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Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis

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Abstract

Purpose of review—Chronic mucocutaneous candidiasis (CMC) is characterised by recurrent or persistent symptomatic infection of the nails, skin and mucosae mostly by *Candida albicans*. CMC is common in patients with profound primary T-cell immunodeficiency, who often display multiple infectious and autoimmune diseases. Patients with syndromic CMC, including autosomal dominant (AD) hyper IgE syndrome (HIES) and autosomal recessive (AR) autoimmune polyendocrinopathy syndrome type I (APS-I), display fewer other infections. Patients with isolated CMC (CMCD) rarely display any other severe disease. We review here recent progress in the genetic dissection of these three types of inherited CMC.

Recent findings—Low IL-17 T cell proportions were reported in patients with AD-HIES bearing heterozygous *STAT3* mutations, prone to CMC and staphylococcal diseases, and in a kindred with AR CARD9 deficiency, prone to CMC and other fungal infections. High levels of neutralising autoantibodies against IL-17 cytokines were documented in patients with APS-I presenting with CMC as their only infectious disease. The first three genetic aetiologies of CMCD were then reported: AR IL-17RA and AD IL-17F deficiencies and AD STAT1 gain-of-function, impairing IL-17-producing T cell development.

Summary—Inborn errors of human IL-17 immunity underlie CMC. Impaired IL-17 immunity may therefore account for CMC in other settings, including patients with acquired immunodeficiency.

Keywords

Primary immunodeficiencies; chronic mucocutaneous candidiasis; interleukin-17 immunity; *Candida albicans*

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Introduction

Chronic mucocutaneous candidiasis (CMC) is characterised by recurrent or persistent symptomatic mucocutaneous infections caused by fungi of the genus *Candida*, mostly the commensal *Candida albicans*, affecting the nails, skin, and oral and genital mucosae (1–5). CMC is frequent in newborns and children (6) and is also common in patients with broad and profound quantitative or qualitative, acquired or inherited T-cell deficiencies, in whom it manifests principally as severe recurrent oral candidiasis (7–10). Severe oropharyngeal candidiasis remains common in HIV-infected patients and was the most frequent opportunistic fungal infection in these patients before the introduction of effective antiretroviral treatments (7, 11). It is also seen in patients on immunosuppressive, antibiotic or steroid treatments (1). Patients with primary immunodeficiencies (PIDs) affecting T cells, including severe combined immunodeficiency (SCID) (12) and combined immunodeficiencies (CIDs) (12, 13), are also prone to CMC. However, in these PIDs, CMC is only one of many infections to which patients are susceptible and there may also be other clinical signs, such as autoimmunity. By contrast, CMC is the principal or only infectious disease frequently observed in patients with autosomal dominant hyper IgE syndrome (AD-HIES), who also display severe skin and pulmonary staphylococcal disease, bearing dominant negative mutations of the *STAT3* transcription factor gene (14), and in patients with autosomal recessive autoimmune polyendocrinopathy syndrome type I (AR APS-I) due to *AIRE* mutations, who are not susceptible to any other infectious disease (3). Finally, CMC has been reported together with dermatophytosis and *Candida* meningitis in the only family with CARD9 deficiency identified to date (15). We will refer to these three conditions as “syndromic CMC” below.

Some patients with CMC have no other prominent, overt clinical manifestations (1, 2, 4). This rare condition (about 1/100,000 individuals) is often referred to as CMC disease (CMCD) (OMIM 114580, 607644, 212050, 613953, 613956). The first sporadic cases were described in the 1960s and the first familial cases, typically with segregation as an AD trait or, more rarely, as an AR trait in some consanguineous families, were reported in the 1970s (16–19). Over the next 40 years, other sporadic and familial cases were reported (15, 20–60), suggesting that CMCD results from single-gene lesions in at least some patients. Invasive candidiasis (15, 34), dermatophytosis (25, 26), bacterial infections of the respiratory tract and staphylococcal diseases of the skin (32, 33, 61) have been reported in a few patients. In addition, some patients with CMCD display thyroid autoimmunity (2, 22, 27, 35, 38, 45, 54, 56–58). Finally, CMCD is generally debilitating, but may also be life-threatening, due to the associated risks of oral or oesophageal squamous cell carcinoma (20, 30, 50, 54, 56) and cerebral aneurysm (31, 36, 37, 49, 56). However, no robust immunological phenotype has emerged from the many studies carried out, despite the large number of patients with CMCD reported (1, 2, 21, 28, 29, 33, 39, 41, 44, 51, 53, 62–69). Various immunological treatments were proposed in the 1970s (18, 22, 70–74) but, from the 1980s onwards, with the advent of antifungal agents, research into CMCD declined, probably accounting for the paradoxical lack of published reports on the clinical features of patients with CMCD. We review here recent progress in the genetic dissection of the primary T-cell deficiencies underlying CMC, syndromic CMC, and CMCD.

1. CMC associated with primary T-cell immunodeficiencies

Patients with SCID lack autologous T cells and are highly vulnerable to a broad range of microorganisms, including *C. albicans* in particular. Indeed, severe oropharyngeal candidiasis is common in these patients (8–10, 12, 63). Patients with CIDs and impaired T-cell development and/or function are also often prone to CMC, although they generally also develop other often more severe infectious diseases (12). CMC has been reported in patients with AR CD25 deficiency, who have low T-cell counts and are highly susceptible to viral

and bacterial diseases, persistent oral thrush and *Candida* esophagitis (75, 76). It has also been found in patients with X-linked recessive (XR) NEMO disorders or autosomal dominant (AD) IκBα disorders, both of which result in a complex PID conferring susceptibility to invasive encapsulated pyogenic bacterial and environmental mycobacterial infections, in particular (77). CMC has also been reported in patients with AR DOCK8 deficiency, a severe CID associated with recurrent viral and bacterial infections (78, 79), impaired T-cell activation and low IL-17-producing T-cell counts (80, 81) and in patients with AR TYK2 deficiency, which is associated with susceptibility to viral, intracellular and extracellular bacterial diseases (82). Patients with AR TCR-α deficiency, which is associated with susceptibility to viral and bacterial diseases, have also been reported to display CMC (83), and CMC has also been described in patients with AR ORAI1 deficiency, which is associated with severe viral, bacterial, mycobacterial and fungal infections (84), in patients with AR MST1 deficiency, which is associated with recurrent bacterial and viral infections (85) (Crequer A., manuscript in preparation) and in patients with AR IRF8 deficiency, most of whom present severe mycobacterial disease (86). Finally, CMC has been documented in more complex T-cell disorders (13). By contrast, PIDs not affecting T-cell number and/or function, such as those affecting mostly B cells, phagocytes or complement, are not usually associated with CMC (13, 87). These findings demonstrate the essential role of human T cells in mucocutaneous immunity to *C. albicans*.

2. Syndromic CMC

CMC is one of the two main infectious diseases affecting patients with AD-HIES, bearing mutations in *STAT3*, the other being recurrent staphylococcal disease of the skin and lungs (14, 88). These patients have very small proportions of IL-17- and IL-22-secreting T cells, probably due to impaired STAT3-dependent signalling downstream from IL-6, IL-21 and/or IL-23 (Figure 1) (89–93), which have been shown to be essential for the differentiation or maintenance of Th17 cells in mice (94). An albeit smaller decrease in the proportion of IL-17 T cells was also observed in patients with AR IL-12p40 or IL-12Rβ1 deficiency, who suffer from Mendelian susceptibility to mycobacterial disease (MSMD) and, to a lesser extent, mild CMC, probably due to impaired IL-23 signalling (91, 95, 96) (Rodríguez-Gallego C., manuscript in preparation). A small proportion of IL-17-producing T cells was also found in the only kindred with AR CARD9 deficiency reported to date, some of the members of which presented CMC, superficial skin dermatophytosis and invasive candidiasis (meningitis) (15). As only one CARD9-deficient kindred has been reported, it would be premature to draw firm conclusions about the possible dependence of IL-17-producing T-cell development on CARD9. However, CARD9 is an adaptor that acts downstream from various receptors, including Dectin-1, Dectin-2, and MINCLE, which can recognise *C. albicans* (Figure 1) (97). The observed IL-17-producing T-cell deficiency may thus result from defects in the production of cytokines promoting IL-17-producing T-cell development or maintenance upon fungal recognition (98, 99). Isolated CMC with an unclear mode of inheritance was reported in a family bearing the Y238X mutation of the *Dectin1* gene with apparent impairment of IL-17 production (52). However, this variation is too frequent (7% in Europeans and up to 40% in the South Africa San population) to be considered disease-causing in AR, AD or codominance models. Finally, high levels of neutralising autoantibodies directed against IL-17A, IL-17F and/or IL-22 have been found in the plasma of patients suffering from AR APSI, in which CMC is the only major infection (Figure 1) (100–102). Together, these findings strongly suggest that impaired IL-17 immunity may underlie CMC (Figure 1) (5).

3. “Isolated” CMC or CMCD

This clinical entity usually begins early in infancy and affects otherwise healthy individuals (1, 2, 4, 5). However, some patients also display mild staphylococcal infections of the skin,

albeit less severe than those observed in AD-HIES patients (32, 33, 61), fungal diseases (e.g. dermatophytosis) (25, 26), recurrent herpes virus disease (59) or autoimmune diseases (e.g. thyroid autoimmunity), albeit less severe than that observed in APS-I patients (2, 22, 27, 35, 38, 45, 54, 56–58). The clinical boundaries of this entity have still not clearly described in a large series of patients. The molecular study of these patients led, in 2011, to the identification of the first three genetic aetiologies of CMCD, providing formal proof that IL-17 cytokines are crucial for mucocutaneous protection against *C. albicans* (103, 104). Complete AR IL-17R deficiency and the abolition of cellular responses to IL-17A and IL-17F homo- and heterodimers were observed in a single child born to consanguineous parents. This child displayed CMC, *S. aureus* skin abscesses and folliculitis (105). Partial AD IL-17F deficiency was discovered in a multiplex kindred displaying CMCD, with impaired cellular responses to IL-17F homo- and heterodimers containing the mutant protein (105). More recently, a patient presenting CMC alone was also reported to have a heterozygous mutation in *IL17F*, which has yet to be characterised (106). In the same year, heterozygous missense gain-of-function (GOF) mutations of *STAT1* were identified in patients displaying CMC, autoimmune manifestations and other mild bacterial or viral diseases, together with intracranial aneurysms or squamous cell carcinoma (56–58). In total, 13 heterozygous missense GOF *STAT1* mutations have since been reported, in 73 patients from 29 kindreds (56–60, 69, 103, 104). IL-17-producing T-cell development is impaired in these patients (56, 60, 69), probably due to enhanced STAT1-dependent cellular responses to IL-17-producing T-cell repressors, such as IFN-γ, IL-27 and IFN-α/β (107–120), and/or enhanced IL-6-, IL-21- and IL-23- STAT1 responses, which normally activate predominantly STAT3, to induce IL- 17 T-cell development (56, 104, 121–123). However, no genetic aetiology has yet been identified for a number of patients with CMCD.

Conclusion

It is almost 40 years since it was first suggested that CMCD was a PID, but the first three genetic aetiologies of this disease were not identified until last year. These experiments of Nature demonstrate the essential role of IL-17A and IL-17F in protective mucocutaneous immunity to *C. albicans* and, to a lesser extent, *S. aureus* in the nails, skin and oral and genital mucosae. These cytokines appear to be otherwise redundant in host defence against other common pathogens. However, description of the precise clinical features of a larger number of patients with inborn errors of IL-17 immunity is required, to determine the role of these cytokines with a greater degree of certainty. We will need to identify more patients with inborn errors of IL-17RA, IL-17F or GOF mutations in *STAT1* or other as yet unknown genetic disorders affecting IL-17 immunity to draw definitive conclusions concerning the impact of these genetic lesions on susceptibility to infection. Nevertheless, the studies carried out to date have already provided invaluable insight into the role of human IL-17 immunity in host defence *in natura* (124–129). They also suggest that the pathogenesis of CMC in settings other than CMCD, whether in inherited disorders or in acquired immunodeficiencies, such as AIDS, probably involves impaired IL-17 immunity. Finally, these studies have also had important clinical implications, as they have made it possible to offer genetic counselling to families with inherited CMC and have provided a rationale for developing new approaches to the treatment of CMC (e.g. treatment with IL-17, GM-CSF or G-CSF) (130) for families with inherited or acquired CMC, based on an understanding of the pathophysiology of human fungal diseases.

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Key points

- This article provides an overview on the recent molecular dissection of various primary immunodeficiencies with chronic mucocutaneous candidiasis (CMC) and of isolated CMC (CMCD).
- Altogether these studies have demonstrated the essential role played by human IL-17-mediated immunity in mucocutaneous protection against *C. albicans* and to a lesser extent *against S. aureus in natura.*
- The further genetic and immunological dissection of the pathogenesis of CMCD should delineate the function of various genes controlling IL-17 immunity, of genes only remotely involved in the IL-17 circuit, of genes not previously connected with IL-17, and even of genes governing circuits unrelated to IL-17.

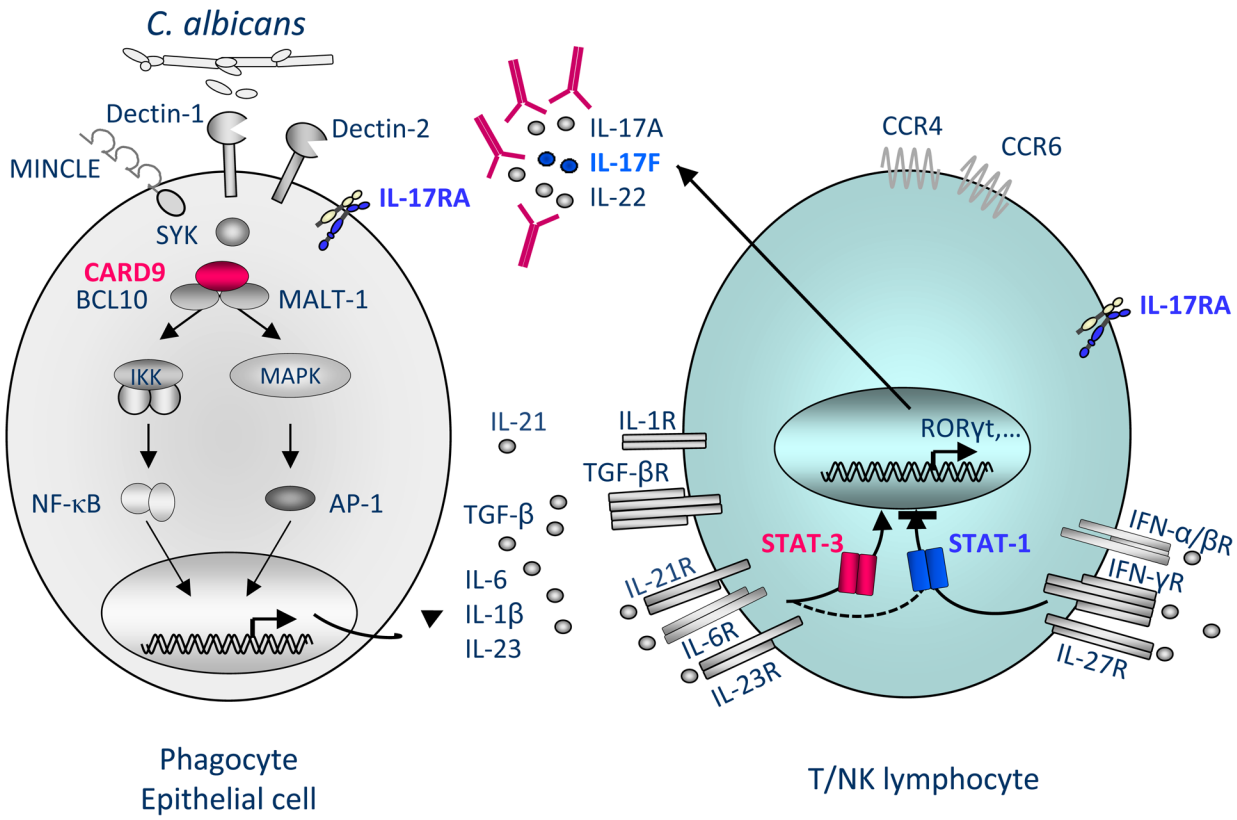

Figure 1. Inborn errors of IL-17 immunity underlie chronic mucocutaneous candidiasis

Schematic representation of IL-17 mediated immunity with the cooperation between cells recognizing *C. albicans* (phagocytes and epithelial cells) and IL-17 cytokine producing cells (T and innate lymphocytes). Upon *C. albicans* recognition by PRRs (pathogen recognition receptors, including Dectin-1, Dectin-2, or Mincle), the adaptor molecule CARD9 mediates the induction of pro-inflammatory cytokines by myeloid or epithelial cells, such as IL-1β, IL-6 and IL-23. Upon binding to their receptors expressed on T and innate lymphocytes, pro-inflammatory cytokines, such as IL-6 or IL-23, activate T lymphocytes via the transcription factor STAT3 resulting in their differentiation into IL-17-producing T cells. Patients with AR CARD9 deficiency (pink), AD STAT3 deficiency (pink), or AR AIRE deficiency (not represented here) with high levels of neutralizing autoantibodies against IL-17A, IL-17F and/or IL-22 (pink), suffer from syndromic CMC and display impaired IL-17 mediated immunity. Patients with AR IL-17RA or AD IL-17F deficiency and impaired IL-17 response or function, respectively, or with AD STAT1 gain-of-function and impaired development of IL-17 producing T cells suffer from CMCD (in blue).