway (73). Deficiencies include pattern recognition of *Candida* (*CARD9, DECTIN1*), factors involved in Th17 cell differentiation (*IL12B, IL12RB1, STAT1, STAT3, TYK2*), IL-17 signaling (*IL17F,IL17RA, ACT1, IL17RC*) and anti-IL-17 autoantibodies (*AIRE*) (73, 99).

6A. Pattern Recognition—Dectin-1 engagement on *C. albicans* is an important initiator of Th17 responses (28), and a *DECTIN1* polymorphism is associated with increased susceptibility to CMC. APCs from patients with these SNPs showed defective production of IL-6 upon exposure to *Candida*. While disease is typically mild, these individuals present with VVC and onychomycosis, thought to be due to decreased IL-17 production (100). This polymorphism was also associated with increased *Candida* colonization in hematopoietic stem cell transplant recipients (101). Consistently, Dectin-$1^{-/-}$ mice show increased susceptibility to GI colonization with *C. albicans* and disseminated candidiasis, though this is somewhat dependent on the strain of *C. albicans* employed (102). Common lab strains of *C. albicans* adapt to the *in vivo* environment, leading to differences in cell wall composition and nature, which can in turn influence dectin-1 recognition. For exaple, differences in chitin deposition influence dectin-1 recognition of β-glucans and consequent susceptibility to candidiasis (103). Understanding how to manipulate the fungal cell wall is a ripe area for therapeutic intervention; as noted (section 2), caspofungin disrupts fungal cell walls to unmask β-glucan moieties (31).

CARD9 is an adaptor downstream of most CLRs (104). CARD9-deficient mice are susceptible to disseminated candidiasis and Th17 differentiation capacity is impaired (105). CARD9 is likewise critical for adaptive Th17 responses to OPC, but was unexpectedly dispensable for IL-17-mediated innate responses in the oral cavity (75). This intriguing finding raises the possibility that CARD9-independent pathways, perhaps through Dectin-1/Raf signaling, may dominate in the innate response (28). Such a model would be consistent with the concept of "trained immunity" to *Candida* described by Netea and colleagues, in which primary exposure to a pathogen improves the activity of monocytes to respond to re-challenge (106). In humans, a rare loss of function mutation in CARD9 has been described that is associated with Th17-deficiency. Disease was far more severe than in patients with a *DECTIN1* mutations, suggesting that additional CARD9-dependent CLRs contribute to the response to *C. albicans* (107). Notably, CARD9 deficiency is the only setting where invasive candidiasis is described in humans.

6B. JAK-STAT pathway—Several mutations in the JAK-STAT pathway are associated with CMC and the Th17 pathway. Hyper-IgE syndrome (HIES, Job's syndrome) is a primary immunodeficiency characterized by elevated IgE, dermatitis, recurrent infections of the skin and lungs and CMC (73). Autosomal dominant-HIES is caused by dominant negative mutations in the DNA-binding or SH2 domains of STAT3 (108, 109). STAT3 signals downstream of IL-6, IL-21 and IL-23, and is required for development of conventional Th17 cells. The promiscuous role of STAT3 signaling in the IL-23/IL-17 axis helps explain the Th17-deficiency and the concomitant increased susceptibility to CMC in HIES (Figure 1). Surprisingly, mice lacking STAT3 in CD4+ cells are not susceptible to acute OPC, perhaps indicating a reduced requirement for this transcription factor in innate Type 17 cells (65, 110). In addition to Th17 cells, salivary components are also defective in HIES. Increased oral colonization with *C. albicans* occurs in HIES patients, correlating with defects in IL-17-regulated salivary components such as BD2 and histatins. Consistently, saliva from individuals with HIES had decreased *Candida*-killing capacity compared to controls (86). This was also true in mice, as saliva from IL-23- and IL-17RA-deficient mice exhibited decreased levels of BD3 (orthologue of BD2) and *Candida*-killing properties in vitro (40). Thus, STAT3 exerts multifunctional antifungal activities in the context of candidiasis.

Multiple CMC patients with gain-of-function mutations in STAT1 have been identified (111–113). The link to Th17 pathways is somewhat indirect; STAT1 is downstream of Th17-pathway inhibitors, including IL-27, IFNγ and IFNα/β. Indeed, these mutations are associated with reduced Th17 frequencies. STAT1 mutations are comparatively common, with one report describing 12 missense mutations in 47 patients from 20 kindred groups. It is unclear exactly why these patients are susceptible to candidiasis, since Type I interferons are implicated in *Candida* immunity (114). Nonetheless, STAT1 mutations clearly lead to CMC susceptibility, likely via downstream signaling pathways that impact Th17 generation.

6C. IL-17 pathway—Individuals with mutations in IL-17A or IL-17RA offer compelling evidence for a direct role of IL-17 in antifungal immunity. A homozygous null mutation in IL-17RA was indentified in which fibroblasts were refractory to IL-17A and IL-17F

signaling (115). Two individuals with *IL17RC* mutations were also recently identified (99). A family with autosomal dominant CMC due to a lack of IL-17A, IL-22 and Th17 cells has also been described (116). Additionally, a dominant-negative mutation in *IL17F* was discovered in a family with autosomal dominant CMC (115). IL-17F is a weaker agonist than IL-17A, but IL-17F and IL-17A form a heterodimer with intermediate signaling capacity (79). Indeed, the mutant IL-17F protein blocked signaling through the IL-17A:F heterodimer (115). In addition, *ACT1* mutations in patients with CMC have been found that disrupt Act1 association with the IL-17R, underscoring the importance of IL-17 signaling (117).

Autoimmune polyendocrinopathy syndrome-1 (APS-1) is caused by mutations in the autoimmune regulator (*AIRE*) gene, causing aberrant thymic self-tolerance and multiorgan autoimmune disease. Intriguingly, most AIRE patients present with CMC. This singular susceptibility to candidiasis was at least partly explained by the discovery of neutralizing autoantibodies against Th17-related cytokines in these patients (118, 119). The most common are directed against type I interferons and Th17-related cytokines. Neutralization of IL-17 and related cytokines by these autoantibodies is thought to account for the increased susceptibility of APS-1 patients to CMC.

Cumulatively, these rare but informative genetic disorders provide compelling evidence for the centrality of the Th17/ IL-17 pathway in controlling *Candida* infections. That most of these mutations (except CARD9) are restricted to mucosal disease indicates that mucosal barriers are maintained even without functional Th17/IL-17 activity. The direct link between neutralizing autoantibody production and *Candida* infection seen in APS-1 also raises concerns regarding the clinical use of anti-IL-17 antibody therapies, as outlined below.

7. Anti-IL-17 Therapies and implications for antifungal immunity

Aberrant IL-17 production is linked to inflammation in autoimmunity. Psoriasis is emerging as a particularly strong IL-17-driven disorder (43, 89). Psoriasis is linked to IL-23-mediated activation of CD4+Th17 cells and innate Type 17 cells. IL-17 and IL-22 produced by these subsets interact with skin-resident keratinocytes, fibroblasts and endothelial cells to promote cell division and production of cytokines, chemokines and AMPs (120). This enhanced inflammatory state leads to exacerbated recruitment of neutrophils, mast cells and macrophages, and ultimately epidermal hyperplasia. The roles of IL-23 and IL-17 in psoriasis consequently make them attractive therapeutic targets (43). A number of biologic drugs targeting IL-17A/F, IL-17RA, and the IL-12p40 or IL-23p19 subunits of IL-23 are being used or evaluated in patients with psoriasis with impressive efficacy (121–123).

On the flip side, an obvious prediction of biologic anti-IL-17 therapies is an increased risk of *Candida* infections. Trials with anti-IL-17A antibodies indeed indicate that OPC is a side effect, though all cases so far are mild (121). A meta-analysis of opportunistic infections from anti-TNF therapies in IBD revealed that candidiasis occurs more frequently than often realized (124), which could conceivably relate to the characteristic signaling synergy between TNFα and IL17. In this regard, PBMCs from RA patients showed increased colonization and decreased oral anti-*Candida* responses compared to healthy controls (125).

Since other human fungal pathogens also seem to involve the Th17 response, monitoring for fungal infections will be important facet of anti-IL-17 biologic agent usage.

8. Conclusions

The importance of IL-17 in candidiasis is now firmly established. In response to *Candida* at mucosal surfaces, IL-17 induces a protective neutrophil influx and AMPs that cooperate to control overgrowth and morphotype switching of *Candida*. The relative contribution of each component is an active area of research, and many questions remain (40, 88). Individuals with a wide-range of underlying conditions receive therapies that induce susceptibility to *Candida* infections, including glucocorticoids, radiotherapy or antibiotics. How the IL-17R signaling pathway is impacted in each modality of immunosuppression is poorly defined. With the advent of specific anti-Th17 therapies, the potential pool of patients at risk for *Candida* and other fungal opportunistic infections may expand considerably. The lack of effective vaccines for fungi and the increasing problem of antifungal resistance makes it imperative to understand the components involved in protection to this important pathogen (3, 59).

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Abbreviations

CMC	chronic mucocutaneous candidiasis
OPC	oropharyngeal candidiasis
BD	β-defensin
AMP	antimicrobial peptide
VVC	vulvovaginal candidiasis
CLR	C-type lectin receptor
HIES	hyper-IgE syndrome
APS-1	autoimmune polyendocrinopathy syndrome
PRR	pattern recognition receptor

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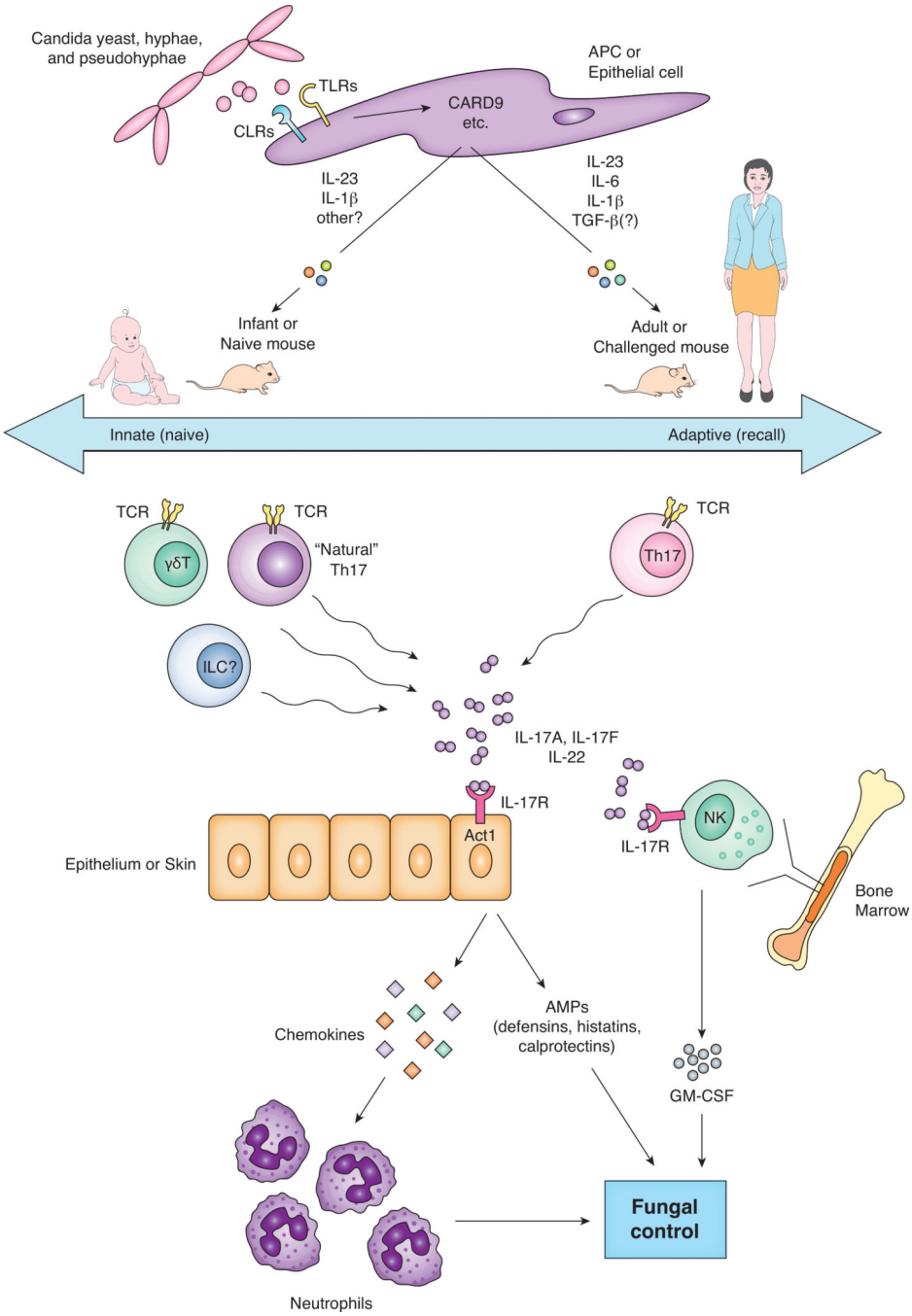

Figure 1. Adaptive and Innate Immune Responses to *C. albicans*

C. albicans exists in various morphologies, which are sensed by PRRs such as C-type lectin receptors found on APCs as well as epithelial cells. Exposure to *C. albicans* induces expression of innate cytokines, many of which are inductive for IL-17-expression cells. Various sources of IL-17 are documented in the context of candidiasis, including innate and adaptive cell types. IL-17 signaling on epithelial or other non-hematopoietic cells leads to expression of chemokines, AMPs and other factors that contribute to fungal control.