

REVIEW

Mucocutaneous candidiasis: the IL-17 pathway and implications for targeted immunotherapy

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Abstract

IL-17 and related cytokines are direct and indirect targets of selective immunosuppressive agents for the treatment of autoimmune diseases and other diseases of pathologic inflammation. Insights into the potential adverse effects of IL-17 blockade can be drawn from the experience of patients with deficiencies in the IL-17 pathway. A unifying theme of susceptibility to mucocutaneous candidiasis is seen in both mice and humans with a variety of genetic defects that converge on this pathway. Mucocutaneous candidiasis is a superficial infection of mucosal, nail or skin surfaces usually caused by the fungal pathogen *Candida albicans*. The morbidity of the disease includes significant pain, weight loss and secondary complications, including carcinoma and aneurysms. This review describes the known human diseases associated with chronic mucocutaneous candidiasis (CMC) as well as the known and proposed connections to IL-17 signaling. The human diseases include defects in IL-17 signaling due to autoantibodies (AIRE deficiency), receptor mutations (IL-17 receptor mutations) or mutations in the cytokine genes (*IL17F* and *IL17A*). Hyper-IgE syndrome is characterized by elevated serum IgE, dermatitis and recurrent infections, including CMC due to impaired generation of IL-17-producing Th17 cells. Mutations in *STAT1*, *IL12B* and *IL12RB1* result in CMC secondary to decreased IL-17 production through different mechanisms. Dectin-1 defects and *CARD9* defects result in susceptibility to *C. albicans* because of impaired host recognition of the pathogen and subsequent impaired generation of IL-17-producing T cells. Thus, recent discoveries of genetic predisposition to CMC have driven the recognition of the role of IL-17 in protection from mucosal fungal infection and should guide counseling and management of patients treated with pharmacologic IL-17 blockade.

Introduction

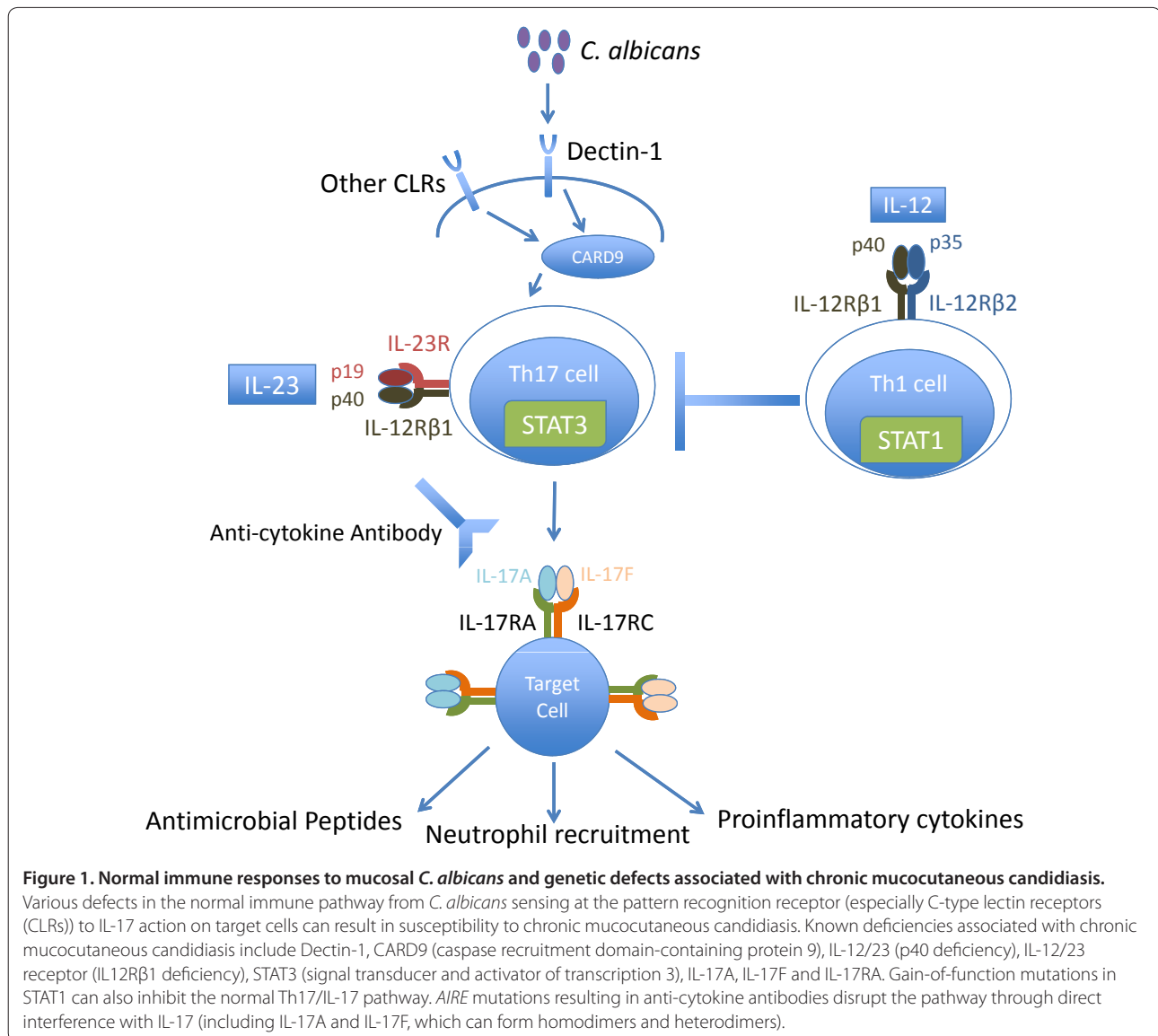
Considerable attention and research dollars have focused on the cytokine interleukin-17 (IL-17 or IL-17A) and the pathology associated with aberrant IL-17 signaling. In many cases, an excess of IL-17 is associated with abnormal inflammation, implicated in rheumatoid arthritis, asthma, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus and autoimmune encephalomyelopathy (reviewed in [1]). Not surprisingly, IL-17 and related cytokines have become a prime target for pharmaceutical management of these diseases (reviewed in [2]). Targeted biologics are an appealing method to combat pathologic inflammation while avoiding non-specific immunosuppression. There are currently Food and Drug Administration-approved monoclonal antibodies for the treatment of rheumatologic and autoimmune diseases

targeting various cytokines and immune factors, including TNF- α , IL-1, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), B cells (CD20), IL-6, IL-12/23p40, and so on. Although not originally designed with that intent, many if not all of these drugs target the IL-17 pathway. Drugs are currently in development that target the T-helper cell 17 (Th17) pathway, including IL-17 and its receptor, IL-23p19 and IL-22, among others [3-9]. Rigorous clinical trials and post-marketing studies are essential to reveal possible unexpected consequences of targeted immune blockade. In addition, attention to 'experiments of nature' in which mutations lead to alterations in cytokine pathways are a useful adjunct to predict adverse effects of the new biologic agents. This review will focus on the IL-17/Th17 pathway and mucocutaneous candidiasis, an opportunistic infection associated with immunodeficiency, with reference to the known or potential impact of cytokine blockade.

IL-17 is secreted by the Th17 subset of CD4⁺ lymphocytes, as well as CD8 T cells and innate cells, including natural killer T cells, lymphoid tissue inducer cells, innate lymphoid cells and $\gamma\delta$ -T cells [10]. Th17 cells are highly

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protective against extracellular pathogens and can participate in immunity to intracellular bacteria and perhaps certain viruses, especially at mucosal surfaces (reviewed in [11]). A notable extracellular pathogen at the oral mucosa is *C. albicans*, a commensal yeast that frequently colonizes the mouth, colon or vagina in healthy individuals [12]. Asymptomatic colonization generally only progresses to disease in the face of an additional risk factor, such as immunosuppression, disruption of normal barriers, surgery or broad spectrum antibiotics [13-15]. We recently demonstrated in mice that the IL-23/IL-17 axis of immunity is critical for immunity to *Candida* in the oropharynx using mice lacking IL-23 or either IL-17 receptor subunit (IL-17RA and IL-17RC) [16,17]. Similarly, immunity to dermal and disseminated candidiasis in mice is regulated by the IL-17 pathway [18,19]. In

humans, the majority of *Candida*-specific memory T cells express IL-17 and CCR6 (a Th17 marker) [20], clearly linking the IL-17 pathway to antifungal immunity (Figure 1).

Candida infections of the mucosal, nail or skin surfaces are termed mucocutaneous candidiasis. In patients with an underlying genetic or immune defect leading to susceptibility to these infections, the disease is often persistent and chronic, termed chronic mucocutaneous candidiasis (CMC). The direct manifestations of CMC are *Candida* plaques (usually *C. albicans*) on the oral, esophageal or genital mucosa or thickened skin and nails (reviewed in [21]). Susceptible individuals may also experience recurrent infections with dermatophytes. Although symptoms can be benign, they often cause significant morbidity due to pain, weight loss or failure to

thrive, or more severe secondary complications such as squamous cell carcinoma, debilitating hands, esophageal stricture or cerebral aneurysms [22-25]. Interestingly, mucocutaneous candidiasis is rarely associated with disseminated candidal disease [26]. In the past few years, multiple genetic etiologies causing this disease have been described. Strikingly, most relate directly or indirectly to defects in IL-17, supporting the notion that not only is the IL-17 pathway critical for regulating anti-fungal immunity, but defects in IL-17 predispose primarily to infection with *C. albicans* and surprisingly few other microbes.

Defects in the IL-17 pathway

AIRE deficiency

Autoimmune polyendocrinopathy syndrome-I (APS-I), also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), is an autosomal recessive disorder caused by mutations in the autoimmune regulator (*AIRE*) gene. Mutations in *AIRE* lead to aberrant thymic self-tolerance mechanisms and loss of thymic deletion of autoreactive T cells. The classic triad of this disease is CMC, typically presenting by age 6, hypoparathyroidism and adrenocortical failure [27,28]. The prevalence of the disease varies worldwide, but is highest in Iranian Jews (about 1:9,000), Sardinians (1:14,000), and Finnish populations (1:25,000), with men and women equally affected (reviewed in [25]). A wide-range of disease manifestations has been described, including, in descending order of prevalence, dental enamel dysplasia, nail dystrophy, alopecia, ovarian failure, vitiligo, diabetes mellitus, testicular failure and hypothyroidism. CMC is nearly universal in APS-I patients [27,29], but they are not prone to other infections. The lone infectious susceptibility associated with this disease was initially mysterious, but now is tied to neutralizing autoantibodies against cytokines detected in these patients [30]. The most common anti-cytokine autoantibodies are directed against the type I interferons (IFNs) and Th17-related cytokines, notably IFN- ω (100% of patients), IFN- α (95%), IL-22 (91%), IL-17F (75%), and IL-17A (41%) [27]. Similar high prevalence of antibodies against IL-17A, IL-17F and IL-22 has been found in APS-1 in other studies [31]. Plasma from patients with autoantibodies against IL-17 abolishes IL-17 responsiveness (measured by IL-6 production) in fibroblasts, confirming that these antibodies interfere with IL-17 activity [31].

Although APS-1 is not the only human disease resulting from abnormal autoantibodies, it is the only such disease associated strongly with CMC. This is most likely due to the unique spectrum of anti-cytokine autoantibodies produced as a result of *AIRE* deficiency. For example, a different pattern of anti-cytokine autoantibodies is found in patients with thymoma.

patients have a high prevalence of antibodies to IFN- ω , IFN α and IL-12, but a low prevalence of antibodies to IL-22, IL-17F or IL-17A [27]. CMC is an unusual manifestation of thymoma, but its occurrence correlates with the presence of autoantibodies against both IL-17A and IL-22 [30], further supporting the concept that neutralizing Th17-specific cytokines increases susceptibility to candidiasis. Thus, the pathogenesis of APECED with respect to CMC seems to be tightly linked to neutralizing Th17 cytokines, suggesting that IL-17 neutralization applied in other settings increases the risk for CMC.

IL-17 receptor mutations

The most direct evidence for a role in the IL-17 pathway in host resistance to CMC comes from a recent report of a case of homozygous mutation in the IL-17A receptor (*IL17RA*). The mutation was found in a French child of Moroccan descent with autosomal recessive CMC [32]. The child presented with *Candida* dermatitis starting in the neonatal period and *Staphylococcus aureus* dermatitis at 5 months of age. Sequencing of multiple genes related to IL-22 or IL-17 signaling (*IL22*, *IL22RA1*, *IL10RB*, *IL17A*, *IL17F*, *IL17RA*, *IL17RC*) revealed a homozygous nonsense mutation in the *IL17RA* gene (c.850C>T/c.850C>T), which results in a premature stop codon in the extracellular domain of the receptor. The child's parents and siblings were heterozygous for the allele and asymptomatic. A database of healthy controls from 52 ethnic groups, as well as French and Moroccan controls, failed to reveal any other cases of this mutation. The patient's blood and tissue were studied in more detail, which revealed a lack of IL-17RA protein on the surface of fibroblasts and peripheral blood mononuclear cells. IL-17RC, IL-22RA1, IL-17A and IL-22 expression levels were normal. The patient's fibroblasts did not respond to IL-17A or IL-17F in terms of producing prototypical IL-17 target proteins such as IL-6 or growth-regulated oncogene- α (GRO α , also known as CXCL1 or KC in mice). Importantly, normal function was restored upon transfection of fibroblasts with wild-type *IL17RA*, verifying that this manifestation was not from another undetected mutation. The phenotype of homozygous *IL17RA* mutation in humans is consistent with findings that IL-17RA- and IL-17RC-deficient mice are more susceptible to oropharyngeal candidiasis, and suggests that data from mouse models are a good predictor of human susceptibility to candidiasis [16,17].

IL-17A deficiency

A kindred with autosomal dominant CMC who lack the IL-17 family member IL-17A and Th17 cells has been described [28]. The exact defect is unknown but it appears to be posttranscriptional since *IL-17* mRNA

levels were preserved [28]. Additional patients with CMC have been described with decreased production of IL-17A and IL-22 of unknown underlying etiology [33]. The emerging evidence of a role for IL-17A in human susceptibility to *Candida* is supported by work in mice. For example, IL-17A-deficient mice have impaired clearance of *C. albicans* infection from the skin [19].

The role of IL-22 is less clear, as *IL22*^{-/-} mice are not susceptible to either dermal or oral candidiasis [17,19]. In a gastric model of candidiasis in mice, IL-22 does appear to be protective [34], perhaps due to its well known role in promoting epithelial repair in the mucosa [35]. More work is needed to determine its precise contribution to antifungal immunity.

IL17F mutation

A form of autosomal dominant CMC with incomplete penetrance results from mutation in the IL-17 family member *IL17F* [32]. This mutation was first described in four members of a family from Argentina with autosomal dominant inheritance of CMC. A thorough analysis of genes related to IL-17 signaling revealed a heterozygous missense mutation in the *IL17F* gene of the index case. The mutation (c.284C>T) resulted in the replacement of a conserved serine with leucine. This mutation was not found in the control patient database. Based on computational analysis, the missense mutation is predicted to interfere with cytokine to receptor binding. All tested members of the kindred with CMC were heterozygous for this mutation. Two apparently healthy family members also had the allele, suggesting incomplete penetrance. By flow cytometry, IL-17F-expressing T cells were absent in affected family members. *In vitro* studies of the mutant protein revealed defective binding to IL-17RA on fibroblasts, with weaker IL-6 and GRO- α induction. Peripheral blood mononuclear cells also had impaired induction of cytokines when stimulated with the mutant protein.

This finding was somewhat surprising, as IL-17F is not a strong agonist of the IL-17 receptor compared to IL-17A, and *IL17F*^{-/-} mice were not highly susceptible to disseminated candidiasis [36]. However, IL-17A and IL-17F form both homodimers and heterodimers [37], and the mutant IL-17F identified in this patient cohort blocks signaling from the IL-17A:F form of the cytokine [32]. Thus, blockade of either IL-17A or IL-17F may predispose to mucosal candidiasis.

Hyper-IgE syndrome

The hyper-IgE syndromes (HIESs, Job's syndrome) comprise a group of primary immunodeficiencies characterized by elevated serum IgE, dermatitis and recurrent infections primarily of the skin and lungs. The infectious predilections in autosomal-dominant HIES include CMC

and bacterial infections with *S. aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. Most cases of HIES are sporadic, resulting from a dominant negative mutation in the signal transducer and activator of transcription 3 (*STAT3*) [38,39]. The mutations are primarily in the DNA-binding domain or Src homology 2 (SH2) domain of *STAT3* and lead to the impaired generation of Th17 cells [40]. Since *STAT3* is downstream of IL-22, cellular responses to this Th17-derived cytokine are also impaired. In fact, IL-17 production by T cells is absent in cells from HIES individuals after stimulation with *Staphylococcus* enterotoxin B or *C. albicans* [41]. The mutations in *STAT3* result in decreased expression of regulator of retinoid-related orphan receptor γ (ROR γ), a transcription factor required for IL-17 expression, and decreased differentiation into Th17 cells by naïve CD4⁺ T cells [42]. The specific infectious susceptibility of HIES patients to skin and pulmonary infections appears to be due to a site-specific requirement of Th17 cytokines to produce antimicrobial factors, found both in skin and salivary gland tissue [43,44].

Autosomal recessive HIES is a related, but distinct disorder. Most patients affected by this disease are deficient in dedicator of cytokinesis 8 (DOCK8), leading to impaired T-cell activation and maintenance of memory. As in autosomal-dominant HIES, these patients have elevated IgE levels, eczema, recurrent bacterial infections and CMC [45,46]. The unique disease manifestations include susceptibility to recurrent viral infections (most commonly herpes viruses, molluscum contagiosum virus and human papillomaviruses), asthma, severe food allergies, malignancy at young age and unusual autoimmune diseases. Some DOCK8-deficient patients have decreased numbers of Th17 cells (reviewed in [47]). One additional case of autosomal recessive HIES associated with a tyrosine kinase 2 (Tyk2) deficiency has been described [48]; however, a case of Tyk2 deficiency resulting in a phenotype without eczema, candidiasis or hyper-IgE has also been reported [49]. Tyk2 is a member of the Janus kinase (JAK) family that signals downstream of IL-23 and hence is needed for efficient Th17 maintenance *in vivo*. Accordingly, HIES can be caused by various genetic lesions, but the common thread appears to be regulation of the IL-17/Th17 pathway.

STAT1 mutation

Using a genome-wide approach based on whole-exome sequencing, gain-of-function *STAT1* mutations were recently associated with isolated CMC [50]. Twelve missense mutations were found in 47 patients from 20 kindreds of CMC without other clinical features. These mutations were in the coiled-coil domain of *STAT1*, in a pocket near residues essential for *STAT1* dephosphorylation. Mutations at this site result in

gain-of-function STAT1 phosphorylation leading to enhanced transcription of STAT-1-dependent genes in response to various cytokines. The *STAT1* mutant products enhance cellular response to cytokines IFN α / β , IFN γ and IL-27, which are all known inhibitors of the Th17 pathway. These patients had disease involving a range of cutaneous and mucosal sites, including nails, oral cavity, oropharynx, genital mucosa, skin and esophagus. Some patients had thyroid autoimmunity (8 of 47) and one had systemic lupus erythematosus. Squamous cell carcinoma was the cause of death in four patients, and cerebral aneurysm in two.

STAT1 mutations were also demonstrated in 14 autosomal dominant cases of CMC from five families [51]. In addition to CMC, members of one family suffered from various autoimmune diseases (autoimmune hepatitis, autoimmune hemolysis, pernicious anemia and antiphospholipid antibodies) as well as symptomatic cytomegalovirus infection and *Pneumocystis carinii* pneumonia. Three families suffered from hypothyroidism while the fifth family did not have associated autoimmune disease. Three families had histories of oral squamous-cell carcinoma or esophageal cancer. Analysis revealed heterozygous mutations in *STAT1* in only the affected family members. These mutations were located in the coiled-coil domain of *STAT1*, and led to defective Th1 and Th17 responses with reduced production of INF- γ , IL-17 and IL-22 in response to *Candida* stimulation [50]. Therefore, *STAT1* gain-of-function mutations result in CMC through a similar final pathway as other IL-17 signaling defects.

IL-12R β 1 or IL-12p40 deficiency

Patients with inborn errors of the IL-12/IL-23 or IFN γ signaling axis, also known as Mendelian susceptibility to mycobacterial diseases (MSMD), are susceptible to mycobacteria. Infectious susceptibility includes weakly virulent species of mycobacteria such as the bacillus Calmette-Guérin (BCG) vaccine and severe disease caused by *Salmonella* serotypes [52]. A recent review of 132 patients with the most common form of this disease, IL-12R β 1 deficiency, found that 24% have mucocutaneous disease caused by *Candida albicans*, usually manifesting as recurrent oral thrush [53]. The two mutated genes associated with MSMD are *IL12B* and *IL12RB1*. Patients with *IL12B* null mutations lack the IL-12p40 subunit, a shared component of both IL-12 and IL-23 [54]. Similarly, the *IL12RB1* gene encodes the shared chain of the IL-12 and IL-23 receptors (Figure 1). The susceptibility to mycobacterial disease is almost certainly rooted in the deficiency in IL-12 signaling and Th1 cells, which are central to clearance of intracellular pathogens. In contrast, defective IL-23 signaling impairs the expansion and maintenance of Th17 cells and IL-17 signaling.

Patients with mutations in *IL12RB1* and *IL12B* have low proportions of IL-17A-producing T cells in circulation, which likely explains the susceptibility to CMC [40].

C-type lectin receptor pathway defects

Dectin-1 defects

Dectin-1 is a fungal pattern recognition receptor (PRR) that recognizes β -glucans, carbohydrates located in the cell wall of the yeast form of *Candida* (Figure 1). C-type lectin receptors (CLRs) such as Dectin-1 are emerging as important mediators of innate anti-fungal immunity, although there are still many unanswered questions about their specific roles *in vivo* [55]. Studies of Dectin-1 knockout mice revealed increased susceptibility to gastrointestinal colonization with *C. albicans* and varying susceptibility to disseminated candidiasis, depending on the strain of *Candida* used (reviewed in [56]). In humans, the Dectin-1 polymorphism Y238X leads to a premature stop codon and increased susceptibility to CMC in three described homozygous patients [57]. CMC in these patients was characterized by vulvovaginal candidiasis or onychomycosis with *Trichophyton rubrum*. Monocytes and macrophages in these patients had lower fungal-sensing capacity, with decreased production of IL-6 after stimulation with β -glucan, heat-killed *C. albicans* or live *C. albicans*. Consequently, impaired Th17 generation resulted in reduced IL-17 production. Compared to other genetic lesions that promote CMC, however, disease was mild in these patients, suggesting that their susceptibility may be multifactorial. Furthermore, while family members heterozygous for the polymorphism exhibited an intermediate reduction in proinflammatory cytokines, there was only mild transient candidal disease in one person. Follow-up studies revealed that this polymorphism was found on a population-wide search in individuals from Europe and Africa and is associated with increased *Candida* colonization in immunosuppressed hematopoietic stem cell transplant recipients [57,58]. Therefore, Dectin-1 appears to contribute to immune recognition of *Candida* and presents a link between pathogen sensing and IL-17 production.

CARD9 defects

Caspase recruitment domain-containing protein 9 (CARD9) is a signal transducer downstream of many fungal PRRs, including most of the CLRs. Mice deficient in CARD9 exhibit severely reduced TNF- α and IL-2 production in response to zymosan, a yeast cell wall component principally composed of β -glucans, but not other PRR ligands [59]. As discussed above, the primary receptor for β -glucans is Dectin-1, a CLR that transduces signals via spleen tyrosine kinase (Syk) activation and PKC δ , ultimately activating the NF- κ B and mitogen-activated protein kinase (MAPK) pathways [60-62]. CARD9-deficient

mice have an impaired immune response to systemic challenge with *C. albicans*, with accelerated mortality and higher organ fungal burdens compared to heterozygous littermates [59]. CARD9 defects in humans were first reported in a large consanguineous Iranian family with CMC and peripheral dermatophytosis [63]. CARD9 deficiency results from a homozygous point mutation, Q295X, on chromosome 9q leading to a premature stop codon and loss-of-function. The mutation was not found in healthy family members or 230 healthy unrelated controls. Patients with this defect have low proportions of IL-17A-producing T cells and an almost complete defect in the generation of a Th17 response. The phenotype in CARD9-deficient patients is distinct from that of other genetic causes of CMC in that it also includes susceptibility to invasive candidiasis. Three of eight affected family members died of central nervous system candidiasis. The fact that the phenotype seems to be so severe compared to the Dectin-1-deficient cohort suggests that other CARD9-utilizing CLR, such as Dectin-2 and/or Mincle, are equally or more important for anti-*Candida* immunity.

Other causes of chronic mucocutaneous candidiasis

There are additional causes of human CMC with defects in known pathways, many of which can be readily linked to Th17. Inborn errors of NF- κ B activation, known as I κ B α deficiency, can cause this disease. IL-17 activates NF- κ B directly [64,65], as do the CLR that bind fungal cell wall components and promote Th17 development. Deficiency in NF- κ B activity leads to severe impairment in T-cell receptor signaling and susceptibility to CMC [65]. Consistently, non-specific inherited defects in T-cell immunity, including DiGeorge syndrome and severe combined immunodeficiency (SCID), are associated with susceptibility to CMC [14]. HIV/AIDS patients are extremely susceptible to oral candidiasis, which is linked to reduced CD4⁺ T-cell counts. Recent data indicate that Th17 cells are lost preferentially during HIV infection, perhaps explaining the specific array of opportunistic infections associated with AIDS [66]. Non-specific immunosuppression secondary to cancer chemotherapy or immunosuppressive agents also increases susceptibility to CMC [15].

Some secondary conditions not directly related to T cells or IL-17 also predispose to CMC, such as hyperglycemia or long-term use of broad-spectrum antibiotics [67,68]. Moreover, the salivary gland plays a critical role in oral mucosal immunity. CMC is prevalent in individuals with dentures, with salivary defects such as Sjögren's syndrome, following head or neck radiation therapy or with drugs causing xerostomia [67]. We recently showed that HIES patients have defective

salivary killing activity towards *C. albicans*, associated with reduced levels of antimicrobial peptides such as defensins and salivary histatins [44]. Although IL-17 can signal directly on salivary gland acinar cells [44], these defects may also be independent of the IL-17 pathway.

Biologic therapies and chronic mucocutaneous candidiasis

The increased understanding of the Th17-IL17 axis in the pathogenesis of autoimmune conditions has given rise to new classes of biologics. In addition to currently available agents that broadly target inflammatory cytokines or T-cell activation, newer drugs with specificity for Th17 effector cytokines (IL-17, IL-21, IL-22) and inhibitors of signaling molecules important for Th17 cell activation are currently in early clinical trials [69]. The rise of these agents brings to the forefront the important question of susceptibility to CMC in patients receiving more targeted biologic therapies. Currently approved agents have thus far not been associated with susceptibility to CMC [70,71]. Cumulative data demonstrate that the primary susceptibilities are to *Mycobacterium tuberculosis*, (presumed) bacterial sino-pulmonary infections, *Histoplasma capsulatum* and JC virus (all associated with TNF α -inhibitors) [72,73]. Surprisingly, IL-1 receptor antagonists, IL-6 receptor antagonists and CTLA4 agonists are not associated with increased infectious risk compared with placebo (although there is trend toward susceptibility) [71,74]. Additionally, antibodies against the shared IL-12/23p40 subunit are associated with a slightly increased risk for (presumed bacterial) sino-pulmonary infections, but not for CMC [75-78]. Similarly, newer agents, which inhibit the JAKs and Syk, are associated with increased risk of (presumed bacterial) sino-pulmonary infections, but not CMC [79,80]. This is perhaps somewhat surprising, since the JAKs, STATs and Syk are all important for induction of Th17 cells downstream of multiple cytokines and/or PRRs. Although the cumulative clinical trial evidence suggests that biologics do not confer susceptibility to CMC, it is important to bear in mind that with their increased use, biologics may be found to increase susceptibility to CMC in patients with otherwise subclinical mucosal *Candida* colonization. This may especially be true when biologics are coupled with other predisposing factors (for example, corticosteroid use). The results of on-going large scale phase 4 studies may identify a subset of patients with a propensity to develop CMC that would benefit from prophylaxis with anti-fungal agents.

Perspectives

In the past several years, many causes of isolated CMC and CMC associated with other abnormalities have been elucidated. Combined with the recent work on IL-17 and

Th17 cells in mice, this has led to an expanded understanding of the mechanism of host defense from *C. albicans* at mucosal surfaces and the role of IL-17 in immunity from infection. IL-17 is essential for normal resistance to *Candida* infection in the oral mucosa, vagina mucosa, skin and nails. The normal functioning of the immune defense requires intact PRRs, including Dectin-1, and signal transduction, including CARD9. Th17 cells are generated and maintained, which requires normal IL-23 signaling (that is, normal *IL12B* and *IL12RB1* gene products). Signal transduction requires normal STAT1 (no gain-of-function) and normal STAT3 (no loss-of-function) activity. Finally, IL-17 and IL-17R are functional without the presence of blocking antibodies (Figure 1).

Use of biologic therapy to treat autoimmune diseases and diseases of abnormal inflammation has been on the rise. Some adverse effects of these medications are known based on vigorous clinical trials, but others can be extrapolated from an expanded understanding of the complex mechanisms of the immune system. In the case of therapy targeting the IL-17 pathway, increased susceptibility to CMC should be anticipated. Prompt recognition and treatment of symptoms of mucocutaneous candidiasis are likely to increase the tolerability and safety of these medications. Some patients with recurrent issues may further benefit from antifungal prophylaxis. Prophylaxis could likely be targeted at mucosal surfaces, since disseminated or invasive candidiasis is rarely seen in patients with isolated defects in IL-17 signaling or CD4 deficiency. However, increased risk of candidiasis, potentially even disseminated disease, may occur in patients on combination immunosuppressive therapy. For example, IL-17 blockade could increase the rate of asymptomatic colonization without signs of overt disease. With the addition of therapeutic agents targeting other segments of the immune system, asymptomatic colonization predisposes patients to invasive disease. Consequently, careful consideration of the cumulative risk for fungal infections is warranted.

This article is part of the series on *Adult immunodeficiency*, edited by Hans-Hartmut Peter. Other articles in this series can be found at <http://arthritis-research.com/series/immunodeficiency>

Abbreviations

APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; APS, autoimmune polyendocrinopathy syndrome; CARD, caspase recruitment domain-containing protein; CLR, C-type lectin receptor; CMC, chronic mucocutaneous candidiasis; CTLA, cytotoxic T-lymphocyte-associated antigen; DOCK, deficient in dedicator of cytokinesis; GRO, growth-regulated oncogene; HIES, hyper-IgE syndrome; IFN, interferon; IL, interleukin; IL-17R, IL-17 receptor; JAK, Janus kinase; MSMD, Mendelian susceptibility to mycobacterial diseases; NF, nuclear factor; PRR, pattern recognition receptor; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase; Th, T helper; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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