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Molecular mechanisms of mucocutaneous immunity against *Candida* and *Staphylococci*

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Abstract

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* may disrupt various cytokine pathways that control mucocutaneous immunity against *Candida species*, especially *Candida albicans*, and *Staphylococci*, 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 *Staphylococci*.

Keywords

Primary immunodeficiency diseases; signal transducer and activator of transcription; STAT1; STAT3; IL-17; *Candida*; *Staphylococcus*

Introduction

Many cases of primary immunodeficiency disorders (PIDs) are the results of defects in hematopoietic cell differentiation or abnormal functioning of leukocytes, in turn the consequences of mutation of genes encoding cell surface or intracellular receptors, or

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Competing interest statement

The authors declare no competing financial interest.

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 (SCID) with the T⁺B⁺NK⁺ immunophenotype was found to be caused by mutations in the gene encoding Janus-associated kinase (JAK)-3 in addition to common gamma chain deficiency caused by mutation of *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 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 commensals of the skin and mucous membranes but they can also cause mucocutaneous or invasive diseases.^{20–23} Invasive candidiasis may involve any internal organ or anatomic site and is a significant cause of morbidity and mortality of immunocompromised individuals, including in particular those with PID affecting granulocytes. Granulocytes and monocytes ingesting and killing serum-opsonized candida yeasts and macrophages phagocytizing candida both in the presence and absence of serum opsonins are of key importance in the host defense against invasive candidiasis.^{24–26} However, mucosal candida infections that are self-limited and transient may occur during menstruation and are frequent during pregnancy and in newborn infants.²³ 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 SCID, complete DiGeorge syndrome, and advanced human immunodeficiency virus 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 commensals of the skin. They are also common pyogenic pathogens that may 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 elimination of *Staphylococci* and *Candida* from tissue compartments and body surfaces; such elimination requires efficient opsono-phagocytosis and bacterial killing.^{32–34} Patients with congenital neutropenia typically suffer from pyogenic bacterial infections of the skin, mouth, and rectum. Chronic granulomatous disease (CGD) is characterized by impaired activation of nicotinamide-dinucleotide-phosphate oxidase (NADPH) activity in phagocytic cells resulting in these cells being unable to generate toxic oxygen radicals and hence to kill catalase positive bacteria.³³ Patients with CGD suffer from recurrent abscesses caused by staphylococci and candida 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 may also play a role in recruiting and activating inflammatory cells and promote anti-staphylococcal defenses. Importantly, STAT1 and STAT3-mediated signaling contributes to innate and adaptive immune responses against candida and staphylococci.¹⁷ The epithelial herpes virus entry mediator (HVEM) may also play a role in mucosal immunity against bacteria and fungi.³⁵ HVEM may induce STAT3 activation, which may promote gene expression relevant to mucosal defense against *Candida* and *Staphylococci*.

STAT family members

Cytokine binding to hemopoietin receptors initiates signaling via Janus kinases (JAK1, JAK2, JAK3, and 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 homo- 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 upon binding of interferon (IFN)- α/β , IFN- γ , IFN- λ and interleukin (IL)-27 to their receptors, and STAT3 is primarily phosphorylated and activated upon binding of IL-6, IL-10 and numerous other molecules.^{17,36}

Mutations in *STAT3* cause autosomal dominant hyper-IgE syndrome (AD HIES)

STAT proteins have been implicated in host defenses against extracellular bacteria, including *S. aureus*, and fungi, including *C. albicans*, by recent investigations of patients with AD HIES.^{38–41} It is now established that heterozygous dominant negative mutations in *STAT3* cause the AD, familial or sporadic form of the disease.^{42–45} AD HIES patients typically suffer skin and sino-pulmonary infections with *S. aureus* and skin and mucosal infections with *Candida* species in addition to eczema, unique facial characteristics, pathological bone fracture, lymphoma, and abnormal dentition (Fig 1">Fig 1).⁴⁶ Recent research has revealed that the IL-17-producing CD4⁺ T helper 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">Fig 2).⁴⁷ In some patients with AD HIES, naïve CD4⁺ T cells may fail to differentiate into IL-17-producing T cells due to dominant negative mutations of *STAT3*; almost all such mutations affect the DNA-binding domain (DNA-BD), Src homology (SH)-2 domain, or the transactivation domain of STAT3 (Fig 3">Fig 3A). DNA-BD and transactivation domain mutations may prevent binding of STAT3 homodimers and STAT3-STAT1 heterodimers to promoter sequences in genomic DNA. Indeed, 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 HIES patients in contrast to that in T cells from healthy individuals.^{39,42} These findings clearly suggest that *STAT3* mutations in HIES patients are dominant negative. Mutations in the SH2 domain may interfere with dimerization of *STAT3* proteins. The severe depletion of IL-17 T cells in patients with AD HIES has led to 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 initiate the secretion of CXC chemokines and granulocyte colony-stimulating factor (G-CSF) by epithelial cells, and these agents may then recruit neutrophils on the body surfaces and eliminate bacteria and fungi (Fig 2">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 (APS)-1

The involvement of IL-17 in the host defense against *Candida* on body surfaces precipitated mechanistic studies in patients with APS-1; these patients suffer from CMC which is one of

the three major criteria of the disease.⁴⁹ Two groups independently discovered that APS-1 patients 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 elevated titers of antibodies to type I IFNs, including antibodies against IFN- ω .^{52–53} High anti-IL-17 cytokine autoantibody titers were also detected in patients with thymoma and CMC.⁵² It therefore is plausible that APS-1 patients are susceptible to *Candida* because of the secretion of neutralizing autoantibodies against IL-17 cytokines. Importantly, anti-IFN- ω , anti-IL-17 and anti-IL-22 may serve as serological markers of the disease in early infancy before manifestations of endocrine organ damage.⁵⁴ These antibodies may 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* may also involve other mechanisms in addition to impaired IL-17 immunity. Unlike patients with AD HIES, APS-1 patients 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 may be IL-6- but not IL-17-dependent.⁵⁵ Patients with APS-1 do not develop autoantibodies against IL-6. It is also possible that the intact STAT3- and STAT1-mediated pathways in autoimmune regulator (AIRE)-deficient patients contributes to the integrity of the host defense against *Staphylococci*.

IL-12R β 1 and IL-12p40 deficiency

CMC often affects patients with PIDs like IL-12R β 1 deficiency, the most common form of Mendelian susceptibility to mycobacterial disease (MSMD). IL-12R β 1 deficiency is characterized by childhood-onset mycobacteriosis and salmonellosis; recurrent thrush caused by *Candida* 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.⁵⁸ Most candidiasis episodes (45 of 59) in these individuals were mucocutaneous, and oropharyngeal candidiasis was the most common (25 of 59 episodes) with esophageal, cutaneous, and genital candidiasis also being recorded. Intriguingly, five 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.⁵⁸

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, may be prone to CMC because of impaired IL-23-dependent immunity, important for the maintenance of IL-17-producing T lymphocytes. Note that patients with INF- γ R 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.⁵⁹

TYK2 deficiency

Most cases of HIES are inherited as an autosomal dominant trait or are sporadic presentations. However, autosomal recessive variant of the syndrome (AR-HIES) have also been described.⁶⁰ A Japanese patient with AR-HIES has been reported, and carries a homozygous nonsense mutation in *TYK2*, which encodes the Tyrosine kinase 2 (TYK2).⁶⁰ The patient presented with atopic dermatitis, markedly elevated serum IgE titers, and recurrent infections with *Staphylococci*, HSV, Bacille-Calmette-Guerin (BCG) and *Candida*, and his PBMCs failed to respond normally to stimulation with IL-6, and IL-10.⁶⁰ A Turkish patient with TYK2 deficiency who suffered from disseminated BCG infection and zoster but did not display staphylococcal or candidal disease has been reported.⁶¹ Intriguingly, in

contrast to the Japanese TYK2-deficient patient, PBMC from the Turkish patient did respond to stimulation with IL-6. Pertinent to this, a patient with auto-antibodies against IL-6 has been reported to suffer from recurrent staphylococcal skin disease but not CMC.⁵⁵ Although no PID of IL-6 or its receptor has been described, the high levels of IL-6-specific autoantibodies production in this patient with recurrent staphylococcal cellulitis and subcutaneous abscesses indicate that such PIDs may exist. This observation is coherent with the poor IL-6 responses observed in patients with STAT3 deficiency, also associated with staphylococcal disease.

IL-17 and IL-17R deficiencies

Patients with CMCD but without any other severe infection or severe non-infectious disease manifestation, such as autoimmunity, or known genetic defect have been described. Investigations in two 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 CMC 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 homo-(IL-17F/F) and hetero-(IL-17A/F) dimers containing the mutant isoform.²⁷ This is the first conclusive evidence that isolated CMC, first described in the late 1960's, is truly a PID. Moreover, these analyses implicated IL-17 immunity in the host defense against *Candida* 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 number of patients in other kindreds all over the world.^{61–63} JAK-STAT1-mediated molecular pathways have been extensively studied in recent years because of the importance of this pathway in IFN- γ -mediated host defense against intracellular pathogens.¹⁷ *STAT1* mutations had long been known to underlie mycobacterial and viral diseases.^{14,15,64,65} New genetic etiologies of CMCD are now being discovered by genome-wide investigations based on whole-genome sequencing, whole-exome 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 by loss of dephosphorylation of STAT1 after dimerization and translocation to the nucleus. Previously reported heterozygous loss-of function mutations affecting the DNA-binding domain, 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 coiled-coil domain (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 (such as IL-6, IL-21 and probably IL-23).⁶¹ This results in impaired IL-17 T cell-development and IL-17 T cell-mediated anti-fungal 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">Fig 5). However, two 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 *Herpes simplex virus* (HSV). Both patients had normal courses of primary VZV infection (chickenpox) and subclinical courses of HSV infection. This is in contrast with patients with autosomal recessive *STAT1* mutations in the DNA-BD who present with severe manifestations of primary HSV infection (herpes virus encephalitis).¹⁷ The recurrent herpesvirus disease in some patients with STAT1 CC-D mutation may 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, as most patients carrying the frequent R274W STAT1 CC-D mutation only develop CMCD, additional immunological factors that compromise the suppression of reactivation of HSV and VZV in the two patients should also be considered.

Caspase recruitment domain (CARD9) deficiency

CARD9 deficiency has been proposed to predispose seven patients in a large consanguineous Iranian family to candidal disease. Only four of the seven patients had CMC since early childhood and one 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.⁶⁸ Several Tunisian, Algerian and Moroccan patients from unrelated families develop deep dermatophytosis as a consequence of homozygous CARD9 mutations. These patients did not present with any previously reported PID and did not suffer from invasive candidiasis, although some had mild but not relapsing CMC.⁶⁸ The different clinical phenotypes and infectious complications associated with CARD9 deficiency in the Iranian family and the North African patients remains to be explained. Genetic and/or environmental factors may 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 al. suggested that familial CMC may be caused by a homozygous or heterozygous Tyr238X defect of the β -glucan receptor Dectin-1.⁶⁹ However, both homozygous and heterozygous early-stop-codon mutations in Dectin-1 have subsequently been found in healthy individuals (L. Maródi and J-L Casanova, unpublished observation). Moreover, 6 to 8% of Europeans may be heterozygous for the disabling variant of Dectin-1 and the allele frequency in some African populations may be as high as 40%, indicating that the Tyr238X mutation itself is not a disease-causing sequence variant^{70–72} Therefore, Dectin-1 is redundant for mucocutaneous immunity to most pathogens, including *Candida* and *Staphylococci*.

Conclusion

Recent research on mechanisms of candidiasis in patients suffering from the mucocutaneous but not the invasive form of the disease has consistently identified and firmly established the involvement of IL-17 in mucocutaneous host defense against *Candida*. Cases with abnormal IL-17 immunity (through impaired IL-17 or IL-17R function or low IL-17 T cell counts due to STAT1 gain-of-function) serve as naturally occurring experiments, the results of which

support the hypothesis that CMC may 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 individuals.^{38–41} Various PIDs with more complex clinical manifestations, like those associated with mutations of IL-12Rβ1, 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 (e.g. IL-17 deficiency, IL-17R deficiency, TYK2 deficiency, and CARD9 deficiency), and even for those diseases which have been diagnosed in a larger number of patients (e.g. 71 gain-of function *STAT1* CMCD patients have now been diagnosed), 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 CMC diseases. 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 (CMS). CMS may be associated with IL-6R-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 (see for example Fig. 5">Fig. 5) among patients with the same germline mutation.

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Abbreviations used

AIRE	Autoimmune regulator
APS	Autoimmune polyendocrine syndrome
AR	Autosomal recessive
BTK	Bruton's tyrosine kinase
CARD	Caspase recruitment domain
CC-D	Coiled-coil domain
CGD	Chronic granulomatous disease
CMC	Chronic mucocutaneous candidiasis
CMCD	Chronic mucocutaneous candidiasis disease
CMS	Chronic mucocutaneous staphylococcosis
DNA-BD	DNA-binding domain
G-CSF	Granulocyte colony-stimulating factor

HIES	Hyper-IgE syndrome
HSV	<i>Herpes simplex virus</i>
IFN	Interferon
IL	Interleukin
JAK	Janus-associated kinase
MSMD	Mendelian susceptibility to mycobacterial disease
HVEM	Herpes virus entry mediator
NK	Natural killer
PID	Primary immunodeficiency
PMN	Polymorphonuclear neutrophil granulocyte
ROR	Retinoic acid orphan receptor
SAP	Signaling lymphocyte activation molecule (SLAM)-associated protein
SH2	Src homology
SLAM	Signaling lymphocyte activation molecule
STAT	Signal transducer and activator of transcription
VZV	<i>Varicella-zoster virus</i>

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What do we know?

- * CMC is a genetically heterogeneous group of disorders that may 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 of *STAT1* are characterized by specific susceptibility to skin and mucous membrane candidiasis and are referred to as CMC disease
- * Defective IL-17 and/or IL-22 immunity 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 body surface against *Candida* and other skin pathogens
- * 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.

Figure 1.

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

Figure 2.

In humans, IL-6 and IL-1 are the major cytokines inducing IL-17 T cell differentiation from naïve CD4 T cells which, may also differentiate into follicular T helper (TFH) cells, T helper 1 (TH1) cells, and T helper 2 (TH2) cells. Dendritic cell-derived IL-23 reinforces and maintains IL-17 T-cell differentiation. In mice, TH17 cell differentiation may also be amplified by the release of IL-21. The IL-17 T cell differentiation involves upregulation of retinoic acid orphan receptor (ROR)- γ t. Signal transducer and activator of transcription (STAT) 3 plays critical role in signaling by both IL-21 and IL-23. TH17-derived cytokines induce secretion of chemokines, colony-stimulating factors, and antimicrobial peptides by epithelial cells. TH17- and TH22-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.

A

B

Figure 3. Representation of the domains of STAT3 (**Fig 3A**) and STAT1 (**Fig 3B**) proteins and disease-causing mutations. Currently, 75 different disease-causing mutations of *STAT3* have been reported. Fourteen morbid mutations in the CC domain and seven mutations affecting the DNA-BD, SH2 domain, and transactivation domain of STAT1 have been described. Roman numerals, coding exons; bold bars, cDNA regions corresponding to various domains, together with their amino acid boundaries; *, recessive mutation associated with partial STAT1 deficiency; N, NH2 terminal; C, COOH terminal.

Figure 4.

The IFN- γ -IL-12/IL-23 circuit and its role in regulation of innate immunity. Following stimulation by IFN- γ and JAK-STAT1-mediated signaling, mononuclear phagocytes (MNPs) and dendritic cells (DCs) produce interleukin (IL)-12, and IL-23. These cytokines induce the production of interferon γ (IFN- γ) by natural killer (NK) and T cells. IFN- γ binds to its receptor resulting in dimerization of the two receptor subunits and phosphorylation of Janus-associated kinase (JAK)1 and JAK2. The activated JAKs phosphorylate IFN- γ R1 leading to recruitment and activation of signal transducer and activator of transcription (STAT) 1 proteins that translocate to the nucleus and bind to responsive elements of IFN- γ -inducible genes that are then transcribed. GAF, gamma activated factor; ISRE, interferon-stimulated response elements; TNF, tumor necrosis factor.

Clubbing

Oral mucositis

Alopecia

Blepharoconjunctivitis

Figure 5.

Severe clinical manifestation of *STAT1* coiled-coil domain mutation. Hippocratic nails (nail clubbing), oral mucositis, total alopecia, and blepharoconjunctivitis in a 19-year-old male patient with the D165G mutation of *STAT1* underlying chronic mucocutaneous candidiasis. The severity of the clinical phenotype is unique in this patient and contrasts with the much milder phenotypes in most patients with *STAT1* CC domain mutations.