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Brief Reviews

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IL-17–Mediated Immunity to the Opportunistic Fungal Pathogen *Candida albicans*

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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 microbe of the human oral cavity, gastrointestinal tract, and reproductive mucosa. The IL-17 pathway regulates antifungal immunity through upregulation of proinflammatory cytokines, including IL-6, neutrophil-recruiting chemokines (e.g., CXCL1 and CXCL5), and antimicrobial peptides (e.g., defensins), which act in concert to limit fungal overgrowth. This review focuses 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. *The Journal of Immunology*, **2015, 195: 780–788.**

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 *Candida albicans*, are commensal microbes of the mouth, gastrointestinal (GI) tract, skin, and vagina of healthy individuals (1). When host immunity is compromised, 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 revealed the central importance of this pathway in controlling *C. albicans* infections, which is the subject of this review.

Infections caused by C. albicans

Several species of *Candida* cause candidiasis, although *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* spp. are dimorphic, existing as yeast or pseudohyphal and 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 *Pattern recognition of C. albicans*).

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 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.

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, although 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).

Disseminated candidiasis. Systemic candidiasis is the most severe form of *Candida* infection. *Candida* spp. represent the fourth most common cause of bloodstream infections in U.S.

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Abbreviations used in this article: AMP, antimicrobial peptide; APS-1, autoimmune polyendocrinopathy syndrome-1; BD, β-defensin; CLR, C-type lectin receptor; CMC, chronic mucocutaneous candidiasis; GI, gastrointestinal; HIES, hyper-IgE syndrome; OPC, oropharyngeal candidiasis; PRR, pattern recognition receptor; VVC, vulvovaginal candidiasis.

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hospitals, with a mortality 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).

Candida in the intestinal tract. Although *C. albicans* does not usually invade intestinal tissue to cause disease, *Candida* spp. colonize the GI tract and can translocate to the bloodstream during intestinal barrier breaches (10, 17). Although 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 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, IFN-γ 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). These models thus offer a cost-effective platform to study the immune response to *Candida* and to facilitate development of new therapeutics.

Pattern recognition of C. 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* spp., 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, Dectin-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, because 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, antifungal 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).

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 naive precursors through signals from IL-1β, IL-6, TGF-β, 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, because *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 are 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, were found to be susceptible to oral infection (40). Consistently, defects anywhere along the IL-17 signaling pathway, including IL-17RA, IL-17RC, and Act1, predispose to oral candidiasis (40–42). Strikingly, parallel defects are also seen in humans (see *Defects in the IL-17 pathway in humans*) (43). Correlating with susceptibility in these settings is defective neutrophil recruitment and impaired antimicrobial peptide (AMP) production (40–42).

The role of IL-17–mediated immune responses in VVC 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). Although 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.

IL-17 is also important in systemic candidiasis, because IL-17A$^{-/-}$ and IL-17RA$^{-/-}$ mice are more susceptible to infection than are wild-type mice (20, 47, 48). In addition, there are key roles for IFN-γ and TNF-α in driving neutrophil recruitment to affected organs, as well as enhancing the fungicidal activity of phagocytes (49–54). Experimental vaccines targeting *C. albicans* are protective in systemic candidiasis and notably generate both Th1 and Th17 responses; 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–*C. albicans* species. Bär et al. (57) identified an epitope from the *C. albicans* ALS1/3 adhesin molecule that is recognized by Th17 cells. This epitope is conserved among *Candida* spp., including *C. dubliniensis*, *C. tropicalis*, *C. krusei*, and *C. glabrata*. 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" (i.e., collection of fungal spp., analogous to the bacterial microbiome) in the mouse intestine, and its proportion increases in colitis-prone Dectin-$1^{-/-}$ mice, correlating with increased levels of IL-17, as well as IFN-γ and TNF-α (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 TNF-α in neutrophils are essential (N. Whibley and S.L. Gaffen, unpublished observations). Clearly more analysis will be essential to understand immune responses to other fungi.

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 RORγt and STAT3 (Fig. 1). IL-23, although not required for Th17 development, promotes the maintenance and function of Th17 cells in a STAT3-dependent manner. In addition, various innate cell types, referred to broadly as "Type 17" cells, express IL-17 in an IL-23– and RORγt-dependent manner (60). Type 17 lymphoid subsets include invariant NKT, LTi γδ-T, and natural Th17 cells. IL-17–expressing cells lacking an AgR are classified as group 3 innate lymphoid cells (61). In some settings, neutrophils were reported to express IL-17, although this does not seem to be the case in candidiasis (62–64). Innate Type 17 cells tend to reside in nonlymphoid tissues, where they are poised to be activated rapidly in an Ag-independent manner (60).

The awareness that IL-17 is produced by innate cell types, as well as conventional Th17 cells, prompted studies to define the cellular sources of IL-17 during *Candida* infections (60). 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 rechallenge model of OPC demonstrated that there is no preexisting cross-reactive immunity to components in commensal microbiota or food (57, 65). Consistently, CD4-deficient mice are resistant to acute OPC (65), and the standard model of OPC used in the field (in which clearance of the fungus from the oral mucosa occurs within 4–5 d) (23) reflects the innate rather than the adaptive response (59, 66) (Fig. 1). Consistently, IL-17 mRNA is detected within 24 h of infection (40, 65), pointing to an innate origin of IL-17. Using a fate-tracking reporter mouse system (67), we identified oral-resident IL-17^+ γδ-T cells and natural Th17 cells following encounter with *C. albicans* (64). Work by Gladiator et al. (68) alternatively suggested a role for group 3 innate lymphoid cells in OPC, although the concept is inconsistent with the high susceptibility of Rag$1^{-/-}$ mice (which have innate lymphoid cells) to OPC (65, 69). An innate source of IL-17 in OPC agrees with data in dermal candidiasis demonstrating IL-17 production by γδ-T cells (67, 70, 71).

In adults, defects in conventional Th17 cells are associated with CMC (72, 73), indicating that the adaptive response is dominant in anti-*Candida* immunity in humans. Although innate responses to mucosal candidiasis apparently predominate in infants and naive mice (Fig. 1), generation of adaptive Th17 cells in murine OPC confers additional protection (65, 74). The relative importance of the innate response in mice compared with humans may reflect important species differences. It is plausible, for example, that mice may require more robust oral innate immunity because they are coprophagic.

Specific morphologies of *C. albicans* direct Th17 differentiation. Kaplan and colleagues (6) recently reported that the yeast form of *C. albicans* promotes the 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. 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* was attributed to signaling differences between yeast and hyphae in oral epithelial cells, with distinct differences in downstream MAPK signaling seen between morphotypes (75).

IL-17–mediated mechanisms of fungal immunity

How does IL-17 mediate antifungal immunity? The IL-17 family consists of six cytokines (IL-17A–IL-17F) and 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 (76–78). 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 as a result of restricted expression of the IL-17RC subunit (79). However, exceptions to this paradigm were observed in studies of fungal infection. Specifically, IL-17RC is reported to be expressed in human neutrophils during *Aspergillus fumigatus* infections, and polymorphonuclear cells were reported to produce and respond to IL-17 (80). 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) (81). 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 (Fig. 1). However, some target genes 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 ortholog, BD2, are ligands for

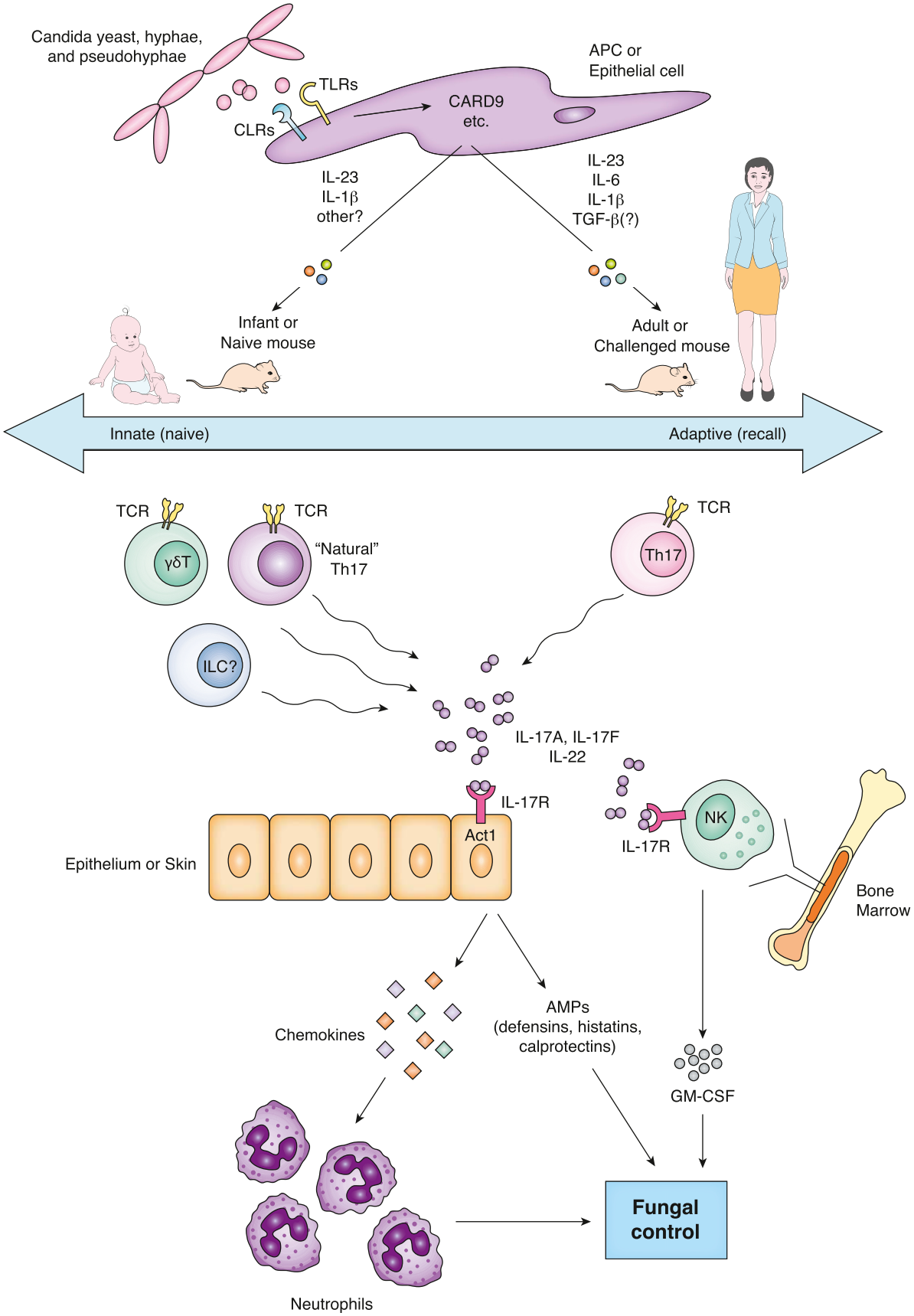

FIGURE 1. Adaptive and innate immune responses to *C. albicans*. *C. albicans* exists in various morphologies, which are sensed by PRRs, such as CLRs found on APCs, as well as epithelial cells. Exposure to *C. albicans* induces the expression of innate cytokines, many of which are inductive for IL-17–expressing 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.

CCR6, although it is not clear whether BD2 and BD3 actually function as chemoattractants for $CCR6^+$ cells in situ (82). BD1 also plays an important protective role in murine OPC (83). Another class of AMPs with candidacidal activity are histatins, which are highly expressed in human salivary glands (84). Patients with hyper-IgE syndrome (HIES)/Job's syndrome exhibit reduced Th17 frequencies due to mutations in STAT3 (see *Defects in the IL-17 pathway in humans*) and exhibit reduced levels of salivary BDs and histatins. Moreover, IL-17 can directly induce histatin expression in human salivary gland cells in vitro (85). 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 (86). IL-17F is the most conserved but does not appear to participate in anti-*Candida* immunity based on knockout mouse or Ab-blocking studies (47, 87). IL-17C signals through a receptor consisting of IL-17RA paired with IL-17RE and has considerable functional overlap with IL-17A (88). Epithelial cells, not hematopoietic cells, produce IL-17C, inducing a gene profile strikingly similar to IL-17A (88–92). However, unlike IL-17A, IL-17C plays no detectable role in protection against oral, dermal, or disseminated candidiasis in mouse models (93). Because 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 and gastric candidiasis (22, 40, 94). Like IL-17, IL-22 exerts its primary activities on nonhematopoietic 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 also implicates IL-22 (see *Defects in the IL-17 pathway in humans*). 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 (95). 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, because single-nucleotide polymorphisms in the genes encoding Dectin-1 (CLEC7A) and CARD9 are associated with a risk for inflammatory bowel disease (59, 96). Although less well studied for other autoimmune conditions, fungal components, such as zymosan, can exacerbate pathology, at least in autoimmune models (97).

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 (72). 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*) (72, 98).

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 single-nucleotide polymorphisms showed defective production of IL-6 upon exposure to *Candida*. Although disease is typically mild, these individuals present with VVC and onychomycosis, thought to be due to decreased IL-17 production (99). This polymorphism also was associated with increased *Candida* colonization in hematopoietic stem cell transplant recipients (100). Consistently, Dectin-$1^{-/-}$ mice show increased susceptibility to GI colonization with *C. albicans* and disseminated candidiasis, although this is somewhat dependent on the strain of *C. albicans* used (101). Common laboratory strains of *C. albicans* adapt to the in vivo environment, leading to differences in cell wall composition and nature, which, in turn, can influence Dectin-1 recognition. For example, differences in chitin deposition influence Dectin-1 recognition of β-glucans and consequent susceptibility to candidiasis (102). Understanding how to manipulate the fungal cell wall is a ripe area for therapeutic intervention; as noted above, caspofungin disrupts fungal cell walls to unmask β-glucan moieties (31).

CARD9 is an adaptor downstream of most CLRs (103). CARD9-deficient mice are susceptible to disseminated candidiasis, and Th17 differentiation capacity is impaired (104). CARD9 is likewise critical for adaptive Th17 responses to OPC but was unexpectedly dispensable for IL-17–mediated innate responses in the oral cavity (74). 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 (105), in which primary exposure to a pathogen improves the activity of monocytes to respond to rechallenge. In humans, a rare loss of function mutation in CARD9 was described that is associated with Th17 deficiency. Disease was far more severe than in patients with *DECTIN1* mutations, suggesting that additional CARD9-dependent CLRs contribute to the response to *C. albicans* (106). Notably, CARD9 deficiency is the only setting in which invasive candidiasis is described in humans.

JAK–STAT pathway. Several mutations in the JAK–STAT pathway are associated with CMC and the Th17 pathway. HIES (Job's syndrome) is a primary immunodeficiency characterized by elevated IgE, dermatitis, recurrent infections of the skin and lungs, and CMC (72). Autosomal-dominant HIES is caused by dominant-negative mutations in the DNA-binding or SH2 domains of STAT3 (107, 108). STAT3 signals downstream of IL-6, IL-21, and IL-23 and is required for the development of conventional Th17 cells. The promiscuous role of STAT3 signaling in the IL-23/IL-17 axis helps to explain the Th17 deficiency and the concomitant increased susceptibility to CMC in HIES (Fig. 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 (64, 109). In addition to Th17 cells, salivary components are 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 with controls (85). This was also true in mice: saliva from IL-23– and IL-17RA–deficient mice exhibited decreased levels of BD3 (ortholog 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 (110–112). The link to Th17 pathways is somewhat indirect; STAT1 is downstream of Th17 pathway inhibitors, including IL-27, IFN-γ, 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, because type I IFNs are implicated in *Candida* immunity (113). Nonetheless, STAT1 mutations clearly lead to CMC susceptibility, likely via downstream signaling pathways that impact Th17 generation.

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 identified in which fibroblasts were refractory to IL-17A and IL-17F signaling (114). Two individuals with *IL17RC* mutations also were identified recently (98). A family with autosomal-dominant CMC due to a lack of IL-17A, IL-22, and Th17 cells also was described (115). Additionally, a dominant-negative mutation in *IL17F* was discovered in a family with autosomal dominant CMC (114). IL-17F is a weaker agonist than IL-17A, but IL-17F and IL-17A form a heterodimer with intermediate signaling capacity (78). Indeed, the mutant IL-17F protein blocked signaling through the IL-17A:F heterodimer (114). 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 (116).

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 explained, at least in part, by the discovery of neutralizing autoantibodies against Th17-related cytokines in these patients (117, 118). The most common are directed against type I IFNs 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 Ab therapies, as outlined below.

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, 88). 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 (119). 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 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 (120–122).

On the flip side, an obvious prediction of biologic anti–IL-17 therapies is an increased risk for *Candida* infections. Trials with anti–IL-17A Abs indicate that OPC is a side effect, although all cases so far are mild (120). A meta-analysis of opportunistic infections from anti-TNF therapies in irritable bowel disease revealed that candidiasis occurs more frequently than often realized (123), which may relate to the characteristic signaling synergy between TNF-α and IL-17. In this regard, PBMCs from rheumatoid arthritis patients showed increased colonization and decreased oral anti-*Candida* responses compared with healthy controls (124). Because other human fungal pathogens seem to involve the Th17 response, monitoring for fungal infections will be an important facet of anti–IL-17 biologic agent usage.

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, 87). Individuals with a wide range of underlying conditions receive therapies, including glucocorticoids, radiotherapy, or antibiotics, that induce susceptibility to *Candida* infections, 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 make it imperative to understand the components involved in protection against this important pathogen (3, 59).

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