HHS Public Access

Author manuscript

Hum Genet. Author manuscript; available in PMC 2021 June 01.

Published in final edited form as:

Hum Genet. 2020 June ; 139(6-7): 1011–1022. doi:10.1007/s00439-020-02141-7.

Human inborn errors of immunity underlying superficial or invasive candidiasis

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Abstract

Candida species, including *C. albicans* in particular, can cause superficial or invasive disease, often in patients with known acquired immunodeficiencies or iatrogenic conditions. The molecular and cellular basis of these infections in patients with such risk factors remained largely elusive, until the study of inborn errors of immunity clarified the basis of the corresponding inherited and "idiopathic" infections. Superficial candidiasis, also known as chronic mucocutaneous candidiasis (CMC), can be caused by inborn errors of IL-17 immunity. Invasive candidiasis can be caused by inborn errors of CARD9 immunity. In this chapter, we review both groups of inborn errors of immunity, and discuss the contribution of these studies to the deciphering of the critical mechanisms of anti-*Candida* immunity in patients with other conditions.

Introduction

The genus *Candida*, which contains about 200 different species, belongs to the phylum Ascomycota. *Candida* spp. are the most common cause of fungal infection in humans[1–2], but only a few species (approximately 20) can cause disease. *Candida albicans, C. glabrata, C. tropicalis, C. parapsilosis*, and *C. krusei* account for about 90% of these diseases, and their prevalence depends on the geographic location, patient populations, and clinical settings[3]. *C. albicans* remains the major cause of invasive candidiasis, but *C. glabrata* (in northern Europe, USA, Canada) and *C. parapsilosis* (in southern Europe, Asia, Latin America) have emerged as important or even major pathogens[4–7]. *Candida* spp. have been reported to be the fourth most common nosocomial pathogen in the bloodstream, or at least within the top ten of such pathogens[1, 8]. These *Candida* spp. are resident commensal yeasts in the oro-gastrointestinal and genitourinary tracts in healthy individuals. However, they can also act as pathogens in humans, causing superficial infections of the skin, scalp, nails, or oral and

genital mucosae, or invasive, often life-threatening, systemic infections (candidemia) that may be disseminated to internal organs (leading to meningoencephalitis, brain abscesses, endophthalmitis, endocarditis, peritonitis, osteomyelitis, intra-abdominal abscesses, lung infections, etc.)[9–11]. The infections they cause are a serious public health problem, with mortality often exceeding 40% (partly due to late diagnosis, the late initiation of antifungal therapies, and the emergence of resistance to antifungal drugs), and substantial costs associated with patient care and long hospital stays[11–18].

Various risk factors, iatrogenic or acquired, are known, such as HIV infection, mainly associated with oro-pharyngeal candidiasis[19]. Invasive candidiasis is mostly associated with organ transplantation, hemodialysis, parenteral nutrition, intravenous catheters, abdominal surgery, extensive burns, long-term stay in intensive care units, or the administration of broad-spectrum antibiotics or of immunosuppressive agents such as chemotherapy[1, 20]. In this context, invasive candidiasis is an increasing problem in elderly patients, with significantly higher mortality rates as compared to younger patients[21–22]. Neonates are also at risk of invasive forms of candidiasis, such as the central nervous system (CNS) candidiasis reported in low-birth weight or preterm neonates[23–26]. These fungal diseases frequently strike individuals with many risk factors. As a result, their pathogenesis remains poorly understood at the molecular and cellular levels. The study of primary immunodeficiencies (PID) with “syndromic” candidiasis, whether superficial or invasive, and, more recently, that of inborn errors of immunity in otherwise healthy patients with “isolated” candidiasis, whether superficial or invasive, has progressively shed light on the mechanisms conferring protective immunity to *Candida* spp.[27–36]. The elucidation of the pathogenesis of these fungal diseases in patients with inherited immunodeficiencies (ID) has important clinical implications for the patients and their families, with the possibility of genetic diagnoses and counseling, but should also facilitate the development of novel prophylactic or curative treatments with a rational basis, for PID patients and patients with other more common conditions (e.g. acquired ID). Research into the genetic basis of *Candida* diseases is important, given the high mortality associated with *Candida* diseases, despite the availability of antifungal drugs, and the increasing frequency of antifungal drug-resistant strains[37].

Chronic mucocutaneous candidiasis and inborn errors of IL-17 immunity

Mucocutaneous candidiasis is characterized by *Candida spp*. infections of the nails, skin, scalp, and/or oral and genital mucosae[35, 38–43]. Mucosal candidiasis, such as oral thrush, is relatively frequent in individuals on steroid or antibiotic treatments. Up to 75% of women present at least one episode of vulvovaginal candidiasis during their lifetime, and recurrent (> 1 episode) vulvovaginal candidiasis has been estimated to have a global annual prevalence of 3,871 per 100,000 women[44]. Chronic mucocutaneous candidiasis (CMC) is characterized by severe, persistent or recurrent (relapse upon discontinuation of treatment) disease[43]. CMC, present as severe oropharyngeal candidiasis, is very common in AIDS patients[19, 45]. Similarly, in the context of PID, CMC is frequent in patients with broad T-cell defects, such as combined or severe combined immunodeficiencies (CID or SCID, respectively)[30–31, 46–47]. This inherited form of CMC, usually referred to as CMC disease (CMCD), is rare, affecting approximately one in every 50,000 individuals. The CMC in

affected patients is syndromic, as it is associated with many other clinical manifestations, mostly infectious and/or autoimmune. Syndromic CMC is also common in some PIDs without major global apparent T-cell deficiencies, albeit with milder clinical features. These PIDs include autosomal dominant (AD) STAT1 gain-of-function (GOF), a complex and heterogeneous PID in which CMC is one of the first features observed and is common to most patients, and often severe[33–34, 48–53]. It is frequently associated with other infectious diseases, typically mucocutaneous bacterial, viral, or fungal diseases, and less frequently with invasive infectious diseases, autoimmune manifestations, and oro-esophageal squamous cell carcinoma[28, 30, 34–35, 43, 49–51, 53–54]. Another such PID is hyper-IgE syndrome (HIES), another complex PID characterized by severe skin and pulmonary staphylococcal disease, severe eczema, high serum IgE levels, and some developmental abnormalities[48, 55]. It may be AD due to heterozygous dominant negative mutations of the gene encoding the transcription factor STAT3[56–57], or autosomal recessive (AR) due to biallelic loss-of-function (LOF) mutations of the gene encoding another transcription factor, Zinc Finger Protein (ZNF)341[58–59]. About 80% of patients develop oral thrush, onychomycosis, and/or vaginal candidiasis. CMC is also frequent and the only infectious disease common to most patients with AR autoimmune polyendocrine syndrome type 1 (APS-1, also called APECED, autoimmune polyendocrinopathycandidiasis-ectodermal dystrophy). This syndrome is characterized by multi-organ autoimmunity due to bi-allelic mutations of the gene encoding the transcription factor *AIRE*[60–62]. Other PIDs in which CMC is milder or less frequent (25% to 35%) include AR ROR / T deficiency, characterized by disseminated BCG-diseases[63], AR IL-12p40 and IL-12R 1 deficiencies, characterized by a selective predisposition to mycobacterial and *Salmonella* diseases[64–65], and AR CARD9 deficiency, generally characterized by invasive fungal diseases[32, 66–68]. A final group of patients displays early CMCD in an otherwise healthy context, with the exception of mucocutaneous staphylococcal disease in some patients. This condition is often referred to as isolated CMCD (see below).

Investigations of the molecular and cellular bases of PID with syndromic CMCD suggested that IL-17A/F-mediated immunity might protect against mucocutaneous candidiasis and that CMCD might result from inborn errors of IL-17A/F immunity[34–35, 69–71]. Indeed, all of them are characterized by impaired IL-17A/F immunity, due to abnormally low levels of circulating IL-17A/F-producing T (Th17) cells, or to the presence of autoantibodies directed against IL-17 cytokines. Indeed, patients with AD STAT1 GOF have very low proportions of Th17 cells, both *ex vivo* or and after differentiation *in vitro*[50, 53–54, 72–74]. This Th17 cell deficiency may result from enhanced/overt STAT1 signaling downstream from the STAT3-dependent IL-6, IL-21, and IL-23 cytokines, which is critical for the development and maintenance of Th17 cells[70–71, 75], enhanced STAT1 signaling downstream from IFN-α/β, IFN-γ, and IL-27, which has been shown to inhibit the development of Th17 cells via STAT1[76–78], or both these mechanisms[53, 79]. Patients with AD HIES also have very low proportions of *ex vivo* and *in vitro*-differentiated Th17 cells[80–83], due to an impairment of STAT3-dependent signaling downstream from IL-6R, IL-21R, and IL-23R[70]. Similarly, patients with AR HIES and ZNF341 deficiency also have abnormally low proportions of *ex vivo* and *in vitro*-differentiated Th17 cells, due to the disruption of ZNF341-dependent STAT3 transcription and activity[55, 58–59]. As expected, patients with AR deficiencies of

ROR / T, a master transcription factor of Th17 cells[84–87], also have barely detectable levels of Th17 cells[63], and patients with IL-12p40 and IL-12R 1 deficiencies, in whom the production of and response to IL-23 and IL-12 are abolished, also have low levels of circulating Th17 cells[74, 83]. Most, but not all of the tested patients with deficiencies of CARD9, an adaptor transducing signals downstream from C-type lectin receptors following the recognition of fungal cell wall components, have low circulating levels of Th17 cells, probably due an impairment of the induction of pro-Th17 cytokines (e.g. IL-6, IL-23) by phagocytes after activation by fungal ligands[32, 66–67, 88] (Figure). Finally, APS1 patients, who suffer from multiple autoimmune endocrinopathies due to LOF mutations of the gene encoding AIRE, a transcription factor involved in the removal of self-reactive T cells[89–90], frequently harbor high levels of antibodies against various self-antigens[91], including neutralizing autoantibodies directed against cytokines such as IFN-α and IFN-ω[62, 92] in particular, but also against Th17 cytokines, such as IL-17A, IL-17F, and IL-22[69, 93–94]. These studies have paved the way for the identification of inborn errors of IL-17-mediated immunity conferring CMC in otherwise healthy individuals, or in individuals with mucocutaneous *Staphylococcus aureus* infections[33–35].

A candidate approach identified AD IL-17F and AR IL-17RA deficiencies, each in a single family, in 2011, as the first genetic etiologies of isolated CMCD[28, 95]. Indeed, a heterozygous private missense variation of *IL17F*, predicted to be deleterious, was identified in five relatives from an Argentinian multiplex family with early-onset CMC. The index patient had also had recurrent upper respiratory tract infections, asthma, and recurrent episodes of furunculosis since infancy. In these patients, the proportions of *ex vivo* IL-17A- and IL-22-producing T cells were within the control ranges, but IL-17F levels were not evaluated. The mutation was shown to impair the binding of IL-17F to its receptor, which consists of IL-17RA/IL-17RC, on the surface of control fibroblasts. Studies with control fibroblasts and keratinocytes revealed an impairment of the responses to mutant IL-17F homodimers, but also of that to heterodimers containing the mutant protein (IL-17A/mutant IL-17F, wild type IL-17F/mutant IL-17F), showing that the mutant IL-17F was hypomorphic and exerted a dominant-negative effect on IL-17A- or wild-type IL-17F-mediated responses[95]. A second family of Tunisian-German origin has since been reported, in which a woman and her son carrying a heterozygous mutation of *IL17F* both presented CMC with an onset in early childhood, with no other infectious phenotype; the causal effect of the variant in this family has yet to be characterized[96]. In parallel, AR complete IL-17RA was reported in a patient born to consanguineous Moroccan parents. This patient suffered from early-onset CMC and cutaneous *S. aureus* infection, and was homozygous for a nonsense mutation affecting the extracellular part of IL-17RA. Additional homozygous nonsense, missense, frameshift, splice site, and large deletion mutations have since been found in a total of 23 patients with AR IL-17RA deficiency, from 13 unrelated kindreds originating from Morocco, Turkey, Japan, Saudi Arabia, Algeria, Argentina, and Sri Lanka[28, 97–98]. All patients displayed early-onset CMC. About 70% of these patients also presented staphylococcal skin diseases, and 40% developed recurrent bacterial infections of the respiratory tract[28, 95, 97–98]. AR complete IL-17RC deficiency was subsequently identified by whole-exome sequencing in three unrelated patients with early-onset CMC in the absence of any other infectious phenotype, including staphylococcal disease in particular; these

patients were born to consanguineous families originating from Turkey and Argentina[99]. AR ACT1 deficiency is the fourth genetic defect responsible for isolated CMCD. It was identified in two siblings, born to consanguineous Algerian parents, with early-onset CMC and recurrent skin and scalp *S. aureus* disease. Both patients were found to carry a homozygous missense mutation of *TRAF3IP2* encoding ACT1, which is a key downstream adapter in the IL-17 response pathway[100–102]. The fibroblasts of all IL-17RA-, IL-17RC-, and ACT1-deficient patients failed to respond to IL-17A and IL-17F homodimers and heterodimers[95, 97–99, 103]. In addition, IL-17RA-and ACT1-deficient PBMCs, unlike PBMCs from patients with AR IL-17RC deficiency, failed to respond to IL17E/IL-25[98, 103], which signals through IL-17RA/IL-17RB in an ACT1 dependent manner[104]. An AD deficiency of JNK1, a component of the MAPK signaling pathway[105–106], was recently identified in a multiplex family originating from France with syndromic CMCD, in which three individuals from three generations presented early-onset CMC, mucocutaneous *S. aureus* infections, and a complex connective tissue disorder[107]. *In vitro* studies showed that the private *MAPK8* c.311+1G>A identified in the three patients was a loss-of-expression variant. JNK1 is involved in various signaling pathways, including the IL-17 pathway in particular[108–110]. Accordingly, the fibroblasts of heterozygous patients displayed impaired cellular responses to IL-17A and IL-17F. JNK1 also acts downstream from TGFβ1, which has been shown to participate in human Th17 differentiation *in vitro*[84, 111–112]. The proportions of *ex vivo* and *in vitro*-differentiated Th17 cells were indeed low for these patients. This study reported a fifth genetic disorder in the IL-17 response pathway, underlying AD CMCD by haploinsufficiency, with impaired cellular responses to IL-17A/F and impaired IL-17A/F production (Figure). Altogether, these five human genetic disorders demonstrate the essential role of IL-17A- and IL-17F-mediated immunity in mucocutaneous protection against *Candida* and, to a lesser extent, as found in IL-17RA-, ACT1- and JNK1-deficient patients, against disease caused by *S. aureus*. They also suggest that IL-17A- and IL-17F-dependent immunity is otherwise redundant for protection against fungi other than *Candida*, bacteria other than *S. aureus*, viruses, or even against invasive candidiasis or staphylococcal disease.

Invasive candidiasis and inborn errors of CARD9 immunity

Invasive candidiasis (IC) is defined as infections of the bloodstream (candidemia) or deep-seated infections caused by *Candida* spp. and it ranks among the most frequent healthcare-associated bloodstream infections[1, 113]. Unlike CMC, patients with broad T-cell disorders are not particularly prone to IC. Furthermore, very few patients with CMC display IC, and *vice versa*. This suggests that T-cell dependent immunity is not essential for protection against IC and that different mechanisms are involved in immunity to superficial and invasive candidiasis. In IC, phagocytes, neutrophils in particular, but probably also, to a lesser extent, based on mouse studies, monocytes, macrophages and dendritic cells, are essential for protective immunity[11]. Indeed, IC is classically described in patients with acquired profound qualitative or quantitative disorders of neutrophils and monocytes/macrophages[8]. IC is relatively rare among patients with PID, and has been reported only occasionally in this context. Patients with severe congenital neutropenia (SCN), and mutations of *ELA2*, *HAX1*, or other genes, may develop syndromic IC. For example, IC was reported in 2% (n=486) of the patients from the French SCN registry[30]. A few patients with

AR leukocyte adhesion disorder type-1 (LAD-1), due to CD18 deficiency resulting from biallelic mutations of *ITGB2* and leading to the impaired endothelial adhesion and transmigration of neutrophils into infected tissues, may display IC[114–116]. In both cases, IC probably results from impaired neutrophil accumulation at the site of infection. Some patients with complete AR myeloperoxidase (MPO) deficiency and concomitant diabetes or with X-linked or AR chronic granulomatous disease (CGD) caused by mutations of genes encoding NADPH oxidase subunits and impaired oxidative burst-dependent *Candida* killing by phagocytes may also display syndromic IC[117–118]. Cases of deep-seated organ candidiasis have been reported in CGD patients, with central nervous system (CNS), soft tissue, lymph node, or liver diseases, and enhanced susceptibility to *C. lusitaniae*, a *Candida* spp. rarely disease-causing in non-CGD patients[119–121]. Finally, in a large international study of patients with STAT1 GOF (n=274), 3.6% were reported to have syndromic IC[50].

Since its discovery in 2009, in a large multiplex consanguineous family from Iran with CMC and possible brain disease caused by *Candida* spp.[66], CARD9 (C-type lectin receptor adaptor caspase recruitment domain-containing protein 9) deficiency has emerged as the only known inborn error of immunity conferring a selective susceptibility to fungal diseases in otherwise healthy individuals, with no other infectious or noninfectious manifestations[32, 36, 122]. Over 70% of patients with CARD9 deficiency have developed IC, with a strong tropism for the CNS. Indeed, about 80% of patients with probable or proven IC have CNS diseases, such as meningoencephalitis, brain abscesses, masses mimicking metastasis, or a combination of these manifestations[32, 66, 68, 123–130]. Strikingly, these patients present no concomitant diseases of the kidney, liver, or spleen, as typically seen in CARD9-expressing infected patients, probably as a result of CARD9-independent mechanisms of protective immunity[131]. Gastrointestinal tract, bone, eye, intra-abdominal organ (liver and mesenteric LNs), or mucocutaneous surface involvement may also occur, as some patients have been reported to have severe colitis, osteomyelitis, endophthalmitis, intra-abdominal candidiasis, or CMC[66–68, 125, 127–128, 132–134]. The onset of invasive disease is particularly variable, with a substantial proportion of CARD9-deficient patients presenting with IC as adults, with a mean age of 21.9 years (median age: 17.5 years; range [3.5–58.0 years]). CARD9-deficient patients with CMC and/or IC have been identified in nine countries around the world (Algeria, Morocco, Iran, Turkey, Pakistan, Canada, Italy, El Salvador, and South Korea), and one patient was of mixed European origin. Of all *Candida* spp., *C. albicans* is the most frequently involved in infections. It has been detected in 93% of patients, the other *Candida* spp. detected, *C. glabrata* and *C. dubliniensis*, each being found in a single patient[32].

CARD9, which is part of the CARD9/BCL10/MALT1 (CBM) complex, is mainly expressed in phagocytic cells, and transduces signals downstream from C-type lectin receptors (CLRs), including Dectin-1 (*CLEC7A*), Dectin-2 (*CLEC6A*), Dectin-3 (*CLEC4D*), and Mincle (*CLEC4E*), which are specific for β-glucans (Dectin-1), α-mannans (Dectin-2 and Dectin-3), and glycolipids (Mincle) from the fungal cell walls[135–136]. In humans, upon receptor stimulation and SYK activation, the CBM complex activates the NF-κB, MAPK, and ERK pathways, thereby stimulating the transcription of genes encoding pro-inflammatory cytokines and chemokines, such as IL-2, IL-10, IL-12, tumor necrosis factor

(TNF)-α, pro-Th17 cytokines (IL-1β, IL-6, IL-23), granulocyte-macrophage colony-stimulating factor (GMCSF), and CXCL1 or CXCL2[137].

CARD9-deficient patients have no overt immunological phenotype: they have normal leukocyte counts; when tested, T-cell proliferation in response to mitogen or antigens is mostly normal, and the phagocyte oxidative burst, tested *in vitro* in the dihydrorhodamine (DHR) assay, is also normal. However, high eosinophil counts, high serum IgE levels, or both, have been observed in several CARD9-deficient patients, and the reasons for this remain unknown[32]. CSF samples were analyzed in some patients and revealed hyperproteinorrhachia, and hypoglycorrhachia and pleocytosis, mostly with mononuclear cells (lymphocytes and/or monocytes) and eosinophils, but, remarkably, no neutrophils[128] (by contrast to patients with *Candida* meningitis wild-type for CARD9, for whom neutrophils generally predominate in the CSF[128]). IL-17-mediated immunity was evaluated in about half the CARD9-deficient patients (with candidiasis or other fungal diseases), and was impaired in two-thirds of those tested, with no clear correlation between impaired or normal IL-17 immunity and the presence or absence of CMC[32]. PBMCs, monocytes, and *in vitro* monocyte-derived macrophages or DCs tested *in vitro* upon stimulation with heat-killed *C. albicans* displayed impaired responses in terms of pro-inflammatory cytokine or chemokine production[32]. A selective defect of the killing of unopsonized (but not opsonized) *C. albicans* yeasts but not hyphae by neutrophils has been reported *in vitro* and has been suggested to contribute to *Candida* CNS disease, due to the lower levels of opsonization in the CNS[32]. However, a lack of neutrophil recruitment to infection sites (e.g. CNS), consistent with the absence of neutrophils from the CSF fluids of CARD9-deficient patients with *Candida* CNS infections, contrasting with their blood neutrophil counts within the normal range, appears to be the major CARD9-dependent mechanism underlying IC in these patients[27, 122, 128]. Recently, based on *Card9*$^{-/-}$ mouse studies, abnormally low levels of IL-1β-dependent CXCL1 production by microglial cells following stimulation with the fungal toxin candidalysin were proposed as an explanation for the defective recruitment of neutrophils to the *Candida*-infected CNS, and impaired CNS *Candida* clearance[128, 138].

Conclusion

The investigation of patients with PID and syndromic CMC or IC, or of otherwise healthy patients with CMC or IC provides us with a unique opportunity to elucidate the molecular and cellular bases of these diseases and to gain insight into the pathophysiological mechanisms underlying them. The knowledge gained in the context of PID can be applied to other settings, such as hematological malignancies or AIDS, for example. The spectrum of inborn errors underlying CMC and, to a lesser extent, IC, is expanding and has already provided important insight into the role of specific immune pathways in anti-*Candida* host defense. Indeed, IL-17-mediated immunity has emerged over the last 10 years as crucial against CMC and, to a lesser extent, mucocutaneous *S. aureus* diseases. However, it seems to be redundant against IC, invasive staphylococcal diseases, and other common microbes (including fungi and bacteria). Inherited CARD9 deficiency is a genetic etiology of CMC and IC. Remarkably, *Candida* diseases can occur at any age, from early childhood to late adulthood. The adult onset seen in several CARD9-deficient patients is an uncommon feature of inborn errors of immunity and should lead clinicians to consider CARD9

deficiency in adults presenting with unexplained *Candida* diseases. Next-generation sequencing in patients with CMC or IC without inborn errors of the IL-17 pathway or CARD9 will probably reveal new genetic defects that may further elucidate the pathogenesis of *Candida* infections in patients with inborn errors of IL-17 immunity or CARD9. The comprehensive genetic dissection of *Candida* diseases (in patients with syndromic PID or in otherwise healthy individuals) should shed new light on the molecular and cellular mechanisms conferring protective immunity to *Candida* spp., and should pave the way for more rational therapies based on a better understanding of the underlying pathophysiological mechanisms. The clinical implications extend well beyond patients with fungal diseases due to inborn errors of immunity, to patients with fungal diseases due to other causes.

Acknowledgments

I warmly thank Jean-Laurent Casanova and the members of the HGID laboratory for helpful discussions. This work was supported by the St. Giles Foundation, the Rockefeller University, INSERM, Paris Descartes University, HHMI, and the French National Research Agency (ANR) under the “Investissement d’avenir” program (grant number ANR-10-IAHU-01), the “LTh-MSMD-CMCD” project (Grant ANR-18-CE93-0008-01), the “HGDIFD” project (grant number ANR-14-CE15-0006-01) and the “EURO-CMC” project (grant number ANR-14-RARE-0005-02).

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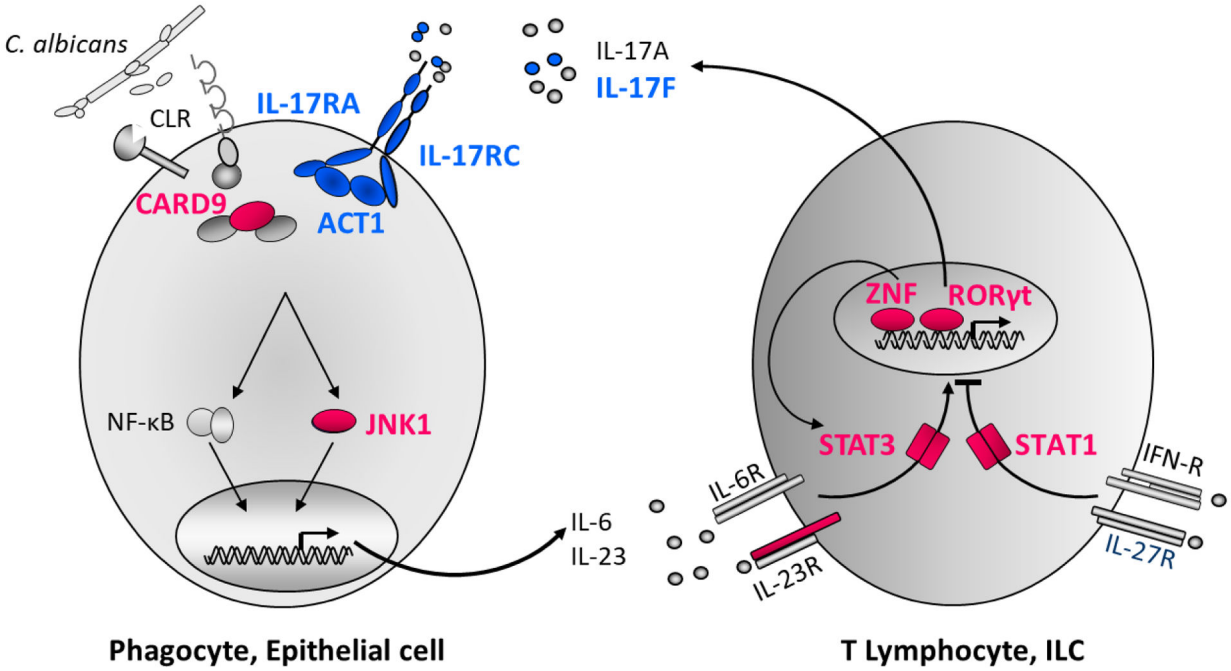

Figure. Inborn errors of IL-17 immunity in patients with isolated or syndromic CMCD.

Schematic representation of IL-17A/F immunity and cooperation between cells recognizing *C. albicans* and responding to IL-17A/F (phagocytes and epithelial cells), and cells producing IL-17A/F (T and innate lymphocytes). Human IL-17A/F immunity is crucial for protective mucocutaneous immunity against *C. albicans*. Proteins for which mutations in the corresponding genes underlie CMCD are shown in blue or red. Monoallelic LOF mutations of *IL17F* and of *MAPK8*, and bi-allelic LOF mutations of *IL17RA*, *IL17RC* and *ACT1* impair IL-17A and IL-17F immunity (via IL-17RA/IL-17RC). Bi-allelic LOF mutations of *IL12RB1*, *RORC*, ZNF341, monoallelic LOF mutations of STAT3 and monoallelic GOF mutations of STAT1 impair IL-17A/F production. Mutations of *IL17F*, *IL17RA*, *IL17RC* and *ACT1* underlie isolated CMCD (blue), whereas mutations of *IL12RB1*, *STAT1*, *STAT3*, *ZNF341* and *RORC* underlie syndromic CMCD (in red).