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Molecular mechanisms of mucocutaneous immunity against *Candida* and *Staphylococcus* speciesLászló Maródi, MD, PhD,^a Sophie Cypowyj, PhD,^b Beáta Tóth, PhD,^a Liudmyla Chernyshova, MD, PhD,^c Anne Puel, PhD,^d and Jean-Laurent Casanova, MD, PhD^{b,d} Debrecen, Hungary, New York, NY, Kiev, Ukraine, and Paris, France

Signal transducer and activator of transcription (STAT) proteins are key components of the innate and adaptive immune responses to pathogenic microorganisms. Recent research on primary immunodeficiency disorders and the identification of patients carrying germline mutations in *STAT1*, *STAT3*, and *STAT5B* have highlighted the role of human STATs in host defense against various viruses, bacteria, and fungi. Mutations in *STAT1* and *STAT3* disrupt various cytokine pathways that control mucocutaneous immunity against *Candida* species, especially *Candida albicans*, and *Staphylococcus* species, especially *Staphylococcus aureus*. Here we consider inborn errors of immunity arising from mutations in either *STAT1* or *STAT3* that affect mucocutaneous immunity to *Candida* and *Staphylococcus* species. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Primary immunodeficiency diseases, signal transducer and activator of transcription, signal transducer and activator of transcription 1 and 3, IL-17, *Candida* species, *Staphylococcus* species

Many cases of primary immunodeficiencies (PIDs) are the results of defects in hematopoietic cell differentiation or

Abbreviations used

AD-HIES:	Autosomal dominant hyper-IgE syndrome
AIRE:	Autoimmune regulator
APS:	Autoimmune polyendocrine syndrome
CARD:	Caspase recruitment domain
CC-D:	Coiled-coil domain
CMC:	Chronic mucocutaneous candidiasis
CMCD:	Chronic mucocutaneous candidiasis disease
DNA-BD:	DNA-binding domain
HIES:	Hyper-IgE syndrome
HSV:	Herpes simplex virus
IL-12Rβ1:	IL-12 receptor β1
JAK:	Janus-associated kinase
PID:	Primary immunodeficiency
SH:	Src homology
STAT:	Signal transducer and activator of transcription
TYK2:	Tyrosine kinase 2
VZV:	Varicella zoster virus

abnormal functioning of leukocytes and in turn the consequences of gene mutations encoding cell-surface or intracellular receptors or receptor-mediated signal transduction pathway proteins.¹⁻¹¹ During the past decade, several inborn errors of immunity caused by defects in receptor-mediated signaling pathways and affecting both innate and adaptive immune responses were discovered and described. For example, severe combined immunodeficiency with the T⁺B⁺ natural killer cell-negative immunophenotype was found to be caused by mutations in the gene encoding Janus-associated kinase (JAK) 3 in addition to common γ chain deficiency caused by mutation of IL-2 receptor γ (*IL2RG*).^{12,13} Primary defects of signal transducer and activator of transcription (STAT) 1 and STAT3 have been described, and the susceptibility of patients to infections by viruses, mycobacteria, staphylococci, and fungi depends, in part, on whether they carry dominant or recessive, gain-of-function or loss-of-function mutations.¹⁴⁻¹⁹ In this review we describe genotypes and phenotypes, as well as the immunopathogenesis of candidal and staphylococcal mucocutaneous infections, in patients with various types of mutations, including those in *STAT1* and *STAT3*.

Candida albicans and other *Candida* species are commensal organisms of the skin and mucous membranes, but they can also cause mucocutaneous or invasive diseases.²⁰⁻²² Invasive candidiasis might involve any internal organ or anatomic site and is a significant cause of morbidity and mortality of immunocompromised subjects, particularly those with PIDs affecting

From ^athe Department of Infectious and Pediatric Immunology, University of Debrecen Medical and Health Science Center; ^bSt Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University Hospital, Rockefeller University, New York; ^cthe Department of Pediatric Infectious Diseases and Immunology, National Medical Academy for Postgraduate Education, Kiev; and ^dthe Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U980, and University Paris Descartes, Necker Medical School, Paris Sorbonne Cité, Paris.

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Corresponding author: László Maródi, MD, PhD, Department of Infectious and Pediatric Immunology, University of Debrecen Medical and Health Science Center, Nagyterdei krt 98, 4032 Debrecen, Hungary. E-mail: lmarodi@dote.hu.

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granulocytes. Granulocytes and monocytes ingesting and killing serum-opsonized *Candida* species yeasts and macrophages phagocytizing *Candida* species both in the presence and absence of serum opsonins are of key importance in the host defense against invasive candidiasis.²³⁻²⁶ However, mucosal *Candida* species infections that are self-limited and transient can occur during menstruation and are frequent during pregnancy and in newborn infants.²² Persistent and recurrent candidiasis (chronic mucocutaneous candidiasis [CMC]) typically occurs in patients with quantitative or qualitative T-cell deficiency and is consequently a major disease manifestation in those with severe combined immunodeficiency, complete DiGeorge syndrome, and advanced HIV infection.²² Recent research reviewed below suggests that increased susceptibility of patients to CMC is largely due to functional impairment of IL-17-dependent T-cell immunity.²⁶⁻²⁸

Staphylococcus aureus and other staphylococcal species are also commensal organisms of the skin. They are also common pyogenic pathogens that can cause bacteremia with or without sepsis, invasive diseases, toxin-mediated systemic and cutaneous syndromes, and peripheral infections most commonly in the skin and soft tissues.²⁹⁻³² Analysis of innate immune defects of granulocytes has taught us that neutrophil granulocytes are important in the elimination of *Staphylococcus* and *Candida* species from tissue compartments and body surfaces; such elimination requires efficient opsonophagocytosis and bacterial killing.³²⁻³⁴ Patients with congenital neutropenia typically have pyogenic bacterial infections of the skin, mouth, and rectum. Chronic granulomatous disease is characterized by impaired activation of nicotinamide adenine dinucleotide phosphate in phagocytic cells, resulting in these cells being unable to generate toxic oxygen radicals and hence to kill catalase-positive bacteria.³³ Patients with chronic granulomatous disease have recurrent abscesses caused by *Staphylococcus* and *Candida* species in soft tissues, liver, bones, and joints.^{33,34} Recruitment by chemokines and activation by colony-stimulating factors of neutrophils on mucosal membranes and the skin are essential for preventing bacterial invasion and the development of subcutaneous abscesses. IL-17-dependent T-cell immunity might also play a role in recruiting and activating inflammatory cells and promoting antistaphylococcal defenses. Importantly, STAT1- and STAT3-mediated signaling contributes to innate and adaptive immune responses against *Candida* and *Staphylococcus* species.¹⁷ The epithelial herpes virus entry mediator might also play a role in mucosal immunity against bacteria and fungi.³⁵ Herpes virus entry mediator might induce STAT3 activation, which could promote gene expression relevant to mucosal defense against *Candida* and *Staphylococcus* species.

STAT FAMILY MEMBERS

Cytokine binding to hemopoietin receptors initiates signaling through Janus kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) and STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6).^{17,36,37} STAT-mediated signaling is the transmission of signals from various receptors of cytokines and growth factors after ligand binding. STAT proteins are present in the cytoplasm as inactive monomers and typically form homodimers or heterodimers after being phosphorylated by receptor-associated JAKs. These phosphorylated STAT dimers translocate to the nucleus, where they act as activators of

transcription; nuclear binding of STAT dimers promotes the expression of a variety of genes important for cell survival, differentiation, proliferation, and migration and for efficient host responses to various pathogens. STAT1 proteins can be phosphorylated and activated on binding of IFN- α/β , IFN- γ , IFN- λ , and IL-27 to their receptors, and STAT3 is primarily phosphorylated and activated on binding of IL-6, IL-10, and numerous other molecules.^{17,36}

MUTATIONS IN STAT3 CAUSE AUTOSOMAL DOMINANT HYPER-IGE SYNDROME

STAT3 has been implicated in host defenses against extracellular bacteria, including *S aureus*, and fungi, including *C albicans*, by recent investigations of patients with autosomal dominant hyper-IgE syndrome (AD-HIES).³⁸⁻⁴¹ It is now established that heterozygous dominant negative mutations in *STAT3* cause autosomal dominant, familial, or sporadic form of the disease.⁴²⁻⁴⁵ Patients with AD-HIES typically have skin and sinopulmonary infections with *S aureus* and skin and mucosal infections with *Candida* species in addition to eczema, unique facial characteristics, pathologic bone fracture, lymphoma, and abnormal dentition (Fig 1).⁴⁶ Recent research has revealed that the IL-17-producing CD4⁺ T_H lymphocytes are central to the host defense against skin and lung infections by producing IL-17 and IL-22 cytokines, which in turn recruit neutrophils and bind to and stimulate epidermal or epithelial cells to induce the release of bactericidal peptides (Fig 2).⁴⁷ In some patients with AD-HIES, naive CD4⁺ T cells might not differentiate into IL-17-producing T cells because of dominant negative mutations of *STAT3*; almost all such mutations affect the DNA-binding domain (DNA-BD), Src homology (SH) 2 domain, or transactivation domain of *STAT3* (Fig 3, A). DNA-BD and transactivation domain mutations might prevent binding of *STAT3* homodimers and *STAT3*-*STAT1* heterodimers to promoter sequences in genomic DNA. Indeed, the electrophoretic mobility shift assay showed that even in the presence of normal levels of phosphorylated *STAT3*, binding of *STAT3* to DNA was undetectable in T cells from patients with HIES in contrast to that seen in T cells from healthy subjects.^{39,42} These findings clearly suggest that *STAT3* mutations in patients with AD-HIES are dominant negative. Mutations in the SH2 domain might interfere with dimerization of *STAT3* proteins. The severe depletion of IL-17-producing T cells in patients with AD-HIES has led to the suggestion that *STAT3*-dependent immunity is required to control infections by pathogens residing on body surfaces.³⁸⁻⁴⁰ Release of IL-17 and IL-22 by T cells in dermal tissue and mucous membranes probably initiates the secretion of CXC chemokines and granulocyte colony-stimulating factor by epithelial cells, and these agents might then recruit neutrophils on the body surfaces and eliminate bacteria and fungi (Fig 2). Another important and relevant role of IL-17 cytokines is to promote the release of bactericidal peptides, including defensins.⁴⁸

AUTOIMMUNE POLYENDOCRINE SYNDROME 1

The involvement of IL-17 in host defense against *Candida* species on body surfaces precipitated mechanistic studies in patients with autoimmune polyendocrine syndrome (APS) 1; these patients have CMC, which is one of the 3 major criteria of the disease.⁴⁹ Two groups independently discovered that patients

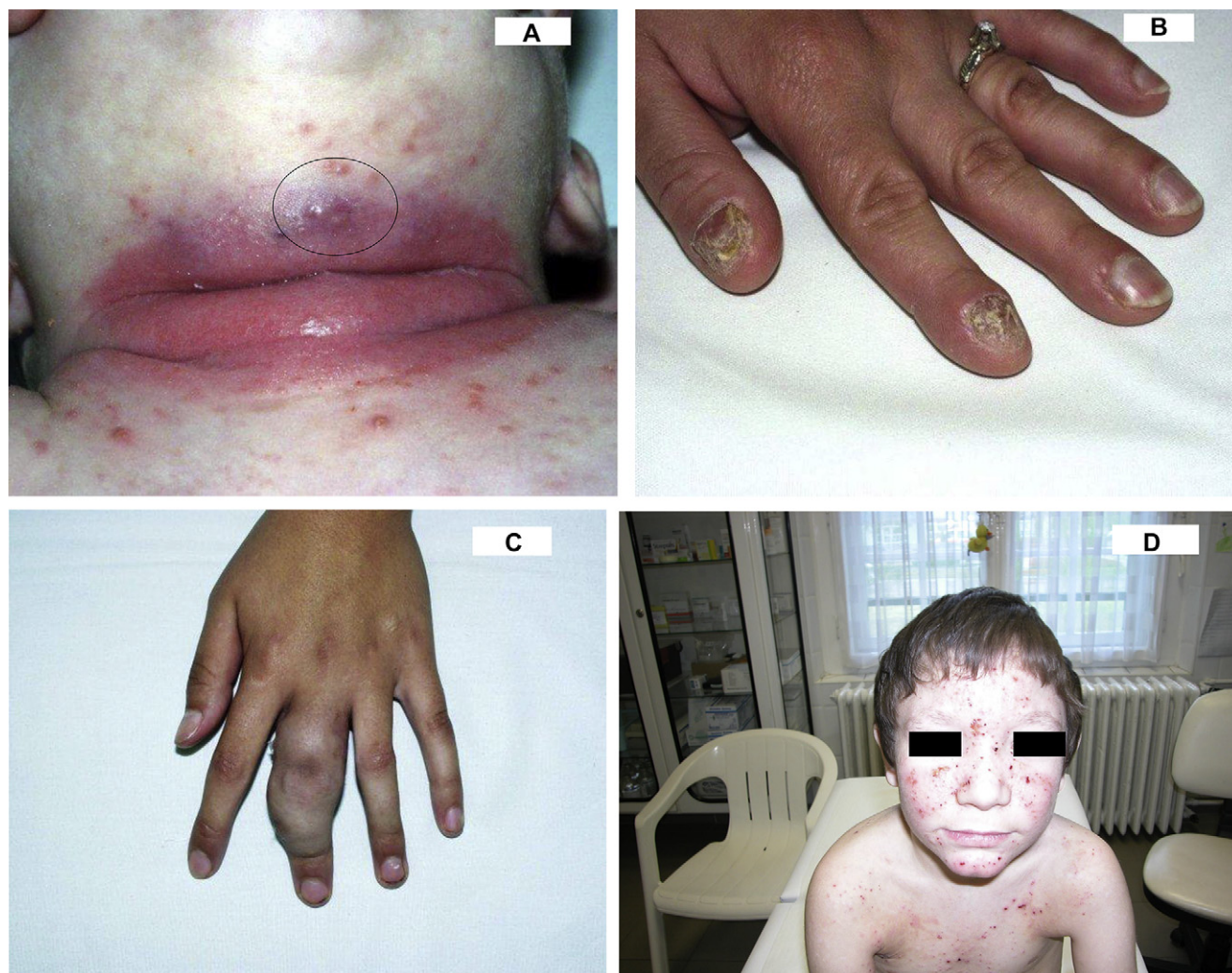


FIG 1. **A** and **B**, Submental staphylococcal abscess (Fig 1, **A**, circle) in a 7-month-old girl and nail candidiasis (Fig 1, **B**) in her mother from a family with AD-HIES and the R382W mutation in STAT3. **C**, Cold staphylococcal abscess in a 10-year-old female patient with AD-HIES and the H332Y amino acid substitution in STAT3. **D**, Severe eczema and typical facial characteristics in a 9-year-old boy with sporadic AD-HIES and the R382W mutation in STAT3.

with APS-1 have high circulating titers of neutralizing antibodies against the cytokines IL-17 (IL-17A and IL-17F) and IL-22.⁵⁰⁻⁵² These patients also have increased titers of antibodies to type I interferons, including antibodies against IFN- ω .^{52,53} High anti-IL-17 cytokine autoantibody titers were also detected in patients with thymoma and CMC.⁵² Therefore it is plausible that patients with APS-1 are susceptible to *Candida* species because of the secretion of neutralizing autoantibodies against IL-17 cytokines. Importantly, anti-IFN- ω , anti-IL-17, and anti-IL-22 might serve as serologic markers of the disease in early childhood before manifestations of endocrine organ damage.⁵⁴ These antibodies can persist for years without the appearance of antibodies to endocrine organs or any clinical manifestation of APS-1 (L. Maródi, unpublished observation). The susceptibility to *Candida* species might also involve other mechanisms in addition to impaired IL-17 immunity. Unlike patients with AD-HIES, patients with APS-1 are not prone to staphylococcal skin disease or invasive staphylococcal infections. The observation of recurrent staphylococcal disease of

the skin in a patient with autoantibodies against IL-6 suggests that the pathogenesis of staphylococcal disease might be IL-6 but not IL-17 dependent.⁵⁵ Patients with APS-1 do not have autoantibodies against IL-6. It is also possible that the intact STAT3- and STAT1-mediated pathways in autoimmune regulator (AIRE)-deficient patients contribute to the integrity of the host defense against *Staphylococcus* species.

IL-12 RECEPTOR β 1 AND IL-12P40 DEFICIENCIES

CMC often affects patients with PIDs, such as IL-12 receptor β 1 (IL-12R β 1) deficiency, the most common form of Mendelian susceptibility to mycobacterial disease. IL-12R β 1 deficiency is characterized by childhood-onset mycobacteriosis and salmonellosis; recurrent thrush caused by *Candida* species has been found in 24% of 141 reported patients.⁵⁶ CMC has also been observed in 7.5% of 44 patients with IL-12p40 deficiency.⁵⁷ We recently reviewed the clinical course of 26 patients with IL-12R β 1 deficiency and CMC (Ouederni et al, unpublished data). Most

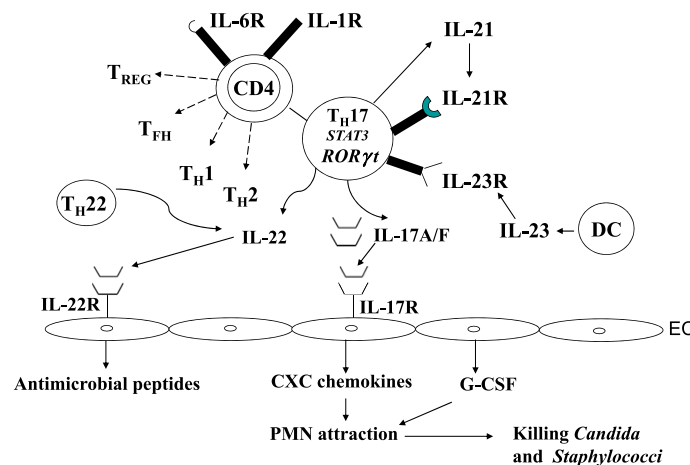


FIG 2. In human subjects, IL-6 and IL-1 are the major cytokines inducing IL-17 T-cell differentiation from naive CD4 T cells, which can also differentiate into regulatory T (T_{REG}), follicular T_H (T_{FH}), T_H1 , and T_H2 cells. Dendritic cell (DC)-derived IL-23 reinforces and maintains IL-17 T-cell differentiation. In mice T_H17 cell differentiation can also be amplified by the release of IL-21. The IL-17 T-cell differentiation involves upregulation of retinoic acid orphan receptor γt ($ROR\gamma t$). STAT3 plays critical role in signaling by both IL-21 and IL-23. T_H17 -derived cytokines induce secretion of chemokines, colony-stimulating factors, and antimicrobial peptides by epithelial cells. T_H17 - and T_H22 -derived cytokines induce the accumulation of phagocytes at the site of pathogen invasion. EC, Epithelial cells; G-CSF, granulocyte colony-stimulating factor; PMN, polymorphonuclear neutrophil granulocyte.

candidiasis episodes (45/59) in these subjects were mucocutaneous, and oropharyngeal candidiasis was the most common (25/59 episodes), with esophageal, cutaneous, and genital candidiasis also being recorded. Intriguingly, 5 episodes of invasive candidiasis were also documented in these patients. Multivariate analysis revealed that the occurrence of any form of candidiasis in patients with IL-12R β 1 deficiency was associated with a poor prognosis.

T cells from patients with *IL12RB1* mutations cannot respond to either IL-12 or IL-23 because these cytokines bind IL-12R β 1 (Fig 4). Patients with IL-12p40 deficiency, a subunit shared by IL-12 and IL-23, might be prone to CMC because of impaired IL-23-dependent immunity, which is important for the maintenance of IL-17-producing T lymphocytes. Note that patients with INF- γ receptor deficiency do not display CMC or staphylococcal disease, and this is further evidence of the requirement for intact IL-23 signaling in resistance to these pathogens.⁵⁸

TYK2 DEFICIENCY

Most cases of HIES are inherited as an autosomal dominant trait or are sporadic presentations. However, the autosomal recessive variant of the syndrome has also been described.⁵⁹ A Japanese patient with autosomal recessive HIES has been reported and carries a homozygous nonsense mutation in *TYK2*, which encodes TYK2.⁵⁹ The patient presented with atopic dermatitis, markedly increased serum IgE titers, and recurrent infections with *Staphylococcus* species, herpes simplex virus (HSV), BCG, and *Candida* species, and his PBMCs did not respond normally to stimulation with IL-6 and IL-10.⁵⁹ A Turkish patient with TYK2 deficiency who had disseminated BCG infection and zoster but did not display staphylococcal or candidal disease has been reported.⁶⁰ Intriguingly, in contrast to the Japanese TYK2-deficient patient, PBMCs from the Turkish patient did respond to stimulation with IL-6. Pertinent to this, a patient with autoantibodies against IL-6 has been reported to have recurrent

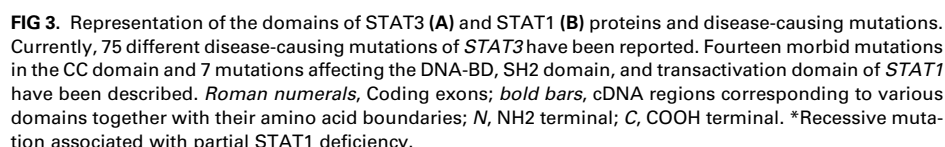
staphylococcal skin disease but not CMC.⁵⁵ Although no PID of IL-6 or its receptor has been described, the high level of IL-6-specific autoantibody in this patient with recurrent staphylococcal cellulitis and subcutaneous abscesses indicate that such PIDs might exist. This observation is coherent with the poor IL-6 responses observed in patients with STAT3 deficiency, which is also associated with staphylococcal disease.⁴¹

IL-17 AND IL-17 RECEPTOR DEFICIENCIES

Patients with chronic mucocutaneous candidiasis disease (CMCD) but without any other severe infection or severe noninfectious disease manifestation, such as autoimmunity, or known genetic defect have been described. Investigations in 2 families led to the discovery of new genetic defects of IL-17-mediated immunity.²⁷ In a Moroccan patient born to consanguineous parents, an autosomal recessive premature stop codon mutation of the *IL17RA* gene, leading to complete loss of protein expression, was found to cause CMCD with neonatal onset. The healthy parents and siblings of this patient were heterozygous for a Q284X mutation of the IL-17RA protein. The autosomal dominant mutation S65L in the IL-17F protein was identified by the same group in several patients of an Argentinean family; this mutation was found to impair the function of both homodimers (IL-17F/F) and heterodimers (IL-17A/F) containing the mutant isoform.²⁷ This is the first conclusive evidence that isolated CMCD, which was first described in the late 1960s, is truly a PID. Moreover, these analyses implicated IL-17 immunity in host defense against *Candida* species at mucocutaneous surfaces.

GAIN-OF-FUNCTION STAT1 MUTATIONS

Surprisingly, a *STAT1* coiled-coil domain (CC-D) mutation was discovered in an index patient from Ukraine and in a large



sequencing, or array-based sequence capture assays. This led to the identification, in autosomal dominant sporadic and familial CMCD cases, of several missense mutations in *STAT1*.⁶¹⁻⁶³ The familial segregation suggested a high clinical penetrance of these alleles, which was confirmed by the demonstration of *de novo* occurrence of the variants in several kindreds.⁶¹ The mutations affect protein function, and the underlying mechanisms probably involve gain of phosphorylation through

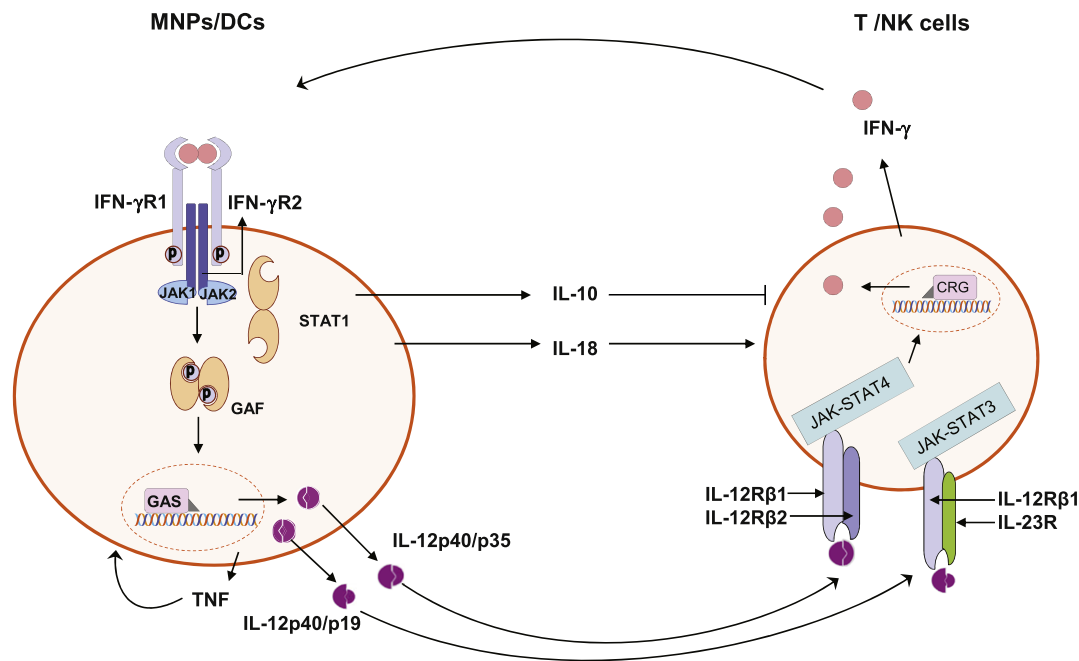


FIG 4. The IFN- γ /IL-12/IL-23 circuit and its role in regulation of innate immunity. After stimulation by IFN- γ and JAK-STAT1-mediated signaling, mononuclear phagocytes (MNP) and dendritic cells (DCs) produce IL-12 and IL-23. These cytokines induce the production of IFN- γ by natural killer (NK) and T cells. IFN- γ binds to its receptor, resulting in dimerization of the 2 receptor subunits and phosphorylation of JAK1 and JAK2. The activated JAKs phosphorylate IFN- γ receptor 1 (IFN- γ R1), leading to recruitment and activation of STAT1 proteins that translocate to the nucleus and bind to responsive elements of IFN- γ -inducible genes that are then transcribed. GAF, γ -interferon activation factor; GAS, γ -interferon activated sequence; ISRE, interferon-stimulated response elements.

loss of dephosphorylation of STAT1 after dimerization and translocation to the nucleus. Previously reported heterozygous loss-of-function mutations affecting the DNA-BD, SH2 domain, and tail-segment domain of STAT1 have been linked to autosomal dominant predisposition to mycobacterial disease as a consequence of impaired STAT1-dependent cellular responses to IFN- γ .^{64,65} In contrast, heterozygous *STAT1* mutant alleles of the CC-D causing impaired dephosphorylation of activated STAT1 in the nucleus predispose patients to CMCD; the mechanism appears to be either stronger cellular responses to STAT1-dependent IL-17 inhibitors (IFN- α , IFN- β , IFN- γ , and IL-27) or increased STAT1 responses to STAT3-dependent IL-17 inducers (eg, IL-6, IL-21, and probably IL-23).⁶¹ This results in impaired IL-17 T-cell development and IL-17 T cell-mediated antifungal responses.

Patients with gain-of-function mutations affecting the *STAT1* CC-D are prone to mucosal and skin/nail candidiasis, and they are generally not considered to be abnormally susceptible to infection by bacterial or viral pathogens (Fig 5). However, 2 Hungarian patients with *STAT1* CC-D mutations and herpes reactivation diseases in addition to CMC were reported recently.⁶³ These patients, a 47-year-old mother and her 16-year-old daughter, carry the recurrent R274W mutation of STAT1 and appear to be unable to control reactivation of varicella zoster virus (VZV) and HSV. Both patients had normal courses of primary VZV infection (chickenpox) and subclinical courses of HSV infection. This is in contrast to patients with autosomal recessive *STAT1* mutations in the DNA-BD, who present with severe manifestations of primary HSV infection (herpes

encephalitis).¹⁷ The recurrent herpesvirus disease in some patients with *STAT1* CC-D mutations might be due to impaired development and maintenance of central memory T cells similarly to those patients with heterozygous *STAT3* mutation and AD-HIES.⁶⁶ However, because most patients carrying the frequent R274W *STAT1* CC-D mutation only have CMCD, additional immunologic factors that compromise the suppression of reactivation of HSV and VZV in the 2 patients should also be considered.

CASPASE RECRUITMENT DOMAIN 9 DEFICIENCY

Caspase recruitment domain (CARD) 9 deficiency has been proposed to predispose 7 patients in a large consanguineous Iranian family to candidal disease. Only 4 of the 7 patients had CMC since early childhood, and 1 patient presented with invasive candidiasis without CMC.⁶⁷ It appears that in patients with CARD9 deficiency, CMC is part of a phenotype more complex than that of patients with CMC disease (CMCD) caused by IL-17F or IL-17RA deficiency or gain-of-function mutations in *STAT1*. Recently, it was shown that CARD9 deficiency can be associated with deep dermatophytosis (Lanternier et al, unpublished data). Several Tunisian, Algerian, and Moroccan patients from unrelated families have deep dermatophytosis as a consequence of homozygous CARD9 mutations. These patients did not present with any previously reported PID and did not have invasive candidiasis, although some had mild but not relapsing CMC. The different clinical phenotypes and infectious complications associated with CARD9 deficiency in the Iranian family

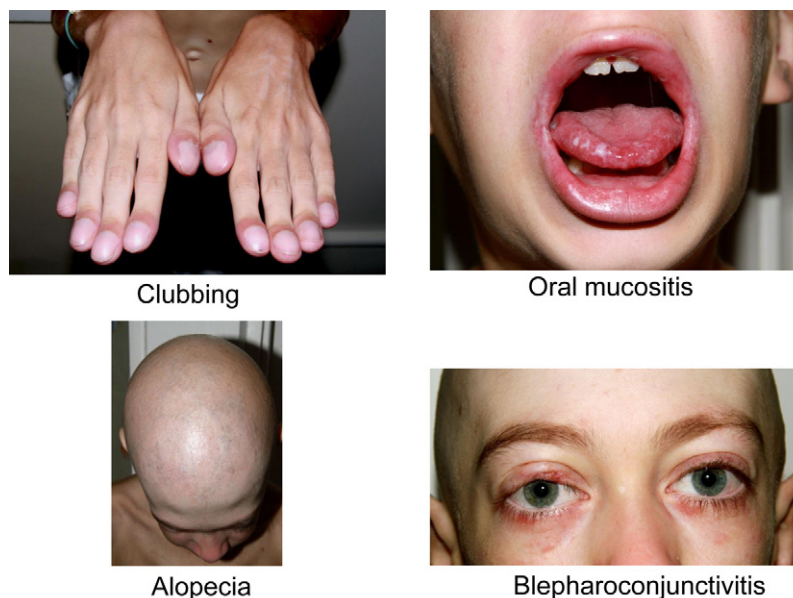


FIG 5. Severe clinical manifestation of the *STAT1* CC-D mutation. Hippocratic nails (nail clubbing), oral mucositis, total alopecia, and blepharoconjunctivitis in a 19-year-old man with the D165G mutation of *STAT1* underlying CMC is shown. The severity of the clinical phenotype is unique in this patient and contrasts with the much milder phenotypes in most patients with *STAT1* CC-D mutations.

and the North African patients remain to be explained. Genetic factors, environmental factors, or both might contribute to the differences in the manifestations of the disease. In any case *CARD9* deficiency appears to underlie invasive more than mucocutaneous fungal infections and dermatophytosis more than candidiasis.

DECTIN-1 POLYMORPHISM

In their recent report about human Dectin-1 deficiency and mucocutaneous fungal infections, Ferwerda et al⁶⁸ suggested that familial CMC can be caused by a homozygous or heterozygous Tyr238X defect of the β -glucan receptor Dectin-1. However, both homozygous and heterozygous early stop codon mutations in Dectin-1 have subsequently been found in healthy subjects (L. Maródi and J.-L. Casanova, unpublished observation). Moreover, 6% to 8% of Europeans might be heterozygous for the disabling variant of Dectin-1, and the allele frequency in some African populations might be as high as 40%, indicating that the Tyr238X mutation itself is not a disease-causing sequence variant.⁶⁸⁻⁷⁰ Therefore Dectin-1 is redundant for mucocutaneous immunity to most pathogens, including *Candida* and *Staphylococcus* species.

CONCLUSION

Recent research on mechanisms of candidiasis in patients with the mucocutaneous but not the invasive forms of the disease has consistently identified and firmly established the involvement of IL-17 in mucocutaneous host defense against *Candida* species. Cases with abnormal IL-17 immunity (through impaired IL-17 or IL-17 receptor function or *STAT1* gain-of-function mutation) serve as naturally occurring experiments, the results of which

support the hypothesis that CMC can be caused by deficiencies affecting these recently recognized cytokines mediating defense mechanisms on body surfaces. This is further supported by the breakthrough observation that patients with dominant negative *STAT3* mutations and AD-HIES have significantly lower CD4⁺/IL-17⁺ T-cell counts than healthy subjects.³⁸⁻⁴¹ Various PIDs with more complex clinical manifestations, such as those associated with mutations of the genes encoding IL-12R β 1, IL-12p40, and AIRE, have also provided informative models for understanding and defining host defense factors that are functionally impaired or missing in patients with PIDs associated with CMC. IL-17F and IL-17RA deficiencies and gain-of-function mutations of *STAT1* alleles have been described with only CMC (CMCD). However, it is important to emphasize that in some of these conditions, genotype-phenotype correlations are difficult to establish because of the limited number of patients described (eg, IL-17 deficiency, IL-17 receptor deficiency, TYK2 deficiency, and *CARD9* deficiency), and even for those diseases that have been diagnosed in a larger number of patients (eg, 71 patients with gain-of-function *STAT1* mutations and CMCD have now received diagnosis), the phenotypic characteristics need to be more precisely documented. We are only just beginning to elucidate the molecular genetic mechanisms and phenotypic characteristics of most CMCDs. The mechanism of host defense against purely mucocutaneous staphylococcal disease is puzzling because no genetic defect has been identified that predisposes patients to chronic mucocutaneous staphylococcosis. Chronic mucocutaneous staphylococcosis might be associated with IL-6 receptor-mediated signaling defects because it is associated with HIES but not with other genetic defects causing CMC, and patients with autoantibodies against IL-6 present with an increased susceptibility to cutaneous *S aureus* infection.⁵⁵ Clinical surveys of large cohorts of patients would help to identify disease-modifying factors

responsible for unusually severe phenotypes (eg, Fig 5) among patients with the same germline mutation.

What do we know?

- CMC is a genetically heterogeneous group of disorders that can result from mutations in *STAT3*, *AIRE*, *IL12RB1*, *IL12B*, *TYK2*, *IL17RA*, *IL17F*, and *STAT1*.
- Autosomal recessive *IL17RA* and autosomal dominant *IL17F* deficiencies and gain-of-function mutations in *STAT1* are characterized by specific susceptibility to skin and mucous membrane candidiasis and are referred to as CMCD.
- Defective IL-17 immunity, IL-22 immunity, or both are the major components of immunopathology of CMC.

What is still unknown?

- The specific mechanisms of action of IL-17 and IL-22 to promote defenses at the body surface against *Candida* species and other skin pathogens need to be identified.
- Genotype-phenotype correlations between various mutations and the clinical manifestation of PIDs remain poorly defined because of the limited number of patients described.
- Disease-modifying factors responsible for severe or unusual phenotypes need to be identified.

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