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Clinical & Translational Immunology (2016) 5, e114; doi:10.1038/cti.2016.71
Australasian Society for Immunology Inc.
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REVIEW

Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity

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Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent or persistent infections affecting the nails, skin and oral and genital mucosae caused by *Candida* spp., mainly *Candida albicans*. CMC is an infectious phenotype in patients with inherited or acquired T-cell deficiency. Patients with autosomal-dominant (AD) hyper IgE syndrome (HIES), AD signal transducer and activator of transcription 1 (STAT1) gain-of-function, autosomal-recessive (AR) deficiencies in interleukin (IL)-12 receptor β1 (IL-12Rβ1), IL-12p40, caspase recruitment domain-containing protein 9 (CARD9) or retinoic acid-related orphan receptor γT (RORγT) or AR autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) develop CMC as a major infectious phenotype that is categorized as Syndromic CMC. In contrast, CMC disease (CMCD) is typically defined as CMC in patients in the absence of any other prominent clinical signs. This definition is not strict; thus, CMCD is currently used to refer to patients presenting with CMC as the main clinical phenotype. The etiology of CMCD is not related to genes that cause severe combined immunodeficiency or combined immunodeficiency, nor to genes responsible for Syndromic CMC. Four genetic etiologies, AR IL-17 receptor A, IL-17 receptor C and ACT1 deficiencies, and AD IL-17F deficiency, are reported to underlie CMCD. Each of these gene defects directly has an impact on IL-17 signaling, suggesting their nonredundant role in host mucosal immunity to *Candida*. Here, we review current knowledge focusing on IL-17 signaling and the genetic etiologies responsible for, and associated with, CMC.

Clinical & Translational Immunology (2016) **5,** e114; doi:10.1038/cti.2016.71; published online 2 December 2016

INTRODUCTION

Candida albicans is a ubiquitous fungus and commensal yeast in humans. It can occasionally be pathogenic causing oral thrush, intertrigo and genital candidiasis in healthy populations. However, in immunocompromised hosts, *Candida* can cause chronic mucocutaneous or invasive infections. Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent or persistent infections affecting the nails, skin and oral and genital mucosae caused by *Candida* spp., often *C. albicans*.[1,2] CMC is one of the infectious phenotypes in patients with inherited or acquired T-cell deficiencies.[3,4] These clinical observations demonstrate the pivotal role of T-cell immunity in host defense against superficial *Candida* infections. Recent studies have revealed that Th17 cells, together with other cells expressing retinoic acid-related orphan receptor γT (RORγT), such as γδT cells and group 3 innate lymphoid cells, produce interleukin (IL)-17 and have an essential role in host defense against mucocutaneous *Candida* infections in mice and humans.[2,3,5,6] In contrast, invasive fungal infections are also observed in patients with quantitative and/or qualitative disorders of neutrophils, such as chronic granulomatous disease (CGD), autosomal-recessive (AR) caspase recruitment domain-containing protein 9 (CARD9) deficiency and neutropenic conditions.[7,8]

Patients with autosomal-dominant (AD) hyper IgE syndrome (HIES), AD signal transducer and activator of transcription 1 (STAT1) gain-of-function (GOF), AR autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), or AR CARD9, IL-12 receptor β1 (IL-12Rβ1), IL-12p40 or RORγT deficiencies, develop CMC as one of the major infectious phenotypes associated with the other clinical and infectious manifestations.[2–4,6–18] These specific conditions are designated as Syndromic CMC (Table 1) and occur in association with impaired IL-17 immunity (Figure 1). Patients with AD HIES develop CMC and staphylococcal infections associated with other clinical manifestations, such as elevated serum IgE, characteristic facial features, pneumatocele and retained primary teeth. These patients have severely decreased frequencies of circulating IL-17A- and IL-22-producing T cells, probably associated with impaired STAT3-dependent signaling downstream of IL-6, IL-21 and/or IL-23.[15,17,19,20] The presence of CMC is also identified in one patient with AR HIES with *TYK2* mutation.[21] However, a follow-up study reported that the core clinical phenotype of TYK2 deficiency is

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Received 12 August 2016; revised 31 October 2016; accepted 2 November 2016

Table 1 Syndromic CMC and CMCD: clinical and immunological phenotype and molecular defects/genetic etiologies

Disease	*Frequency of CMC*	*Other infections*	*Associated symptoms*	*Immunological phenotype*	*Gene*	*Inheritance*	*Refs*
Syndromic CMC							
HIES	85%	*Staphylococcus*, *Aspergillus*	Eczema, scoliosis, pneumatocoele, hyperextensibility, dysmorphic facial features, retention of primary teeth	Increased serum IgE, eosinophilia, decreased IL-17-producing T cells	*STAT3*	AD	14,17,19,20,78
APECED	70–98%		Ectodermal dysplasia, autoimmune dysfunciton of parathyroid and adrenal glands, alopecia	Neutralizing antibodies against IL-17A, IL-17F and/or IL-22	*AIRE*	AR	9,23–25
CARD9 deficiency	35–86%		Dermatophytes, *Candida*, brain abscess	Decreased IL-17-producing T cells, impairment of *C. albicans*-killing by neutrophils	*CARD9*	AR	7,8,18,26
IL-12Rβ1 and IL-12p40 deficiency	6–25%	*Mycobacterium*, *Salmonella*		Decreased IL-17-producing T cells, impaired IL-12 signaling	*IL12RB1* *IL12B*	AR	10,11,16, 27–29
STAT1 gain-of-function	98%	Bacteria, viruses, fungi, mycobacteria	Aneurysm, autoimmune diseases, endocrine diseases	Decreased IL-17-producing T cells, decreased switched memory B cells	*STAT1*	AD	30–34,52–66
RORγT deficiency	6/7 (86%)	*Mycobacterium*	Lack of peripheral lymph node, thymic hypoplasia	Defect of MAIT, type 1 NKT, IL-17-producing T cells, impaired antigen-specific IFN-γ production	*RORC*	AR	12
CMCD							
IL-17RA deficiency	3/3 (100%)	*Staphylococcus*		No response to IL-17A, IL-17E and IL-17F	*IL17RA*	AR	38,72
IL-17RC deficiency	3/3 (100%)			No response to IL-17A and IL-17F	*IL-17RC*	AR	40
IL-17F deficiency	5/7 (70%)			Impaired IL-17F and IL-17A/F function	*IL17F*	AD	38,71
ACT1 deficiency	2/2 (100%)	*Staphylococcus*		No response to IL-17A, IL-17E, and IL-17F	*TRAF3IP2*	AR	39

Abbreviations: AD, autosomal-dominant; APECED, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; AR, autosomal-recessive; CARD9, caspase recruitment domain-containing protein 9; CMC, chronic mucocutaneous candidiasis; CMCD, CMC disease; HIES, hyper IgE syndrome; IFN-γ, interferon gamma; IL, interleukin; RORγT, retinoic acid-related orphan receptor γT.

mycobacterial and/or viral infections, with an association of CMC.[22] Patients with APECED present with CMC in addition to polyendocrinopathy and ectodermal dysplasia.[23,24] These patients produce neutralizing autoantibodies against IL-17A, IL-17F and/or IL-22, leading to development of CMC.[9,13,25] Neutralizing antibodies against these Th17-produced cytokines are also identified in patients with thymoma who develop CMC.[9] Patients with AR CARD9 deficiency develop CMC, deep dermatophytosis and invasive fungal infections.[7,8,26] They present with decreased frequency of circulating IL-17-producing T cells and impaired neutrophil-killing of *C. albicans*. Patients with AR IL-12p40 or IL-12Rβ1 deficiency develop Mendelian susceptibility to mycobacterial disease (MSMD), a primary immunodeficiency with selective host susceptibility to intracellular bacteria such as *Mycobacterium bovis* BCG, environmental mycobacteria and *Salmonella* that is associated with impaired IL-12-induced interferon gamma (IFN-γ) signaling.[27–29] These patients occasionally develop mild CMC and show decreased frequencies of circulating IL-17A- and IL-22-producing T cells as a result of impaired IL-23 responses.[10,16,17]

In 2011, AD STAT1-GOF was found to be responsible for CMC disease (CMCD), typically defined as CMC in patients without any other prominent clinical signs.[30,31] Subsequent studies revealed that AD STAT1-GOF is the major genetic etiology of CMCD, explaining more than half of all CMCD cases.[32–34] In the classification of primary immunodeficiency compiled by the Primary Immunodeficiency Expert Committee of the International Union of Immunological Societies, AD STAT1-GOF, together with four genetic etiologies directly related to defective IL-17 signaling, is categorized as CMC, which is often referred to as CMCD.[35,36] However, recent studies revealed that patients with GOF mutations in *STAT1* present with broad clinical manifestations, including bacterial, viral, mycobacterial and invasive fungal infections, autoimmune diseases, aneurysms and tumors.[33,34] Therefore, AD STAT1-GOF is categorized as Syndromic CMC in this review.

Recently, a new primary immunodeficiency due to biallelic mutations in *RORC*, encoding RORγ and RORγT, was identified (designated as AR RORγT deficiency).[12] RORγT is a master

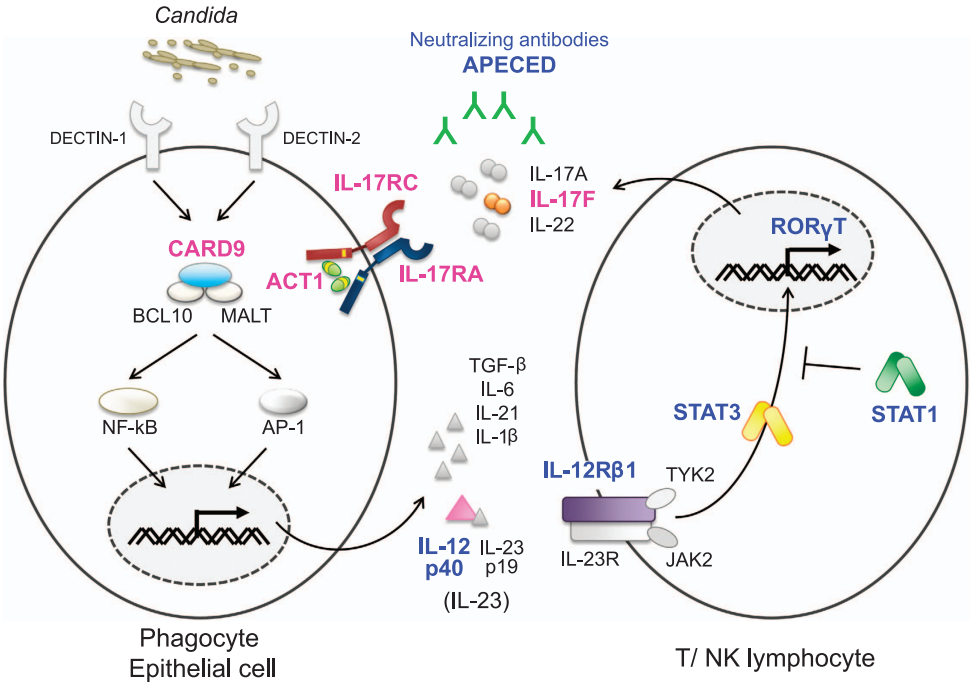

Figure 1 Inborn errors of IL-17 immunity. Phagocytes recognize *C. albicans* via pattern recognition receptors and produce proinflammatory cytokines, such as IL-6 and IL-23. These proinflammatory cytokines activate T cells via STAT3 and upregulate RORγT expression, leading to production of IL-17A, IL-17F and IL-22. Impairment in IL-23-induced STAT3-mediated signaling in AD HIES and AR IL-12Rβ1 and IL-12p40 deficiencies cause Syndromic CMC. Neutralizing autoantibodies against IL-17A, IL-17F and IL-22 in patients with APECED impair IL-17 signaling, underlying Syndromic CMC. Patients with AR RORγT deficiency show developmental defects of Th17 cells, resulting in Syndromic CMC. They also develop MSMD, probably caused by impairment of IFN-γ production associated with mycobacterial infections. AD STAT1 gain-of-function was originally identified as a genetic etiology of CMCD. However, it can be categorized as Syndromic CMC based on its broad clinical manifestations. The majority of patients with GOF-*STAT1* display a decreased frequency of IL-17-producing cells. Defects in four genes (encoding IL-17F, IL-17RA, IL-17RC and ACT1) that are directly involved in IL-17 signaling have been identified in patients with CMCD. Blue: Syndromic CMC-related molecules and neutralizing antibodies (APECED). Magenta: CMCD-related molecules.

transcription factor of Th17 cells; thus, these patients showed a markedly decreased frequency of circulating IL-17A- and IL-22-producing T cells, which probably underlies the CMC seen in these patients. Surprisingly, all RORγT-deficient patients also developed MSMD, probably because of the impairment of IFN-γ production associated with mycobacterial infections.[12]

The definition of CMCD is typically CMC in patients *without any other prominent clinical signs.*[1,37] However, this definition is not strict, and some CMCD patients have other infectious diseases, such as infection with *Staphylococcus aureus.*[38,39] Therefore, the term CMCD is now used to refer to patients presenting with CMC as the major clinical phenotype, and its etiology is neither related to genes known to cause severe combined immunodeficiency or combined immunodeficiency, nor genes responsible for Syndromic CMC. Four of the five genes implicated in CMCD (*IL17F*, *IL17RA*, *IL-17RC* and *TRAF3IP2/ACT1*) are directly involved in IL-17 signaling (Table 1).[38–40] These genetic disorders clearly reveal the pure and nonredundant role of IL-17 in mucocutaneous immunity to *Candida* in humans (Figure 1). Here, we review current knowledge of IL-17-signaling defects and the genetic etiologies of Syndromic CMC and CMCD.

IL-17 cytokines, receptors and signaling

The IL-17 cytokine family consists of six members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F), whereas the IL-17 receptor family consists of five members (IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE; Figure 2).[41] IL-17 cytokines form disulfide-linked homodimers, and IL-17A and IL-17F can also form heterodimers (IL-17A/F). IL-17A and IL-17F share the strongest sequence homology and are produced by a distinct subset of T helper cells, Th17. Receptors for all IL-17 cytokines also form homodimers or heterodimers, and each combination recognizes distinct IL-17 cytokines, with IL-17RA as the common subunit for each complex. For example, the receptor complex formed by IL-17RA/C recognizes IL-17A and IL-17F, whereas the complex formed by IL-17RA/B recognizes IL-17E (CD25). In each case, signaling triggers recruitment of ACT1 as an adaptor molecule for downstream signaling (Figure 2). IL-17A and IL-17RA are the original members of the IL-17 cytokine and receptor families, respectively, and, as such, are commonly referred to as IL-17 and IL-17R. Mutations in four genes, *IL17F*, *IL17RA*, *IL-17RC* and *TRAF3IP2* (which encode ACT1) that directly relate to IL-17A/F-induced, IL-17RA/C-mediated signaling, have been identified in patients with CMCD.[38–40] Furthermore, mutations in *IL17RA* and *TRAF3IP2* also affect IL-17E-induced, IL-17RA/B-mediated signaling (Figure 2). These clinical and experimental observations strongly suggest that defects in IL-17 signaling have a pivotal role in host mucocutaneous immunity against *Candida* in humans.

CLASSIFICATION OF SYNDROMIC CMC

AD Hyper IgE Syndrome

HIES is a primary immunodeficiency disease, which is characterized by elevated serum IgE levels, recurrent staphylococcal skin abscesses, eczema and pulmonary infections. It was first described in 1966 and was originally named Job's syndrome.[42] HIES has either a dominant or recessive pattern of autosominal inheritance, with the rare AR HIES largely shown to be caused by mutations in *DOCK8* (OMIM ID:

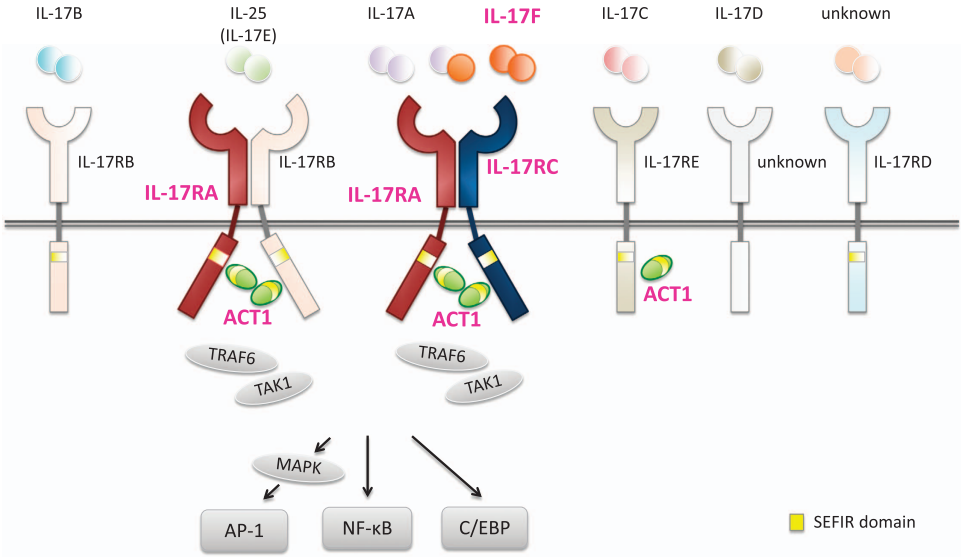

Figure 2 IL-17 and IL-17 receptor family. The IL-17 cytokine family consists of six members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F), whereas the IL-17R family consists of five members (IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE). IL-17 cytokines form disulfide-linked homodimers, whereas IL-17A and IL-17F can form heterodimers. Functional receptors for IL-17 family cytokines are thought to consist of homodimers or heterodimers. Upon stimulation, ACT1 is recruited to IL-17RA, IL-17RB and/or IL-17RC (and probably IL-17RE) by homotypic dimerization of two SEFIR domains, and activates the nuclear factor-κB (NFκB), mitogen-activated protein (MAP) kinase and CCAAT enhancer-binding protein (C/EBP) signaling pathways. In this pathway, mutations in four genes (*IL17F*, *IL17RA*, *IL-17RC* and *TRAF3IP2/ACT1*) have been identified in patients with CMCD. These mutations are directly related to IL-17A/F-induced, IL-17RA/RC-mediated signaling, and mutations in *IL17RA* and *TRAF3IP2* also affect IL-17E-induced, IL-17RA/IL-17RB-mediated signaling. Thus, effective host mucocutaneous immunity against *Candida* in humans is critically dependent on functional and effective IL-17A/F-induced, IL-17RA/C-mediated signaling. Magenta: CMCD-related molecules.

243700); in addition, AD HIES has been shown to be mainly caused by germline heterozygous *STAT3* mutations (OMIM ID: 147060).[15] STAT3 has a central role in signal transduction downstream of multiple cytokines, including IL-6, IL-10, IL-17, IL-22, IL-23 and IL-27. The *STAT3* mutations identified in AD HIES patients are loss-of-function (LOF) and exert a dominant-negative effect on wild-type STAT3-mediated signaling.[15] In addition to their infectious phenotype, patients with *STAT3* mutations present with multiple clinical manifestations, including characteristic facial features, high-arched palate, retained primary teeth, scoliosis, osteoporosis and hyperextensibility of joints. STAT3-deficient patients also frequently develop CMC associated with other infectious and clinical manifestations. A large cohort study, collecting 60 patients with germline *STAT3* mutations, revealed that 85% of the *STAT3*-mutated patients develop CMC, including oral (63%), genital (18%), cutaneous (16%) and esophageal (8%) candidiasis and chronic onychomycosis (57%).[43] *C. albicans* was the major pathogen isolated in 88% of collected samples obtained from infected sites.[43] These patients have severely decreased frequency of circulating IL-17A- and IL-22-producing T cells. Furthermore, naive $CD4^+$ T cells isolated from patients demonstrated significantly impaired differentiation into Th17 cells, probably associated with impaired STAT3-dependent signaling downstream of IL-6, IL-21 and IL-23.[15,17,19,20] Together, AD HIES patients who develop CMC as one of the many clinical manifestations associated with impaired Th17 differentiation are thus categorized as Syndromic CMC.

AR APECED

APECED, also called APS-1 syndrome, is an AR inherited disorder caused by biallelic mutations in *AIRE* (OMIM ID:240300). Affected patients suffer from autoimmune polyendocrinopathy, such as Addison's disease, hypoparathyroidism and hypogonadism. They also develop alopecia areata, vitiligo and ectodermal dystrophy, such as nail dystrophy, or dental enamel dysplasia. CMC is one of the major infectious phenotypes of APECED, observed in up to 98% of patients (Table 1).[25] Patients with APECED develop neutralizing autoantibodies against cytokines IL-17A (41%), IL-17F (75%) and/or IL-22 (91%).[9] However, no other anticytokine autoantibodies have been detected in these patients (including against IL-6, IL-10, IL-12, IL-18, IL-21, IL-23 or IFN-γ).[13] Peripheral blood mononuclear cells from APECED patients with CMC show decreased IL-17F and IL-22 secretion *in vitro*, following stimulation with heat-killed *C. albicans* hyphae,[9] and this cellular phenotype is correlated with the presence of neutralizing antibodies against IL-17A, IL-17F and/or IL-22 in patient serum.[9] These results clearly reveal that autoimmunity in APECED targets not only endocrine organs, but also IL-17 immunity via production of high titer of neutralizing antibodies, resulting in a specific impairment of host mucosal immunity to *C. albicans*.[9]

AR CARD9 deficiency

CARD9 is an intracellular adaptor molecule that, together with its binding partners BCL10, Malt1 and NEMO, mediates signals from C-type lectin-like receptors, Dectin-1 and Dectin-2, to induce transcription and production of proinflammatory cytokines via nuclear factor-κB (NFκB) signaling. In 2009, a primary immunodeficiency, which associates with a genetic defect of *CARD9*, was identified in the patients who suffer from CMC and invasive fungal infections (OMIM ID:212050).[7] A homozygous mutation, Q295X, in *CARD9* was identified in those patients.[7] Subsequent studies revealed that patients with AR CARD9 deficiency also suffer from deep dermatophytosis, invasive *Exophiala dermatitidis*, subcutaneous Phaeohyphomycosis and *Candida*-species meningoencephalitis and/or colitis, and are thus considered Syndromic CMC.[18,26,44,45] There are several reports describing a decreased frequency of

circulating IL-17-producing cells in CARD9-deficient patients, probably explaining the clinical phenotype of CMC.[7,18,45] On the other hand, several studies also report that the frequency of circulating IL-17-producing cells in CARD9-deficient patients is equivalent to healthy controls.[44,46] Therefore, there is some controversy regarding the frequency of circulating IL-17-producing cells in CARD9-deficient patients. Neutrophils kill both serum-opsonized and unopsonized *C. albicans* via distinct mechanisms; reactive oxygen species production by the NADPH oxidase system has an important role for neutrophil-killing of serum-opsonized *Candida*, whereas neutrophil-killing of unopsonized *Candida* requires complement receptor type 3 (CR3) and CARD9.[47] Neutrophils from CARD9-deficient patients show a selective *C. albicans*-killing defect that is CR3- and CARD9-dependent, but NADPH oxidase-independent.[8] Furthermore, patients with AR CARD9 deficiency are particularly predisposed to meningoencephalitis caused by *Candida* species.[18] This might be explained by the enhanced requirement of CR3- and CARD9-dependent neutrophil-killing in the limited access of plasma proteins that is required for opsonization in cerebrospinal fluids,[8] as well as the finding that neutrophils from CARD9-deficient patients normally inhibit germination of *Aspergillus fumigatus*, consistent with the clinical observation that no CARD9-deficient patients were reported to have *Aspergillus* species infection.[8,18]

AR IL-12Rβ1 deficiency and AR IL-12p40 deficiency

IL-12, IL-23, IL-27 and IL-35 belong to the IL-12 cytokine family. Functional IL-12 (also called IL-12p70) consists of a heterodimer of IL-12p35 and IL-12p40 subunits, each of which has distinct effector functions. IL-12p40 is a common component of both IL-12 and IL-23; IL-12 drives T helper 1 (Th1) differentiation, whereas IL-23 is critical for Th17 survival and expansion. IL-12Rβ1 combines with IL-12Rβ2 or IL-23R to form high-affinity receptors for IL-12 or IL-23, respectively. IL-12 binds to the IL-12R complex (IL-12Rβ1 and IL-12Rβ2), on T lymphocytes and NK cells, and induces IFN-γ production. IL-23 binds to its receptor complex (IL-12Rβ1 and IL-23R) on Th17 cells and has an important role in maintenance of Th17 cells and induction of IL-17 and IL-22.

AR-complete IL-12Rβ1 deficiency (OMIM ID: 614891) is the most common genetic cause of MSMD, explaining 44% of MSMD patients with a known genetic etiology.[48] The first cases of AR-complete IL-12Rβ1 deficiency were reported in 1998.[27,28] From the first identification, a total of 180 patients from 136 kindreds have since been reported.[48] A large cohort study, collecting 141 patients from 102 kindreds with AR-complete IL-12Rβ1 deficiency, revealed its heterogeneous clinical manifestations. Mycobacterial disease (83%), Salmonellosis (43%) and CMC (23%) were the three major infectious phenotypes reported in symptomatic patients.[11] Moreover, 78% of BCG-vaccinated patients developed BCG disease. In contrast, 8 of the 29 genetically affected siblings were asymptomatic (27%), suggesting incomplete penetrance of this disorder.

The first case of AR-complete IL-12p40 deficiency (OMIM ID: 614890) was identified in 1998 in a patient born to consanguineous parents who developed disseminated infection with BCG and *S. enteritidis*.[29] A follow-up study, collecting 49 patients from 30 kindreds, revealed that patients with AR-complete IL-12p40 deficiency develop recurrent infections due to *Salmonella* (36.4%) and mycobacteria (25%).[10] Strikingly, BCG disease was observed in 40 of the 41 patients (97.5%) who were vaccinated with BCG. Moreover, CMC was also reported in three patients (6%). The clinical penetrance of IL-12p40 deficiency is incomplete, with 33.3% of genetically affected relatives of index cases showing no symptoms. Therefore, AR-complete IL-12p40 and IL-12Rβ1 deficiencies are clinical phenocopies that show increased susceptibility to intracellular pathogens and develop CMC.[10,11,48]

Genetic defects in *IL12B* or *IL12RB1*, which encode IL-12p40 or IL-12Rβ1, respectively, affect both IL-12- and IL-23-induced signaling. Leukocytes from patients with AR-complete IL-12p40 deficiency show a complete absence of IL-12p40, IL-12 and IL-23 proteins.[10,17,29] T-cell blasts from IL-12Rβ1-deficient patients have undetectable cell surface protein expression of IL-12Rβ1, and thus a complete lack of cellular responses to IL-12 and IL-23.[11] In both cases, the lack of IL-12 protein itself or cellular response to IL-12 results in poor production of IFN-γ by T and NK cells, and is the pathogenic mechanism responsible for susceptibility to intracellular pathogens, such as mycobacteria and *Salmonella*. In contrast, the absence of IL-23 protein or defective cellular responses to IL-23 forms the likely molecular cause of CMC in these patients.[10,16,17,49,50] Indeed, patients with AR-complete IL-12p40 or IL-12Rβ1 deficiencies show decreased frequencies of circulating IL-17-producing cells, albeit a less severe reduction than observed in patients with AD HIES. This difference may explain the disparity in the frequency and severity of CMC between AD HIES and AR IL-12p40/IL-12Rβ1 deficiencies.[10,11,17,43]

AD STAT1-GOF

Germline mutations in *STAT1* cause diverse range of primary immunodeficiencies (Figure 3).[51] Patients with biallelic hypomorphic or LOF-STAT1 mutations (AR STAT1 deficiency; OMIM ID: 613796), which partially or completely impair STAT1 protein expression, show susceptibility to viruses and intracellular bacteria.[48] The infectious phenotype observed in patients with AR-partial STAT1 deficiency is milder than in those with AR-complete STAT1 deficiency who require hematopoietic stem cell transplantation to avoid life-threatening infections. Germline monoallelic hypomorphic or LOF-STAT1 mutations are responsible for AD MSMD (AD STAT1 deficiency; OMIM ID: 614892). These *STAT1* mutations do not disturb STAT1 protein expression, but exert a dominant-negative effect on IFN-γ-induced STAT1-mediated signaling.[48] In 2011, monoallelic GOF-*STAT1* (OMIM ID: 614162) mutations were shown to cause the AD form of CMCD (Table 1).[30,31] These mutations impair dephosphorylation of STAT1, leading to hyperphosphorylation of STAT1 Tyr701 in response to IFN-γ, IFN-α/β and IL-27 stimulation. This finding has enabled the development of a simple flow cytometry-based STAT1 functional test to facilitate the diagnosis of CMCD patients with GOF-*STAT1* mutations.[32] GOF-*STAT1* mutations are preferentially identified in the coiled-coil domain and DNA-binding domain of STAT1, whereas there are no obvious hot spots for LOF-*STAT1* mutations (Figure 3).[30,31,33,48,51,52] Moreover, GOF-*STAT1* mutations are a major mechanism of molecular pathogenesis of CMCD, and are reported to explain more than half of the cases of this disorder.[30–33,52–65]

Although CMC is the major infectious manifestation among the patients with GOF-*STAT1* mutations, some patients develop fungal infections other than candidiasis, or bacterial and viral infections, mycobacterial infections, autoimmune disorders, including IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome) and/or even fatal combined immunodeficiency.[53,54,56–60,65,66] Recently, a large cohort study investigating 274 patients from 167 kindreds reported in detail the clinical manifestations of patients with GOF-*STAT1* mutations.[34] In this large cohort, the majority of patients with *STAT1*-GOF mutations developed CMC (98%), with a median age at onset of 1 year. Many patients also suffered from bacterial infections (74%), mainly due to *S. aureus* (36%), and viral infections (37%) typically caused by

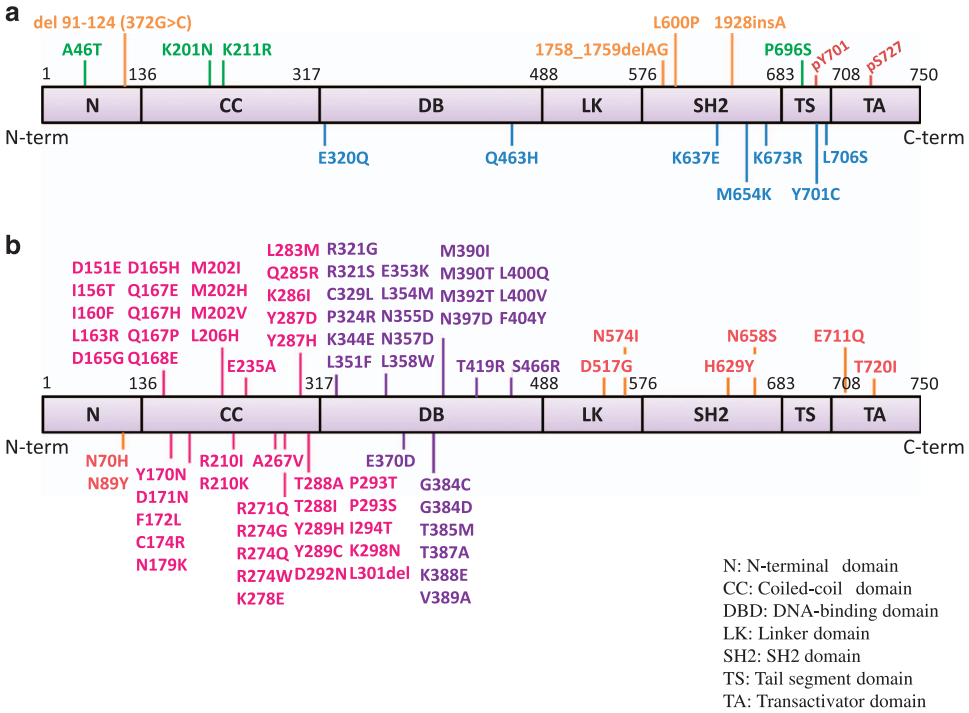

Figure 3 Germline STAT1 mutations identified in patients with primary immune deficiency. (**a**) Loss-of-function or hypomorphic mutations are shown above human STAT1α isoform. Germline *STAT1* mutations identified in patients with an AR form of complete (orange) or partial (green) STAT1 deficiency. Germline *STAT1* mutations identified in patients with AD MSMD are shown in blue. (**b**) Germline GOF-*STAT1* mutations are shown above human STAT1α isoform. Gain-of-function mutations are preferentially identified in coiled-coil domain (magenta) and DNA-binding domain (purple) of *STAT1*. CC, coiled-coil domain; DB, DNA-binding domain; LK, linker domain; N, N-terminal domain; SH2, SH2 domain; TA, transcriptional activation domain; TS, tail segment.

Herpes viruses (88%), whereas others/some experienced invasive fungal infections (10%) and mycobacterial diseases (6%). In addition to the infectious phenotypes reported in these patients, over one-third also presented with autoimmune manifestations (37%), such as hypothyroidism (23%), type 1 diabetes (4%) and blood cytopenias (4%), highlighting the broad and devastating clinical symptoms that can be associated with CMC in many patients with GOF-*STAT1* mutations. Therefore, based on these broad clinical manifestations, AD *STAT1*-GOF can be categorized as Syndromic CMC, rather than the original categorization of CMCD. Immunological test also detects B-cell defects in these patients, with reduced $CD19^+CD27^+$ memory B cells (49%) and low IgG2 (38%) or IgG4 (50%).[34] Although impaired development of IL-17-producing T cells *ex vivo* is consistently observed in patients with GOF-*STAT1* mutations,[30] the molecular mechanism underlying such developmental defects of IL-17-producing T cells is unknown.[30] In mice and humans, IFN-γ, IFN-α/β and IL-27, which predominantly signal via STAT1, inhibit IL-17 T-cell development.[67] In contrast, IL-6, IL-21 and IL-23, which mainly signal via STAT3, promote IL-17 T-cell development.[30,51] Probably, IFN-γ-, IFN-α/β- and/or IL-27-induced enhanced STAT1 activity might inhibit IL-17 T-cell development in patients with GOF-*STAT1* mutations. It is also possible that GOF-*STAT1* mutations affect IL-6-, IL-21- and/or IL-23-induced STAT3 activity.[2,3,6,64] Further studies are required to fully understand the molecular and pathogenic mechanisms of GOF-*STAT1* mutations underlying CMC.

AR RORγT deficiency

RORγT is a lineage-determining transcription factor of Th17 cells and has crucial role for Th17 development, Th17 effector cytokine production and expression of the Th17 chemokine receptor, CCR6.[68] In 2015, germline homozygous mutations in *RORC*, which encodes RORγ and RORγT, were identified in seven patients from three unrelated kindreds presenting with complex infectious phenotypes, with CMC and severe mycobacterial infections (OMIM ID: 616622).[12] Six of seven patients developed mild mucocutaneous *Candida* infections, and mycobacterial infection was severe and observed in all patients. Four of the seven patients developed disseminated mycobacterial infection and one died because of BCG meningoencephalitis. The patients presented with mild T-cell lymphopenia, thymic hypoplasia, lack of palpable axillary and cervical lymph nodes, and absence of MAIT and iNKT cells that were consistent with the phenotype of $Rorc^{-/-}$ mice.[12] Moreover, $Rorc^{-/-}$ mice were also susceptible to mycobacterial infection, suggesting that host susceptibility to mycobacteria was not a human-specific finding.[12] All three homozygous mutations (S17L, Q308* and Q411*) in *RORC* identified in these patients were LOF and impaired DNA-binding ability of the target sequence of RORγT in the promoter region of IL-17A. $CD3^+$ T cells from the patients displayed severe impairment in the production of IL-17A, IL-17F and IL-22, and impaired IFN-γ production in response to mycobacterial challenge. These clinical and experimental observations demonstrate the essential role of RORγT not only for the development of IL-17-producing lymphocytes to protect the mucocutaneous barriers against *Candida*, but also for the activation of IFN-γ-producing T cells required for systemic protection against *Mycobacterium*.

CMCD: MOLECULAR DEFECTS AND PATIENT MANAGEMENT

AD IL-17F deficiency

The first identification of AD IL-17F deficiency (OMIM ID: 613956) was in a multiplex family from Argentina in 2011.[38] A heterozygous

missense mutation, S95L (c.284C>T), in *IL17F* was identified in this family. The S95L mutation was found in four patients with CMC, as well as two asymptomatic family members (aged 9 months and 21 years), suggesting incomplete clinical penetrance. All four patients developed CMC from the first year of life. In addition to CMC, recurrent furunculosis and recurrent upper respiratory tract infections were observed in one patient. One sibling, who lacked genetic testing for *IL17F*, died at the age of 6 years from encephalopathy of unclear etiology associated with extensive oral candidiasis. The S95L IL-17F mutant (IL-17F^{S95L}) was normally expressed and formed homo- and heterodimers with IL-17F, IL-17F^{S95L} and IL-17A. However, IL-17F^{S95L} was severely hypomorphic and exerted a dominant-negative effect by impairing the binding of its complexes to the receptor. Curiously, *Il17f*$^{-/-}$ mice do not show susceptibility to experimental infection with intravenously administered *Candida*.[69] In contrast, *Il17a*$^{-/-}$ mice are susceptible only to cutaneous and systemic candidiasis.[69,70] Possible explanations for this discrepancy could be a different function of IL-17F between mice and humans, or the dominant-negative effect of IL-17F^{S95L} on IL-17A signaling. A subsequent study identified a second multiplex family with AD IL-17F deficiency.[71] The proband and his mother, carrying an undescribed heterozygous *IL17F* variation, developed CMC. Although no functional validation was performed, this might be the second family reported with AD IL-17F deficiency.

AR IL-17RA deficiency

The first patient reported with AR IL-17RA deficiency (OMIM ID: 613953) was born to consanguineous Moroccan parents.[38] A homozygous nonsense mutation, Q284*, in *IL17RA* that was inherited from asymptomatic consanguineous parents was identified. The patient developed recurrent CMC, and was resistant to local antifungal treatment from the first month of life. He was also susceptible to *S aureus*, presenting with skin abscess and folliculitis on the buttocks. Although the patient had several episodes of conjunctivitis, acute media otitis, lower respiratory tract infections and folliculitis, he never developed severe bacterial infection. Analysis of peripheral blood mononuclear cells and patient-derived fibroblasts showed no IL-17RA protein expression on their surface. Moreover, no response to homo- and heterodimeric IL-17A and IL-17F was observed in fibroblasts[38] and no response to IL-17E (IL-25) was observed in peripheral blood mononuclear cells from the patient[39] (Figure 2). A subsequent study identified a multiplex family with the combination of AR IL-17RA and adenosine deaminase 2 deficiency.[72] Two siblings with CMC identified in this study shared a homozygous large deletion including entire regions of *IL17RA* and *CECR1* (encoding adenosine deaminase 2). The absence of IL-17RA surface protein expression was confirmed with flow cytometry on patient neutrophils, monocytes and CD4$^+$ T cells. Overall, the clinical observations in patients with AR IL-17RA deficiency are comparable to those in *Il17ra*$^{-/-}$ mice that show susceptibility to mucocutaneous pathogens, such as *Candida* and *Staphylococcus*.[5,73] Together with the original case of AR IL-17RA deficiency, complete clinical penetrance was observed in this disorder.

AR IL-17RC deficiency

So far, three unrelated CMCD patients, one from Argentina and the others from Turkey, have been reported with AR IL-17RC deficiency (OMIM ID: 616445).[40] Three different nonsense homozygous mutations, Q138*, R376* and R378*, in *IL-17RC* that were inherited from asymptomatic parents, were identified in the patients. All patients with biallelic mutations in *IL-17RC* developed CMC, suggesting complete clinical penetrance for this disorder. Unlike AR IL-17RA and ACT1 deficiencies, patients with AR IL-17RC deficiency did not have recurrent staphylococcal infections. Moreover, none of the patients suffered from severe or recurrent bacterial infections. All mutations were shown to be loss-of-expression, with a lack of IL-17RC cell surface expression in HEK293T-transfected cells and normal IL-17RA expression on SV-40-immortalized fibroblasts obtained from the patients. The specific IL-17RC defect in these patients was demonstrated by a lack of cellular responses to homo- and heterodimers of IL-17A and IL-17F, but normal responses to IL-17RC-independent signaling via IL-25 (Figure 2). Staphylococcal disease is frequently observed in patients with AR IL-17RA and ACT1 deficiency (described below), whereas it is not obvious in patients with AD IL-17F or AR IL-17RC deficiency. The infectious phenotype of patients with AR IL-17RC deficiency resembled that of/ observed in patients with AD IL-17F deficiency, and was consistent with that of *Il17rc*$^{-/-}$ mice.[74] This clinical observation supports the contribution of an additional defect in the signaling pathway, downstream of IL-17E, in patients with AR IL-17RA and ACT1 deficiency.

AR ACT1 deficiency

AR ACT1 deficiency was first reported in 2013 in two siblings born to consanguineous Algerian parents.[39] A homozygous mutation, T536I, in the SEF/IL-17 receptor (SEFIR) domain of *TRAF3IP2* (encodes ACT1) that was inherited from asymptomatic parents was identified. Both patients developed CMC, suggesting complete clinical penetrance for this disorder. One patient also had recurrent episodes of folliculitis decalvans and bilateral blepharitis caused by *S. aureus*. ACT1 is an adaptor molecule that interacts with multiple partners, including members of the IL-17R family.[39,41] Upon stimulation, ACT1 is recruited to IL-17RA, IL-17RB and/or IL-17RC (and probably IL-17RE) by homotypic dimerization of two SEFIR domains, and activates the NFκB, mitogen-activated protein kinase and CCAAT enhancer-binding protein pathways (Figure 2).[39] ACT1 also has an inhibitory role in B-cell survival by negatively regulating CD40 and B-cell-activating factor receptor through interaction with TRAF3.[75] The T536I *ACT1* mutation does not disturb its protein expression. However, this mutation specifically impairs the homotypic interaction of ACT1 with IL-17RA, IL-17RB and IL-17RC, abolishing responses to IL-17A and IL-17F in fibroblasts and to IL-17E in leukocytes [39] (Figure 2). In contrast, the T536I mutation does not affect SEFIR domain-independent interactions. This mutant normally interacts with CD40 and other SEFIR-independent interaction partners such as heat-shock proteins 70 and 90.[39] The selective defect in the IL-17 signaling due to T536I-specific *ACT1* mutation in the SEFIR domain may explain the phenotypic discrepancy between identified human AR ACT1 deficiency and *Act1*$^{-/-}$ mice. Unlike human AR ACT1 deficiency, *Act1*$^{-/-}$ mice display enhanced B-cell responses to CD40L and BAFF, resulting in hypergammaglobulinemia.[75] In conclusion, the specific *TRAF3IP2* mutation that selectively impairs the function of ACT1 SEFIR domain is responsible for CMCD.

MANAGEMENT AND TREATMENT OF PATIENTS WITH CMCD AND AD STAT1-GOF

Most patients with CMCD are treated with topical and/or systemic antifungal agents.[30,31,33,38–40] Fluconazole is the main first-line oral therapy, followed by itraconazole, posaconazole and/or voriconazole. As for topical treatment, nystatin is a good alternative to triazoles.[33] CMC in approximately one-third of patients with GOF-*STAT1* mutations is successfully treated with azoles, whereas a partial response is observed in the others.[33,34] In general, long-lasting treatments and/or prophylaxis are required to treat persistent and prevent

recurrence of CMC.[30,31,33,38–40] Patients with AR IL-17RA and ACT1 deficiency develop staphylococcal infections in addition to CMC. Antibiotic prophylaxis with sulfamethoxazole–trimethoprim seems to be effective to treat these patients.[38,39] Patients with GOF-*STAT1* mutations present various clinical manifestations in addition to CMC. Many patients suffer from bacterial infections, such as lower respiratory infections (in 47% patients), ear-nose-and-throat infections (44%) and skin infections (28%), associate with infections of *S. aureus* (36%), *Streptococcus* spp. (20%), *Pseudomonas aeruginosa* (13%) and *Haemophilus influenzae* (9%).[34] Thus, some patients are also considered for antibiotic prophylaxis, such as sulfamethoxazole–trimethoprim, to prevent bacterial infections. Moreover, patients with GOF-*STAT1* mutations occasionally develop severe autoimmune disorders that require immunosuppressive treatment.[57] The Janus kinase inhibitor, ruxolitinib, has been trialed in two patients with GOF-*STAT1* mutations, leading to improvement of CMC and autoimmune syndrome, without significant adverse effects.[62,76] Hematopoietic stem cell transplantation might be considered as a treatment option for patients with GOF-*STAT1* mutations, especially for those with severe clinical presentations, such as recurrent severe viral and/or bacterial infections, IPEX-like syndrome or hemophagocytic syndrome.[66] Indeed, invasive infections, cerebral aneurysms and cancers are considered to be strong predictors of poor outcome.[34] Hematopoietic stem cell transplantation seems to be an effective cure of CMC, but large case studies are required to validate the wider application of this treatment for all individuals with CMC.[55]

CONCLUSION

The recent identification of genetic etiologies of Syndromic CMC and CMCD has revealed the nonredundant role of IL-17 in mucocutaneous immunity to *Candida* in humans. These discoveries have improved our understanding of CMC, by revealing inheritance, clinical course and prognosis. Furthermore, clarification of the molecular pathogenesis potentially gives us the opportunity to find target molecules, such as Janus kinase inhibitors, which target signaling, to improve the clinical symptoms. It might also inform of the potential risk of increased susceptibility to *Candida* in patients treated with anti-IL-17-targeted immunotherapies.[77] The discovery of GOF-*STAT1* mutation as a molecular pathogenesis of Syndromic CMC was a breakthrough in this field. From the first identification, more than 300 of patients with GOF-*STAT1* have been identified.[34] However, there are still many patients with CMC who lack a genetic etiology. Further studies are required to reveal the entire picture of this congenital disorder.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Miyuki Tsumura, Shiho Nishimura Sonoko Sakata and Reiko Kagawa for helpful discussions. This study was supported by JSPS KAKENHI Grant Numbers 16K15528 and 16H05355, and by the Practical Research Project for Rare/Intractable Diseases from Japan Agency for Medical Research and development, AMED. This research was also funded by grants from the Institut National de la Santé et de la Recherche Médicale (INSERM), University Paris Descartes, the French National Research Agency (ANR; Grant no ANR-11-BSV3-0005 to AP), the 'Investments for the future' program (grant no ANR-10-IAHU-01), US National Institutes of Health (NIH; Grant no 5U01AI109697-02), the Rockefeller University and the St Giles Foundation.

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