Inborn errors of mucocutaneous immunity to *Candida albicans* in humans: a role for IL-17 cytokines?

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Abstract

The various clinical manifestations of chronic mucocutaneous candidiasis (CMC) often result from acquired T-cell immunodeficiencies. More rarely, CMC results from inborn errors of immunity, the recent dissection of which has shed light on the molecular mechanisms of mucocutaneous immunity to *Candida albicans*. CMC may accompany various other infectious diseases in patients with almost any broad and profound T-cell primary immunodeficiency. By contrast, CMC is one of the few key infections in patients with autosomal dominant hyper IgE syndrome (mutations in *STAT3*), and in rare patients with autosomal recessive predisposition to mucocutaneous and invasive fungal infections (mutations in *CARD9*). In patients with mutations in *STAT3* and *CARD9*, the development of IL-17-producing T cells is impaired. Moreover, CMC is the principal, if not only infection in patients with autosomal recessive autoimmune polyendocrinopathy syndrome-I (mutations in *AIRE*). Patients with this condition have high titers of neutralizing autoantibodies (auto-Abs) against the IL-17 cytokines IL-17A, IL-17F, and IL-22. Collectively, these data suggest that human IL-17A, IL-17F, and IL-22 are essential for mucocutaneous immunity to *Candida albicans*. They also suggest that the distinct syndrome of isolated CMC, without auto-immunity or other infections, may be caused by inborn errors of IL-17 immunity.

Introduction

Candidiasis, one of the most frequent fungal diseases in humans, is generally caused by *Candida albicans* ~~[1]~~. This fungus is a commensal organism of the oro-gastrointestinal tract and the vulvovaginal cavity. However, in some individuals, *C. albicans* causes disease, either by infecting mucosal and epidermal surfaces (mucocutaneous candidiasis, which is typically chronic) or, more rarely, by disseminating in the blood (systemic candidiasis, which is typically acute) [2~~,3~~]. Patients with inherited or acquired disorders of granulocytes usually present systemic candidiasis, whereas patients with inherited or acquired disorders of T lymphocytes develop chronic mucocutaneous candidiasis (CMC) ~~[3-5]~~[4,5]. Various alterations of the internal (e.g. a central line) or peripheral (e.g. xerostomy) milieu may also predispose to invasive or mucocutaneous CMC. CMC is highly heterogeneous clinically, with recurrent and/or persistent infections of the upper gastro-intestinal mucosa, skin, and nails with *C. albicans*, which may respond poorly to anti-fungal treatment or relapse upon discontinuation of treatment [2,6]. The mucocutaneous lesions are not themselves life-threatening, but they have been associated with intracranial aneurisms in several patients with CMC, at least in patients with isolated, unexplained CMC [7-9].

CMC is usually associated with many other, frequently more severe infections, particularly in patients with broad and profound inherited or acquired T-cell immunodeficiencies. Oropharyngeal infections with *Candida* species are commonly found in HIV-infected individuals [~~10,~~11]. Persistent oral candidiasis and other mucocutaneous fungal infections are also often observed in infants with severe combined immunodeficiency (SCID) [12-~~16~~]{Casanova, 2007 #495}. T cells therefore play a critical role in protective immunity against mucocutaneous *C. albicans* infections ~~[14,15,17]~~. By contrast, CMC is a prominent

feature of hyper IgE syndrome (HIES), a complex primary immunodeficiency characterized by high levels of serum IgE, severe atopic dermatitis, connective tissue and skeletal abnormalities, recurrent skin and lung infections caused by *Staphylococcus aureus*, and CMC [18]. The typical form of HIES is autosomal dominant (AD) and caused by dominant-negative mutations in *STAT3* [19,20]. A related syndrome without developmental features and with very mild CMC has been documented in a patient with autosomal recessive TYK2 deficiency [21].

CMC is also an important infectious phenotype in the rare patients displaying susceptibility to mucocutaneous and systemic fungal infections who carry autosomal recessive mutation~~s~~ in *CARD9* [22]. It remains unclear whether ~~dectin~~Dectin-1 deficiency is the cause of a predisposition to fungal infections, including CMC [23]. CMC may also strike patients not prone to invasive candidiasis and normally resistant to most other infectious agents, including other fungi. Such patients include those with autoimmune polyendocrine type I syndrome (APS-I, also known as autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy, APECED) [24] and patients with CMC and thyroid diseases [25]. APS-I results from autosomal recessive mutations in the autoimmune regulator gene *AIRE* [26]. In addition, other patients present with a distinct syndrome of isolated CMC, with no other severe infectious or autoimmune disorder [2,27,28]. Abnormalities of T-cell immunity to *C. albicans* have occasionally been reported in these patients, but no genetic etiology has yet been identified [2,6,29-34].

In recent years, the molecular pathogenesis of CMC in patients with primary immunodeficiencies has begun to be deciphered{Conti, 2010 #513}. This process has been facilitated by the development of ~~a~~ mouse model~~s~~ for CMC ~~[35]~~ and the discovery of IL-17

cytokines: IL-17A, IL-17F, IL-22 and IL-26 in humans [36,37]. Mouse IL-17 cytokines are essential for mucocutaneous immunity to *C. albicans* [5,38]. However, these cytokines are also essential for protective immunity to many other pathogens, including Gram-positive and Gram-negative bacteria, such as *Staphylococcus*, *Klebsiella* and *Salmonella*, in various tissues, including the respiratory and gastro-intestinal tracts [39-43]. Patients with mutations in *STAT3* have been shown to lack IL-17-producing circulating T cells [44-46]{Minegishi, 2009 #401; Renner, 2008 #511}, patients with mutations in *CARD9* have been shown to have significantly lower than normal proportions of IL-17-producing T cells [22] and patients with mutations in *AIRE* have high titers of neutralizing auto-Abs against IL-17 cytokines [47,48]. We review here the published studies of inborn errors of immunity conferring CMC, collectively identifying IL-17 cytokines as essential components of human mucocutaneous immunity to *C. albicans*.

AD-HIES syndrome

Cutaneous and pulmonary staphylococcal diseases affect most, if not all patients with AD-HIES, but CMC is the second most frequent presentation, affecting about 80% of AD-HIES patients [18,49-51] [18,49,51]. CMC generally manifests as oral thrush, onychomycosis, and/or vaginal candidiasis, cases of median rhomboid glossitis have also been reported [51]. Dermatophytosis has also been described in some patients. In 2007, dominant-negative mutations in the *STAT3* gene, encoding signal transducer and activator of transcription 3, were found to be responsible for AD-HIES [19,20]. STAT3 regulates multiple cytokine signaling pathways, including IL-6, IL-21, and IL-23, which are involved in the development of IL-17-producing T cells in mice [36,52,53]. Several groups investigated the presence of IL-17-producing T cells in STAT3-deficient patients with AD-HIES, based on the findings that mouse IL-17-producing T cells play a role in immunity to both systemic and mucosal *C.*

albicans infection [38,54,55], these T cells are involved in skin and mucosal host defense [56,57], and mouse STAT3-deficient $CD4^+$ T cells are unable to differentiate into IL-17-producing T cells [58]. ~~In~~ From2008 onwards, ~~three~~five ~~–~~studies documented an almost complete lack of circulating IL-17-producing T cells in patients heterozygous for *STAT3* mutations, as assessed *ex vivo* [44-46] {Minegishi, 2009 #401; Renner, 2008 #511} . T cells from PBMCs or naive $CD4^+$ T cells were unable to differentiate *in vitro* into memory $CD4^+$/IL-17^+ T cells in response to stimulation with various cytokines [44-46]. This lack of differentiation was associated with the impaired induction of RORγt mRNA upon stimulation of the patients' $CD4^+$ T cells, suggesting an intrinsic T-cell defect [44,45]. ~~Two studies~~Three studies reported a concomitant decrease in IL-22 production [45,46]{Minegishi, 2009 #401; Renner, 2008 #511}, whereas a ~~third~~ fourth did not [44]. The other IL-17 cytokines, IL-17F and IL-26, were not studied. The strong impairment of T-cell differentiation seemed to be specific to IL-17-producing T cells, although other lymphokines (such as IL-2 and IFN-γ) were also found to be affected, but to a lesser extent [44-46]. The proportion of circulating $CD4^+$/$CCR6^+$ T cells among PBMCs is low in AD-HIES patients, consistent with CCR6 being a marker of IL-17-producing T cells [59]. It is still unclear if TYK2 deficiency is associated with CMC, as a very mild form of mucocutaneous candidiasis was reported in the single TYK2-deficient patient described so far. IL-17-producing T cells were not evaluated in this patient {Minegishi, 2006 #456}. In any event, t~~T~~he identification of the genetic basis of AD-HIES ~~thus~~ paved the way for cellular and molecular dissection of the pathogenesis of its associated CMC phenotype.

IL-12p40 and IL-12Rβ1 deficiencies

Another study showed that IL-12p40- and IL-12Rβ1-deficient patients, displaying a lack of production and of response, respectively, to both IL-12 and IL-23 have smaller proportions of

circulating IL-17-producing T cells than normal individuals, but that this deficiency is much milder than that in patients with AD-HIES [46]. IL-12p40- and IL-12Rβ1-deficient patients typically suffer from the syndrome of Mendelian susceptibility to mycobacterial diseases (MSMD), which has been historically recognized and characterized on the basis of selective predisposition to mycobacteria and *Salmonella* in otherwise healthy children and adults ~~[60-63]~~ [62,63].. Nevertheless, it recently became apparent that about 25% of IL-12p40- and IL-12Rβ1-deficient patients also suffer from mild signs of CMC (but not dermatophytosis), even when not clinically ill from other infections or on antibiotic treatment ([64], Carlos Rodriguez-Gallego *et al.* manuscript in preparation). This mild and surprising phenotype may be partly accounted for by the small proportion of IL-17-producing T cells in these patients, itself probably resulting from the abolition of signaling by IL-23, an important IL-17-inducing cytokine in the mouse model ~~[65]~~ (reviewed in {Conti, 2010 #513}). This is consistent with the apparent lack of CMC in other patients with MSMD and mutations impairing cellular IFN-γ responses [62]. The lack of overt staphylococcal disease in IL-12p40- and IL-12Rβ1-deficient patients, by contrast to the situation observed in AD-HIES patients, may be due to the presence of a sufficiently high proportion of IL-17-producing T cells in IL-12p40- and IL-12Rβ1-deficient patients. The almost complete lack of IL-17-producing T cells in patients heterozygous for *STAT3* may therefore account for the susceptibility of these patients to both staphylococcal disease and CMC, the two key infections in such patients. This susceptibility may involved impairment of the recruitment of granulocytes to infected tissues and their activation, and of the induction of antimicrobial peptides in epithelial cells [42]. Consistent with this hypothesis, epithelial cells in the skin and lungs, the organs most frequently affected by staphylococcal disease and CMC in STAT3-deficient patients, have been shown specifically to require IL-17 stimulation for the induction of antimicrobial target genes [42,66].

CARD9 deficiency

Caspase recruitment domain-containing protein 9 (CARD9) is an adaptor acting downstream from C-type lectin receptors, such as Dectin-1 [67,68]. Dectin-1 recruits and activates the spleen tyrosine kinase SYK [69]. The Dectin-1/SYK complex then engages CARD9, promoting pro-inflammatory cytokine production by dendritic cells, thereby inducing the differentiation of T cells into IL-17-producing T cells [70]. Card9-deficient mice are susceptible to systemic *C. albicans* infection [68] and fail to mount a *Candida*-specific IL-17-producing T-cell response [70]. In humans, autosomal recessive CARD9 deficiency (Q295X allele) was recently reported in a large multiplex Iranian kindred with CMC (oral and/or vaginal candidiasis), dermatophytosis, and invasive candidiasis, causing the death of at least two, and possibly three of the eight patients with proven or probable CARD9 deficiency [22]. No history of severe bacterial or viral infection was reported. Heterozygous family members were healthy. CARD9 expression was not detected in homozygous patients and the mutant allele was shown to be loss-of-expression when used to transfect bone marrow-derived macrophages from Card9-deficient mice. Moreover, the expression of wild-type but not mutant human *CARD9* restored Dectin-1 signaling in Card9-deficient cells. Patients also displayed significantly smaller than normal proportions of IL-17-expressing T cells [22], suggesting that CARD9 is involved in the maturation of T cells for IL-17 cytokine production. The much greater severity of CARD9 deficiency than of Dectin-1 deficiency (see below) suggests that the pathogenesis of mucosal and systemic fungal infections in CARD9 deficiency involves receptors other than Dectin-1, such as Dectin-2, MINCLE, OSCAR, TREM-1 and, possibly, other as yet unknown receptors [71-74]. TLRs are unlikely to play a major role, as IRAK4- and MyD88-deficient patients do not present even mild forms of CMC ~~[75-78]~~ [76,78]. Overall, CARD9 deficiency is essentially an autosomal recessive trait

conferring a predisposition to dermatophytosis and candidiasis, including both the mucocutaneous and systemic forms, possibly due, at least partly, to impaired IL-17 cytokine production. The presence of a sufficiently high proportion of IL-17-producing T cells may account for the lack of staphylococcal disease, and invasive candidiasis may involve other mechanisms in these patients. Finally, it is tempting to speculate that the association of CMC with low proportions of IL-17-producing T cells in STAT3-, IL-12Rβ1-, and CARD9-deficient patients may pave the way for treatment of CMC in these and possibly other patients with recombinant IL-17 cytokines.

DECTIN-1 deficiency?

Dectin-1, a C-type lectin cell-surface receptor expressed, in particular, by myeloid and epithelial cells, serves as a receptor for β-glucans, a major component of the yeast cell wall [79]. *C. albicans* recognition by Dectin-1 induces, via SYK and CARD9, the production of pro-inflammatory cytokines, thereby promoting the differentiation of naive T cells into cells producing IL-17 cytokines [70]. Dectin-1-deficient mice were shown to be susceptible to systemic *C. albicans* infection in one study [80] but not in another [81]. Recently, three human adult siblings with onychomycosis caused by *Trichophyton rubrum* (dermatophytosis) and vulvovaginitis caused by *C. albicans* were reported to be homozygous for a loss-of-expression and loss-of-function *DECTIN1* allele (Y238X) [23]. This appears to be a mild form of CMC, as vulvovaginitis caused by *Candida* is common in the population. The syndrome is apparently dominant or co-dominant, as the heterozygous parents had a milder, but similar clinical phenotype. A causal relationship between the *DECTIN1* genotype and both the expression of Dectin-1 and the cellular responses to stimulation of this receptor with β-glucan or *C. albicans* has been established. In particular, heterozygous cells have a response profile intermediate between those of wild-type and Y238X-homozygous cells. Interestingly,

the induction of IL-17-producing T cells is impaired in some experimental conditions, including stimulation with *C. albicans*. By contrast, the phagocytosis or killing of *C. albicans* by Dectin-1-deficient monocytes and granulocytes has been shown to be normal. However, no causal relationship between *DECTIN1* homozygosity or heterozygosity and the clinical phenotypes of vulvovaginitis and onychomycosis has been demonstrated. Indeed, the Y238X *DECTIN1* allele is a common polymorphism, with a frequency of around 7% in European populations and of up to 40% in the San population of South Africa ([23] and http://hapmap.ncbi.nlm.nih.gov/). In the absence of a population-based study, it is therefore premature to attribute any role to this mutant *DECTIN1* allele in terms of host defenses against fungi, including *C. albicans* in particular. Further studies are required to determine whether Dectin-1 deficiency is a genetic etiology of CMC and/or other fungal diseases. In the mean time, it is premature to consider Dectin-1 deficiency as a *bona fide* primary immunodeficiency. In any event, even if Dectin-1 deficiency could be shown to confer a predisposition to fungal infections, as a dominant, co-dominant, or recessive trait, its clinical penetrance would be low. The available data show that Dectin-1 is largely redundant for protective immunity to fungi in human populations.

APECED/APS-I syndrome

APS-I/APECED is a rare autosomal recessive syndrome characterized by multiple autoimmune polyendocrinopathies, such as hypoparathyroidism and adrenal failure [82,83]. The genetic etiology of APS-I was identified in 1997, with mutations in the autoimmune regulator (AIRE)-encoding gene [84,85]. AIRE governs a T-cell tolerance pathway, by inducing the production, in the thymus and peripheral lymphoid organs, of transcripts encoding proteins normally present in various peripheral tissues [83,86], thereby triggering the deletion of autoreactive T cells. Human AIRE deficiency therefore results in

overwhelming auto-immunity. Intriguingly, up to 90% of APECED patients develop early-onset CMC. In 2006, high levels of neutralizing IgG auto-Abs against IFN-α and IFN-ω were found in APS-I patients [87]. These auto-Abs were unlikely to predispose the patients to CMC, as patients with STAT1 deficiency and impaired responses to IFN-α/β and patients with NEMO, UNC-93B or TLR3 deficiencies and impaired production of IFN-α/β ~~[88-92]~~ [91] do not present CMC. No more than mild manifestations of oral candidiasis were observed in the only known TYK2-deficient patient, whose cellular defects are not restricted to the IFN-α/β pathway [21]. In turn, the lack of severe viral diseases in APS-I patients probably reflects the compensatory role of other anti-viral IFNs. These studies nonetheless led two groups to detect high titers of neutralizing IgG auto-Abs against IL-17A, IL-17F and/or IL-22 (but not IL-26) in the plasma of almost 200 patients tested [47,48]. No such Abs were found in the plasma of the 90 healthy individuals, 54 unaffected heterozygous patients' relatives and almost 200 other patients with other autoimmune/endocrine disorders tested. Auto-Abs against all other cytokines tested, including those known to cause distinct clinical syndromes, such as IL-6, IFN-γ, and GM-CSF [93-97], were undetectable. Remarkably, two patients with thymoma and CMC were found to have auto-Abs against IL-17 cytokines [48], unlike patients with thymoma without CMC, suggesting that the auto-Abs against IL-17 cytokines were responsible for the CMC. Moreover, auto-Abs were found in some patients with APS-I but without CMC, and even before the onset of CMC in some cases, suggesting that these auto-Abs are probably a cause rather than an effect of CMC. However, although correlative [98], the high titers of neutralizing auto-Abs against IL-17 cytokines in APS-I patients are probably sufficient to account for CMC. Clearly, these findings pave the way for the treatment of CMC in these patients with B cell-depleting, CD20-specific monoclonal Abs. Immunosuppression was used reluctantly in APS-I patients, in part because of the fear to aggravate CMC. The discovery that CMC has an auto-immune basis suggests that

immunosuppression, CD20 mAbs in particular, may actually improve CMC along with other auto-immune phenotypes in these patients. Interestingly, IL-17 cytokines are thought to be key auto-immune cytokines in the mouse model. The multiple and severe auto-immune phenotypes in APS-I patients develop despite neutralizing auto-Abs to IL-17 cytokines, indicating paradoxically that multiple auto-immune phenotypes are IL-17-independent, and implying that neutralization of IL-17 in patients without APS-I and with these or even possibly other auto-immune phenotypes may not be beneficial. Nevertheless, the treatment of APS-I patients with CD20 Abs and the ensuing recovery of IL-17 immunity might reveal new auto-immune phenotypes, which conversely may be IL-17-dependent and good targets for anti-IL-17 therapy in patients without APS-I.

Conclusion

Three human inborn errors of immunity (AD-HIES, CARD9 deficiency, and APS-1) are associated with CMC as a key infectious phenotype. Patients with AD-HIES are also vulnerable to other infections, including staphylococcal disease in particular, and patients with CARD9 deficiency are vulnerable to systemic candidiasis, whereas CMC seems to be the only infection of note in patients with APS-I. In patients with these three disorders, the pathogenesis of CMC seems to involve impaired IL-17 immunity, involving IL-17A, IL-17F, and/or IL-22. This conclusion is strongly correlative, but further human genetic studies are required to document the collective and individual impact of IL-17 cytokines in host defense. The investigation of patients with isolated CMC, with no other autoimmune or infectious phenotype, may be rewarding [34]. No genetic etiology has yet been identified in patients with isolated CMC. Definitive proof of the role of IL-17 cytokines in immunity to *C. albicans* infection must await the identification of patients with isolated CMC and inherited disorders specifically affecting IL-17 immunity [99~~,100~~].

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Figure legend. Inborn errors of mucocutaneous immunity to *Candida albicans* in humans

The recognition of *C. albicans* by myeloid and epithelial receptors induces the production of pro-inflammatory cytokines. One such pathway is triggered by the Dectin-1-mediated recognition of the *C. albicans* cell wall component β-glucan, and is mediated by SYK and CARD9, which is also essential for other pathways (DECTIN-2, MINCLE, TREM-1, NOD etc). Pro-inflammatory cytokines, such as IL-6 and IL-23, activate T lymphocytes via STAT3, which induces production of the transcription factor ROR-γt and T-cell differentiation into IL-17-producing T cells. These T cells express the skin and mucosa homing receptors CCR4 and CCR6, and secrete IL-21 and the IL-17 cytokines IL-17A, IL-17F, IL-22, and IL-26. These cytokines act locally to activate epithelial cells and to induce the recruitment and activation of granulocytes (e.g. by inducing anti-microbial peptides, such as β-defensins), thereby helping to clear the fungal infection. In patients with autosomal recessive CARD9 deficiency (pink), autosomal dominant STAT3 deficiency (blue), or in patients with autosomal recessive APS-I (mutations in AIRE, not represented here) with high titers of neutralizing autoantibodies against IL-17A, IL-17F, and IL-22 (purple), IL-17-mediated immunity is impaired, probably

accounting for the greater susceptibility of these patients to CMC. It will not be possible to confirm this conclusion until CMC-causing mutations are found in the genes encoding individual IL-17 cytokines or their receptors.

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