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Inborn Errors of Human JAKs and STATs

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Abstract

Inborn errors of the genes encoding two of the four human JAKs (*JAK3* and *TYK2*) and three of the six human STATs (*STAT1*, *STAT3*, and *STAT5B*) have been described. We review the disorders arising from mutations in these five genes, highlighting the way in which the molecular and cellular pathogenesis of these conditions has been clarified by the discovery of inborn errors of cytokines, hormones, and their receptors, including those interacting with JAKs and STATs. The phenotypic similarities between mice and humans lacking individual JAK-STAT components suggest that the functions of JAKs and STATs are largely conserved in mammals. However, a wide array of phenotypic differences has emerged between mice and humans carrying bi-allelic null alleles of *JAK3*, *TYK2*, *STAT1*, or *STAT5B*. Moreover, the high level of allelic heterogeneity at the human *JAK3*, *STAT1*, and *STAT3* loci has revealed highly diverse immunological and clinical phenotypes, which had not been anticipated.

Introduction

None of the known Janus kinases (JAKs), or Signal Transducer and Activator of Transcription (STAT) molecules, or associated upstream receptors and downstream targets was discovered through investigations of human patients [1]. Nevertheless, the discovery of germline mutations in two of the four human JAKs (*JAK3* and *TYK2*) and three of the six human STATs (*STAT1*, *STAT3*, *STAT5B*) has provided considerable biological insight. The phenotypic similarities between mice and humans lacking individual JAK-STAT components suggest that the functions of JAKs and STATs are largely conserved in mammals. However, a wide array of phenotypic differences has emerged between mice and humans with defects in a single JAK-STAT component. Differences in immunological phenotypes may reflect intrinsic mechanistic differences between the two species, as illustrated, for example, by the insertion of a minisatellite into the mouse STAT2 gene, preventing the recruitment of STAT4 in response to IFN-α/β [2]. Differences in infectious phenotypes may also reflect differences between experimental infections in mice and natural infections in humans [3]. We will review here the inborn errors affecting five human JAKs

and STATs, which mostly manifest as immunological and infectious phenotypes, although extrahematological clinical features have also been documented for at least two of these disorders (STAT5B and STAT3). We will specifically focus on the biological lessons learned from these experiments of Nature.

Human severe combined immune deficiency reveals a critical role for JAK3-mediated signaling in lymphoid development and function

In 1950, Glanzman and Riniker described two infants with severe infections, diarrhea and failure to thrive, both of whom died with disseminated candidiasis. Postmortem examination revealed a marked depletion of lymphoid tissue [4]. These cases probably represent the first description of severe combined immune deficiency (SCID) in humans, a genetically heterogenous group of conditions characterized by a lack of autologous T cells and extreme susceptibility to infections caused by a broad range of pathogens. SCID is inevitably fatal within the first few years of life, unless immune reconstitution is achieved therapeutically [5]. The initial descriptions of SCID were consistent with autosomal recessive (AR) inheritance, but it soon became clear that most of the patients with SCID identified in the United States were male [6], and that SCID was often inherited as an X-linked recessive (XR) trait [7]. Patients with XR SCID (X-SCID) typically lack circulating T and NK lymphocytes, but have normal numbers of B cells ($T^- B^+NK^-$ SCID phenotype).

In 1992, Takeshita *et al.* cloned the *IL2RG* gene, encoding the γ chain of the interleukin-2 receptor (IL-2R) [8]. One year later, Warren Leonard's group mapped the *IL2RG* gene to Xq13, where the X-SCID locus had been previously mapped, and showed it to be mutated in patients with X-SCID [9] (Table 1; Figure 1). The IL-2Rγ chain was initially defined as a component of the heterotrimeric high-affinity IL-2R, which also includes IL-2Rα and IL-2Rβ [8]. However, over the course of a decade, it was progressively demonstrated that the IL-2Rγ chain is common to the receptors for IL-4, IL-7, IL-9, IL-15 and IL-21 [10–15]. This led to its being renamed the common γ chain, or γc. None of these cytokine receptors has intrinsic kinase activity, and their ability to mediate signal transduction upon ligand binding is dependent on the activation of JAK1 and JAK3 [16]. In particular, JAK1 associates with the cytokine-specific receptor subunit, whereas JAK3 binds to the γc [17]. This observation led to the discovery that *JAK3* mutations account for an AR variant of $T^- B^+ NK^-$ SCID in female and male patients without *IL2RG* mutations [18,19]. The molecular mechanisms accounting for the impaired development of T and NK lymphocytes in patients with defects of γc and JAK3 signaling were unraveled by studies in humans and mice showing that IL-7 serves an essential role for T lymphocyte differentiation [20,21], whereas IL-15 is involved in NK cell development[22,23].

The identification of patients with γc and JAK3 defects preceded the generation of mice lacking the corresponding genes [24–27]. These mice had a $T^- B^- NK^-$ phenotype, indicating a requirement for γc-JAK3 signaling in B-cell development in mice, but not in humans. The generation of circulating B lymphocytes in humans is not disturbed by defects in γc and JAK3 signaling, but the B cells produced harbor intrinsic abnormalities, with impaired class-switch recombination and defective antibody production [28,29]. The molecular basis of B cell autonomous functional abnormalities in patients with defects of γc and JAK3 signaling has been recently unraveled. T follicular helper (T_{FH}) cells secrete IL-21, a potent inducer of proliferation, Ig isotype switching, plasma cell generation and Ab secretion by human B cells [30,31]. The binding of IL-21 to a heterodimeric receptor composed of IL-21R and γc induces activation of the JAK-STAT pathway. In particular, IL-21-induced STAT3 activation results in the upregulation of *PRDM1* (encoding BLIMP-1) and *XBP1*, which are required for plasma cell generation [32,33]. *In vitro* stimulation of X-SCID and JAK3-deficient B cells with CD40 ligand (CD40L) and IL-21 does not induce proliferation, plasmablast

differentiation or Ab secretion, strongly suggesting that IL-21 is the primary γc-dependent cytokine required for the maturation of human Ab responses [34]. Studies of infants with SCID have thus provided insight into the essential role played by γc and JAK3 signaling in the development of T and NK cells, and in the function of B cells.

Whereas null mutations in *IL2RG* and *JAK3* are responsible for SCID, hypomorphic mutations in the same genes may cause other immunodeficiencies, ranging from life-threatening Omenn's syndrome to milder combined immunodeficiencies [35–38]. Mutations in the intracytoplasmic tail of γc allowing residual JAK3 binding have been associated with a delay in the appearance and gradual decline of circulating T cells [39]. The development of autologous T cells has also been reported in patients with *JAK3* mutations partially permissive for JAK3 expression and for JAK3 and STAT5 phosphorylation [35]. The autologous T cells that develop in such patients display an activated phenotype and a restricted TCR repertoire indicative of very low levels of thymopoiesis and homeostatic proliferation [40,41]. However, the R222C mutation in the intracytoplasmic tail of γc is associated with normal numbers of circulating T lymphocytes, a normal polyclonal T-cell repertoire and normal thymus morphology [42,43]. Some γc mutations may thus be permissive for IL-7-mediated signaling and, hence, for normal thymic T-cell development. However, T cells carrying the R222C γc mutation bind IL-2 much less strongly than wild-type T cells, thus accounting for the patients' immunodeficiency and infectious diseases [42]. Other patients have been identified in whom hypomorphic mutations in the *IL2RG*, *IL7R* and *JAK3* genes are even associated with prominent clinical features of immune dysregulation, including lymphoproliferation and autoimmunity [44]. In one such patient with residual levels of JAK3 protein, the stimulation of circulating T lymphocytes with IL-2 *in vitro* led to normal proliferation, but no induction of Fas ligand (FasL) expression [44]. Observations in patients with mutations of the *IL2RA* and *STAT5B* genes neatly confirm the critical role played by IL-2 in immune homeostasis.

Inborn errors of STAT5B, at the crossroads of immunodeficiency and immune dysregulation

In 1997, Sharfe *et al.* described an infant with severe bacterial, viral and fungal infections [45]. Counts of autologous T lymphocytes were moderately low, T cells displayed a weak proliferative response to mitogens *in vitro*, and the patient displayed no rejection of an allogeneic skin graft. However, unlike children with SCID, the patient not only had circulating T cells but also developed peripheral lymphocytic proliferation and autoimmune primary biliary cirrhosis [46]. The disease was caused by a homozygous mutation of the *IL2RA* gene, which prevented expression of IL-2Rα (CD25) [45] (Table 1; Figure 1). Ten years later, Caudy *et al.* described another child with biallelic *IL2RA* gene mutations, and a history of severe viral infections, autoimmune enteropathy, lymphoproliferation, insulin-dependent diabetes, autoimmune neutropenia and eczema [47]. The clinical phenotype of these two patients included features of both combined immunodeficiency and severe autoimmunity, reminiscent of immune dysregulation-polyendocrinopathy-enteropathy-X-linked (IPEX) syndrome, an XR disorder caused by mutations of the *FOXP3* gene, which is critically required for the development and function of $CD4^+$ $CD25^{hi}$ T regulatory (Treg) cells [48,49]. The association of immunodeficiency and autoimmunity in patients with CD25 deficiency reflects the biological role of IL-2-mediated signaling. In fact, interaction of IL-2 with its high-affinity receptor, composed of IL-2Rα, IL-2Rβ and γc is important both for the activation of effector $CD4^+$ and $CD8^+$ T cells and for the generation of $Foxp3^+$ induced Treg (iTreg) lymphocytes from naive peripheral T lymphocytes [50]. Moreover, CD25 deficiency impairs survival and the fitness of mature nTregs in mice [51,52].

In 2003, Kofoed *et al.* described a patient with short stature and growth hormone (GH) insensitivity syndrome (GHIS), facial dysmorphism, severe infections and lymphoid interstitial pneumonitis, with a homozygous missense mutation in the *STAT5B* gene, which encodes a key component of the IL-2R signaling pathway [53]. Several other patients with biallelic *STAT5B* mutations have since been reported [54], in whom GHIS was associated with susceptibility to various infections, autoimmune manifestations and eczema. Human *STAT5A* and *STAT5B* are very similar (>90% identity) in terms of their cDNA and protein product sequences, suggesting that they may have been generated by gene duplication. However, the STAT5A and STAT5B proteins differ in the last six amino acids of the DNA-binding domain and in 20 amino acids of the transactivation domain. These differences have important biological and clinical implications, as demonstrated by the identification of STAT5B-deficient patients. The interaction of GH with its receptor (GHR) triggers JAK2 activation and STAT5B phosphorylation, leading to the production of insulin growth factor 1 (IGF-1), a key factor for body growth (Figure 1). Patients with GHR deficiency display the same extrahematological signs as STAT5B-deficient patients, with postnatal growth retardation and GH insensitivity [55,56]. By contrast, mice lacking STAT5B present a loss of sexually dimorphic body growth, such that *Stat5b*$^{-/-}$ males are similar in size to wild-type females, whereas wild-type males are much larger [57].

STAT5B-deficient patients also display various autoimmune and allergic signs, including autoimmune thyroiditis, idiopathic thrombocytopenic purpura, lymphocytic interstitial pneumonitis and severe eczema [53,54,58–60]. Individual targeting of the *Stat5a* and *Stat5b* genes in mice is not associated with significant immune abnormalities [57,61]. By contrast, *Stat5a, Stat5b* double-deficient (Stat5a$^{-/-}$Stat5b$^{-/-}$) mice have very small numbers of Treg cells in both the thymus and the periphery [62–64], leading to signs of autoimmunity and lymphocytic infiltration in multiple target organs [65]. These data are consistent with the role of Stat5 in the IL-2-induced upregulation of Foxp3 [66]. The very small number of CD4^{+} CD25^{hi} Foxp3^{+} cells and the impairment of their function in STAT5B-deficient patients [67] may therefore result from impaired IL-2 signaling, accounting for the signs of immune dysregulation associated with the disease, which are clinically related to those seen in CD25-deficient patients. These patients also display severe infections. So, what is the mechanism underlying this immunodeficiency? Higher rates of T-lymphocyte apoptosis are observed only in mice lacking both STAT5A and STAT5B [68]. Nevertheless, an increase in T-lymphocyte apoptosis may contribute to the T-cell lymphopenia observed in STAT5B-deficient patients. Defects of effector T cells may therefore account for the patients' broad and profound susceptibility to infections. These observations indicate that STAT5A and STAT5B play largely redundant roles in the development and function of the immune and endocrine systems in mice, whereas STAT5B has unique, non-redundant functions in growth and immunity in humans.

Inborn errors of STAT1 immunity: loss-of-function and gain-of-function alleles reveal a double-edged sword

Mutations in *STAT1* were first identified in studies of patients with Mendelian susceptibility to mycobacterial diseases (MSMD), who are prone to clinical disease caused by weakly virulent mycobacterial species, such as Bacille Calmette-Guérin (BCG) vaccines and environmental mycobacteria (Figure 2) (Table 1) [69]. They are also prone to tuberculosis and salmonellosis, and, more rarely, to other infections caused by intramacrophagic bacteria, fungi and parasites. The first genetic studies, carried out between 1996 and 2000, implicated the *IFNGR1* and *IFNGR2* genes, encoding the two chains of the IFN-γ receptor (Table 1; Figure 2). Allelic heterogeneity at the *IFNGR1* locus defined four forms of IFN-γR1 deficiency, including two forms of complete and two forms of partial deficiency [70]. There is also allelic heterogeneity at the *IFNGR2* locus, with at least three forms of disease [71]. The

narrow range of infectious diseases in these patients was surprising, given the broader susceptibility observed in the mouse model [72], although it gradually became apparent that pathogens other than *Mycobacterium* and *Salmonella* posed a threat to these patients [70,73].

The disorder is intrinsic to the hematopoietic lineage, as mycobacterial disease can be cured by HSCT, in both mice and humans [74,75]. It is however unclear whether IFN-γ is required to activate T cells or phagocytes, or both, during the course of mycobacterial infection, and whether its activation of T cells results indirectly in activation of phagocytes. The intramacrophagic nature of most of the pathogens seen in these patients suggests that human IFN-γ functions more as a macrophage-activating factor than as an antiviral interferon. It has also been shown that human IL-12, which is secreted by phagocytes, is an essential IFN-γ-inducing factor, as patients with IL-12p40 (Prando C. et al., unpublished) or IL-12Rβ1 deficiency [76] display MSMD with poor production of IFN-γ by both NK cells and T cells. The nature of the phagocytic cells producing IL-12 in this process remains unclear, although MSMD patients with AD IRF8 deficiency lack a potent IL-12-producing leukocyte subset, the $CD1c^+$ $CD11c^+$ dendritic cells [77]. The genes controlling the microbe-induced production of IL-12 by phagocytes in this process have remained elusive. However, the T cell-dependent, CD40-dependent induction of IL-12 has been shown to be important in this process, as this pathway is disrupted in patients with an XR form of MSMD due to specific mutations in the NEMO gene whereas most other NF-κB pathways are intact [78,79].

In macrophages, IFN-γ controls the constitutive and inducible expression of a wide range of genes. The IFN-γ-inducible target genes in leukocytes, including those operating specifically in macrophages in the control of mycobacteria, remain to be determined. However, clues to the identity of these targets were provided serendipitously by the discovery of MSMD-causing mutations in *CYBB*, which encodes the gp91 subunit of the phagocyte NADPH oxidase. *CYBB* alleles selectively deleterious in monocyte-derived macrophages, but not in monocytes and granulocytes, were found in two kindreds with another XR form of MSMD [80]. This observation suggests that *CYBB* and, perhaps, other genes controlling the respiratory burst may be key targets of IFN-γ in host defense against tuberculous mycobacteria. IFN-γ target genes must, in any case, be STAT1-dependent, because various heterozygous mutations of *STAT1* were shown, from 2001 onwards, to be associated with the impairment, but not abolition of IFN-γ responses and MSMD [81,82]. This finding was surprising, because STAT1 is also required for responses to IFN-α/β. Human STAT1 was the first member of the STAT family to be identified as a key molecule required for cellular responses to IFN-α/β [83], and its role in this and IFN-γ pathways has been clearly described in both human and mouse cells [84]. The *STAT1* alleles found in these MSMD patients are intrinsically null for both signaling pathways: the activation of both STAT1 homodimers (GAF) and STAT1-STAT2-IRF9 heterotrimers (ISGF3). However, it was dominant for GAF activation (by negative dominance) but recessive for ISGF3 activation (without negative dominance and even without haplo-insufficiency) in heterozygous cells. In other words, heterozygosity for the STAT1 mutations resulted in a normal response of the patients' cells to IFN-α/β (for ISGF3), but not to IFN-γ (for GAF), accounting for the patients displaying MSMD but no viral phenotype.

Viral diseases have not been documented in patients with AD MSMD carrying *STAT1* mutations, and have been reported in only a few patients carrying *IFNGR1* or *IFNGR2* mutations [70]. The observation that *STAT1* alleles may underlie MSMD without susceptibility to viral diseases was confirmed indirectly in 2003 by the identification of the first patients with an AR form of complete STAT1 deficiency [85]. These patients display overt susceptibility to both mycobacterial and viral infections. Their cells do not respond to either IFN-γ or IFN-α/β. Unlike MSMD patients with *STAT1* mutations, whose outcome is favorable, these patients died in the absence of HSCT. The underlying defect was

subsequently shown to be broader, impairing responses to IFN-λ and IL-27 [86]. Other patients with a similarly broad and profound susceptibility to viral infections have since been described [87,88]. Hypomorphic alleles underlie partial forms of AR STAT1 deficiency with a milder bacterial and viral phenotype [86,89–91]. Patients with either form of AR STAT1 deficiency are broadly susceptible to viruses, including herpes simplex virus-1 (HSV-1) infections, which may cause HSV-1 encephalitis (HSE) (Figure 3) (Table 1) [85,92]. The existence of a STAT1-independent IFN-α/β-responsive pathway, together with the action of antiviral molecules other than IFNs, might account for the control of at least some viral infections in patients lacking STAT1 [87]. Conversely, the contribution of IFN-α/β and IFN-λ to the viral phenotypes seen in patients bearing *STAT1* mutations is unknown, as no patient lacking either the IFN-α/β receptor or the IFN-λ receptor has been described [93]. However, IL-10Rβ-deficient patients would be expected to be unresponsive to IFN-λ, but not IFN-α/β, and such patients have never yet been reported to display susceptibility to any particular viral disease [94]. The cells requiring STAT1 to control viruses have not been identified. The IFN-α/β and –λ target genes controlling viruses including HSV-1 have also remained elusive. The identification of more patients with inborn errors of IFN-α/β and –λ immunity, including AR forms of STAT1 deficiency, should help to define the molecular and cellular basis of human viral infections.

Surprisingly, a whole-exome sequencing study aiming to identify genetic etiologies of chronic mucocutaneous candidiasis (CMC) identified patients with AD CMC carrying heterozygous missense mutations affecting the STAT1 coiled-coil domain (CCD) (Figure 4) (Table 1) [95]. A genome-wide linkage analysis led to the independent identification of similar mutations in other patients with CMC [96]. These patients seem to be affected by a broader range of fungal diseases, as the same *STAT1* mutations were recently found in patients with CMC and disseminated disease caused by *Coccidioides immitis* and *Histoplasma capsulatum* (Holland SM, personal communication). An explanation for this paradox was provided by the demonstration that the CMC-causing *STAT1* alleles are actually gain-of-function [95]. This observation accounts for the development, in some patients with CMC, of autoimmune signs, which may result from enhanced IFN-α/β immunity [97]. Nuclear dephosphorylation, rather than hyperphosphorylation in the cytoplasm, is thought to be the principal mechanism underlying the gain of function of these alleles [95]. These alleles have been shown to be both gain-of-function and dominant for all cytokines tested: IFN-α/β, IFN-γ, IFN-λ and IL-27. The CMC phenotype can also be accounted for by the very poor development of IL-17-producing T cells [95]. Indeed, patients with AD IL-17F or AR IL-17RA deficiency are prone to CMC [98]. The mechanism by which *STAT1* gain-of-function alleles impair the development of IL-17 T cells remains to be deciphered. One possibility, based on work in the mouse model, is that IFNs and IL-27 strongly inhibit the development of IL-17-producing T cells [99]. Alternatively, the gain-of-function STAT1 molecules may divert signals that are normally dependent on STAT3, downstream from IL-6, IL-21 and IL-23, all of which are potent inducers of IL-17 T cells [100]. The search for new genetic etiologies of CMC should provide insight into the mechanisms actually involved. In any case, *STAT1* is an example of a human gene for which loss-of-function mutations have been shown to cause certain infectious diseases, whereas gain-of-function mutations cause other infectious diseases.

Inborn errors of STAT3 have hematological and extrahematological consequences

The AD form of hyper IgE syndrome (HIES), first described as Job's syndrome in 1966, is characterized by the triad of eczema and recurrent staphylococcal skin and lung infections [101]. In 1972, IgE elevation was added to the syndrome [102]. Closer examination also revealed that these patients had somatic features, such as a characteristic facial

appearance, for which simple immunologic explanations were unconvincing. The range of infections in these patients is relatively limited, restricted principally to a number of bacteria and fungi, including *Staphylococcus aureus* and *Candida albicans*. High IgE levels [102,103] and the impairment of antibody synthesis [33,104] and neutrophil chemotaxis [103,105] in some patients have been documented, but T-cell function was normal [103]. The transmission of HIES in multiplex families suggested an AD mode of inheritance [103,106].

The seminal observation of *TYK2* deficiency with atopy, staphylococcal disease and high levels of IgE, prompted detailed exploration of the IL-6 signaling pathway in patients with AD HIES [107], leading to the identification of dominant-negative *STAT3* mutations as the cause of AD HIES (Figure 5) (Table 1) [108,109]. The clinical penetrance of these alleles appeared to be complete, as sporadic cases were caused by *de novo* mutations. Most of the HIES-causing mutations in *STAT3* are missense or in-frame deletions in the SH2 or DNA-binding domains. The mutations are intrinsically loss-of-function but result in inhibition of STAT3 function in a dominant-negative manner [108]. Homozygous *Stat3* deficiency led to the death of deficient mouse embryos, whereas heterozygotes had no reported phenotype. Therefore, *Stat3* was necessary for survival, but there was no overt haploinsufficiency [110]. This finding is consistent with the observation that dominant-negative *STAT3* mutations decrease STAT3 homodimer activity to about 25% of the normal level [108,111]. The embryonic lethality of $Stat3^{-/-}$ mice has made it necessary to explore various hematological and extrahematological tissue-specific deletions. These deletions are important models for STAT3 function in various tissues, but are far from exact mimics of AD HIES, which is partial and affects all tissues simultaneously.

STAT3 was discovered on the basis of sequence similarities to STAT1, and was initially recognized as a signal transducer for IL-6 and epidermal growth factor (EGF), but not for IFN-γ [112]. STAT3 is directly involved in signaling from a multitude of hematological and extrahematological receptors, especially those using the common β chain, gp130 [113–116]. At least six classes of receptors other than gp130-dependent receptors are known to activate STAT3, which has been implicated in the signal transduction pathways involving γc-dependent cytokines, type I and II interferons, the IL-10 family of cytokines, IL-12 and- 23, receptor tyrosine kinases, and other stimuli [116–119]. Following stimulation of the cell, JAKs phosphorylate a key tyrosine residue of STAT3 and the resulting phosphorylated STAT3 forms homo- and heterodimers that are translocated to the nucleus, where they activate a complex array of genes, depending on the stimulus and cell type. There is an extraordinarily high diversity of genes being regulated by STAT3, in a wide range of cell types and tissues.

So, what does the discovery of STAT3 mutations tell us about the pathogenesis of infectious diseases in patients with AD HIES? In a murine T-cell transfer model, STAT3 is required for the development of Th17 cell-mediated colitis [120], due to the STAT3 dependence of cytokines, which induce Th17 development. The development of IL-17 CD4 T cells is thus profoundly impaired in patients with HIES [121–124]. The observation of CMC in patients with AD IL-17F or AR IL-17RA deficiency suggests that the development of CMC in AD HIES patients results from impaired IL-17 immunity [95,98]. Interestingly, heterozygous loss-of-function *STAT3* alleles and heterozygous gain-of-function *STAT1* alleles are both associated with impaired development of IL-17 CD4 T cells. Respiratory epithelial cells and keratinocytes, unlike endothelial cells and fibroblasts, have been shown to be tightly dependent on IL-17 for the induction of antimicrobial target genes, probably accounting for CMC [124]. The observation that patients lacking IL-17A and IL-17F immunity mostly present with CMC [98] suggests that other mechanisms probably underlie the pathogenesis of pulmonary lesions in HIES. The development of severe staphylococcal diseases in HIES patients, particularly in the lungs, remains unexplained, as infections of this type are not observed in patients with other inborn errors of IL-17 immunity. A high proportion of AD

HIES patients were recently shown to have recurrent episodes of varicella zoster infection, which was attributed to the impairment of memory T cells [125]. Patients had fewer $CD4^+$ and $CD8^+$ central memory T cells than normal, and these cells displayed low levels of proliferation *in vitro*. They also displayed specific impairment of the control of varicella zoster and Epstein Barr viruses, but normal control of cytomegalovirus and herpes simplex virus.

What molecular mechanisms underlie some of the hematological and immunological phenotypes not directly related to the infectious diseases seen in HIES patients? The much higher risk of aggressive, predominantly B-cell lymphomas in patients with AD HIES [126] is surprising, since constitutive *STAT3* gain-of-function somatic mutations are found in many tumors, including lymphomas [127]. The patients' B cell anomalies have begun to be unraveled. T follicular helper (Tfh) cells are critical for the formation of germinal centers, and the differentiation of both Tfh cells and B cells is controlled by IL-21 [34,128,129]. Human IL-21 uses STAT3 and IRF-4 to drive B cell differentiation into plasma cells [33,130]. AD HIES patients have very low numbers of antigen-specific memory B cells despite intact class switch recombination [33,131,132]. However, their germinal centers are relatively normal and the contribution of these B-cell abnormalities to clinical disease remains unclear. B-cell immaturity is strongly linked to the preferential production of IgE in mice, and might explain the IgE elevation in patients [133]. Finally, we must consider atopy. Patients with AD HIES have normal numbers of nTreg cells with normal activity, but their ability to respond to IL-10 and the development of iTregs are impaired, potentially accounting for the atopic and inflammatory complications that are so common in this disease [134]. Residual IL-10 responses, whether dependent on or independent of STAT3, may account for the inflammatory diseases of HIES patients being less severe than those of patients with deficiencies of IL-10, IL-10RA or IL-10RB [94,135]. Atopy is exacerbated by a high skin staphylococcal burden and improved by the control of these bacteria with antibiotics or topical antiseptics.

Many primary immunodeficiencies have extrahematological aspects [136], but the variety and complexity of such manifestations in HIES were initially confusing and the identification of *STAT3* as the morbid gene has been startling. One of the most striking features of AD HIES is the characteristic pulmonary cyst formation after pneumonia. The need for lung epithelial cells to migrate, orient and ciliate after injury are severely impaired in mice with lung epithelium-restricted STAT3 and gp130 deficiencies [137]. STAT3 also regulates the expression of matrix metalloproteinases (MMPs), which are involved in tissue response to injury, and are aberrant in HIES [138]. Arterial remodeling and inflammation are tightly controlled by the TNF-α-induced production of RANTES, which is dependent on both NF-κB and STAT3, ultimately resulting in vascular smooth muscle cell proliferation and atherosclerosis [139]. Whether this explains the high rate of coronary artery tortuosity and aneurysm formation seen in HIES patients, and the associated aneurysms in cerebral vessels and lesions in brain white matter [140,141] remains to be determined. A similar process may operate in CMC patients heterozygous for gain-of-function *STAT1* mutations, who are also prone to cerebral aneurysms [95]. Chandesris *et al.* demonstrated a direct link between STAT3 and aneurysm formation in mice. Interestingly, HIES patients are not at high risk of atherosclerosis, suggesting that STAT3 deficiency causes arterial aneurysm for reasons distinct from atherosclerosis [142](Chandesris et al., unpublished). Finally, the reasons for the delayed primary dental deciduation and craniosynostosis observed in HIES patients remained a mystery for many years. The recent identification of families with isolated mutations in the gp130-associated IL-11RA who have a similar phenotype [143] suggests that the IL-11 pathway is indeed impaired in STAT3-deficient patients and that this defect may explain some of the craniofacial aspects of Job's syndrome.

Inborn errors of TYK2 immunity: clinical and immunological phenotypes; progress to date

We arrived at a more complicated page in the story of human inborn errors of the JAK-STAT pathway in 2006, with the description of a Japanese patient with AR *TYK2* deficiency (Figures 2, 3, 4, 5) (Table 1) [107]. Consistent with a previous classification of HIES on the basis of mode of inheritance into two distinct forms, AD and AR [144], TYK2 deficiency was considered to be an AR genetic etiology of HIES. This was based on the observation that the patient lacking wild-type TYK2 had atopy, susceptibility to cutaneous staphylococcal diseases and high serum concentrations of IgE. However, like MSMD patients, this patient was also susceptible to intramacrophagic bacteria, such as BCG and *Salmonella* in particular. This infectious phenotype is not classically seen in patients with AD HIES due to dominant-negative STAT3 mutations [106,111,145]. The TYK2-deficient patient also developed viral diseases, including recurrent cutaneous herpes simplex virus disease in particular, which is not a characteristic feature of HIES. However, patients with *STAT3* mutations have also recently been reported to be prone to viral diseases that reactivate from latency, including VZV and EBV, and this susceptibility has been attributed to an exhaustion of their memory T cells rather than the impairment of IFN responses [125]. Thus, clinically, this TYK2-deficient patient may be considered to have HIES. However, the absence of the multiple, non hematological, developmental signs of AD HIES, and the presence of intramacrophagic infections suggest that TYK2 deficiency may be an AR genetic etiology of a phenotype related to, but different from HIES.

Consistent with this view, a Turkish patient was recently found to have TYK2 deficiency with no hematological or extrahematological features of HIES [146]. This adult patient had never developed staphylococcal disease, had no history of atopy, and his serum IgE titers never reached the values seen in HIES patients, including the previously described TYK2-deficient patient. However, like this previous patient, he was susceptible to the reactivation of cutaneous viral infections, with recurrent varicella zoster virus lesions. He was also prone to intramacrophagic bacterial infections. Indeed, he initially presented with disseminated BCG disease and later suffered from neurobrucellosis, which resolved but resulted in cognitive impairment. These two TYK2-deficient patients also differed somewhat in terms of fungal susceptibility, as the Japanese patient displayed mild CMC, which was not documented in the Turkish patient. With only two TYK2-deficient patients displaying such overlapping but nonetheless different phenotypes, it is difficult to delineate the clinical hallmark of TYK2 deficiency.

The biological role of human TYK2 in various pathways was investigated in cells from the Japanese patient. TYK2 is a member of the JAK kinase family [147], but it has proved difficult to determine its precise role in various signaling pathways in the mouse model [148]. TYK2 seems to be non-redundant in mice, for cellular responses to receptors for at least two classes of cytokines, including IL-12 and IFN-α/β [149,150]. Residual responses to mouse cytokines were observed in the complete absence of TYK2. The cells of the Japanese patient did not respond to IFN-α/β, providing a plausible basis for the susceptibility to viral infection observed in the two patients. The cells of this patient also failed to respond to IL-12, possibly accounting for vulnerability to *Salmonella*, *Mycobacterium* and *Brucella*. These responses were rescued by transfection with wild-type *TYK2*. TYK2-deficient patients can therefore be seen almost as immunological and clinical phenocopies of patients with a partial form of AR STAT1 deficiency, displaying impaired, but not abolished IFN-γ and IFN-α/β immunity and a particular susceptibility to diseases caused by intracellular bacterial and viral pathogens [86,91]. The cellular response to other members of the IFN-α/β and IL-12 receptor families has not been investigated. The Japanese TYK2-deficient patient also had impaired responses to IL-10 [107,134], but neither he nor the Turkish patient displayed

the early-onset, severe colitis observed in patients with IL-10, IL-10R1 and IL-10R2 deficiencies [94,135], suggesting that there are residual, TYK2-independent responses to IL-10. The atopy seen in the Japanese patient may result from an impaired, but not abolished IL-10 response [134]. Cellular responses to IFN-λ and other members of the IL-10 family were not tested. Finally, the Japanese patient responded poorly to IL-6; responses to the other members of the IL-6 family of cytokines were not tested. Overall, the atopy, staphylococcal disease and high IgE titers documented in the Japanese patient and their absence in the Turkish patient remain largely unexplained. In any case, the lack of extrahematological manifestations in the two TYK2-deficient patients implies that the STAT3-dependent pathways responsible for such phenotypes, such as the IL-11 pathway, are not TYK2-dependent [143].

Concluding remarks

The characterization of inborn errors of JAK3, TYK2, STAT1, STAT5B and STAT3 in humans has provided answers to key questions about the function of these molecules. Some of these answers preceded or confirmed observations in mouse or human cells *in vitro*, and observations in mice *in vivo*. More surprising observations include the association of gain-of-function STAT1 mutations with AD CMC, due to inhibition of the development of IL-17-producing T cells, the profound endocrinological and immunological phenotype of STAT5B-deficient patients, and the association of loss-of-function STAT3 mutations with AD HIES, a complex disorder combining hematological and extrahematological signs. The dissection of clinical and immunological phenotypes associated with germline mutations in related receptors engaging JAKs and STATs has been essential, to decipher the pathogenesis of the disorders of these five genes. For example, we would not understand some dental and skeletal manifestations of AD HIES if patients with AR IL-11RA deficiency had not been identified, and the immune dysregulation of STAT5B-deficient patients if AR IL-2RA deficiency had not been identified. The identification of other inborn errors of immunity, affecting receptors that do not engage JAKs and STATs, has also been illuminating. We would not understand the basis of CMC in patients with gain-of-function STAT1 mutations if we had not identified patients with inborn errors of IL-17F or IL-17RA. In turn, the discovery of germline mutations in human JAK and STAT genes has raised new questions. Many of the immunological and clinical phenotypes seen in these patients remain unexplained at the molecular and cellular levels. For example, we still do not understand the molecular and cellular basis of staphylococcal abscesses in patients with HIES. The advent of whole-exome and whole-genome sequencing will, undoubtedly, facilitate the discovery of new inborn errors of known and unknown genes, shedding light on the pathogenesis of the disorders involving these five genes. It is also probable that germline mutations in the remaining two JAKs (JAK1 and JAK2) and the remaining three STATs (STAT2, STAT4, STAT5A) will soon be discovered. Despite 20 years of outstanding research on these molecules, it remains difficult to predict, with any degree of confidence, the phenotypes of the corresponding patients. With an expanding world population that has already reached seven billion people, increasingly efficient and widespread “phenotyping” by physicians worldwide, a mean mutation rate in the germline of about 10^{-8}, a human genome of about 3.2 billion bp, approximately 2% of which corresponds to 25,000 RNA and protein genes, and a cost of whole-genome sequencing already approaching $1,000, you do not need to be a mathematician to work out that it is now only a matter of years, decades at most, until germline mutations in most of the human genes controlling JAK- and STAT-dependent responses will have been collected and analyzed. Exciting times lie ahead.

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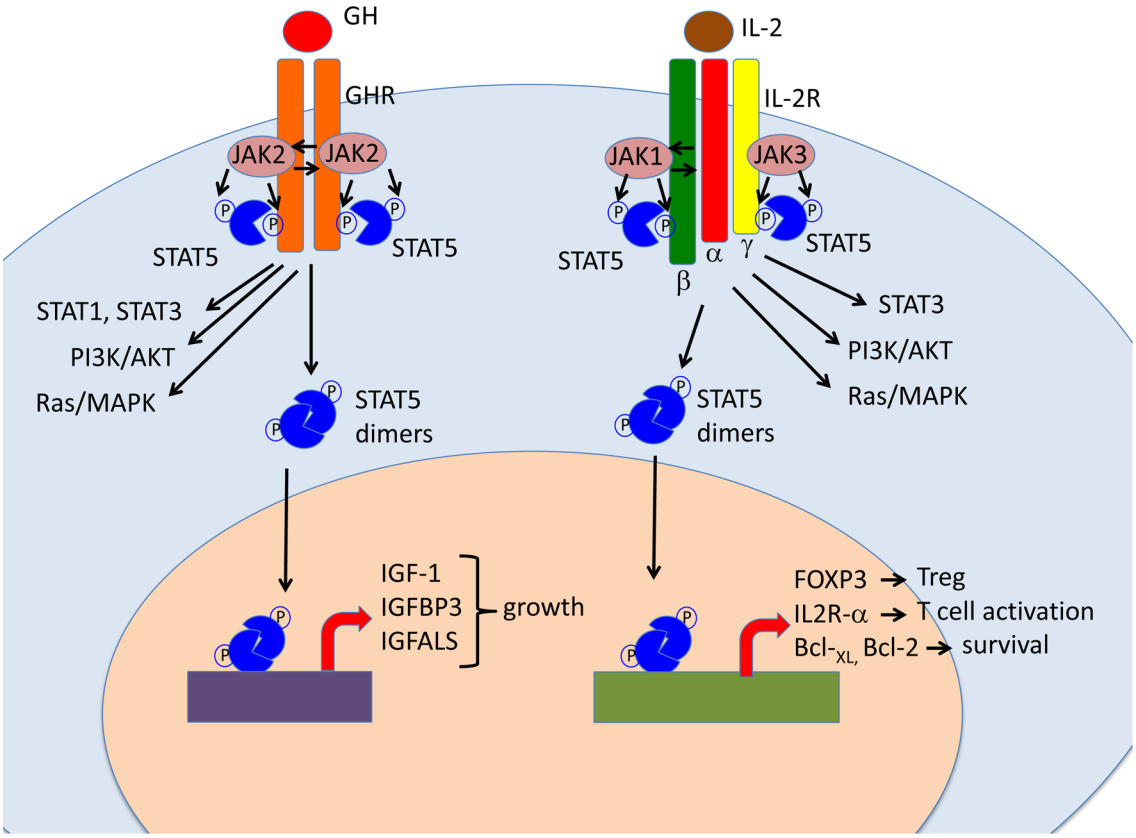

Figure 1. Schematic representation of the role of JAK/STAT5 signaling in response to growth hormone and to interleukin-2

Left: Binding of growth hormone (GH) to GH receptor (GHR) homodimer triggers activation of the JAK2 kinase that phosphorylates the GHR, creating docking sites for STAT proteins. In the Figure, recruitment and JAK2-mediated phosphorylation of STAT5 is shown, but STAT1 and STAT3 are also activated. In addition, GH also triggers activation of the PI3K/AKT and Ras/MAPK pathways. Phosphorylated STAT5 proteins dimerize and translocate to the nucleus where they drive activation of target genes. Although both STAT5A and STAT5B are activated in response to GH, the genes that encode for Insulin Growth Factor-1 (IGF-1), IGF binding protein 3 (IGFBP3) and for the acid labile subunit of IGF-like binding protein (IGFALS) are under the direct control of STAT5B, and their expression is markedly repressed in *STAT5B*-mutated patients. This results in severe growth failure.

Right: binding of interleukin-2 (IL-2) to its high-affinity receptor comprising IL-2Rα, -β and -γ chains promotes activation of JAK1 and JAK3 proteins, and recruitment of STAT3 and STAT5 to the phosphorylated IL-2R chains. PI3K/AKT and the Ras/MAPK pathways are also activated. STAT5A and STAT5B are phosphorylated and form homo- and hetero-dimers that translocate to the nucleus. Genes that are directly controlled by STAT5B and whose expression is significantly reduced in *STAT5B*-mutated patients include: *FOXP3* (that promotes development and function of Treg cells), *IL2RA* (that favors T cell activation), and the genes that encodes for anti-apoptotic factors Bcl-2 and Bcl-$_{XL}$. Failure to activate these genes in response to IL-2 explains the association of immunodeficiency and immune dysregulation in patients with STAT5B deficiency.

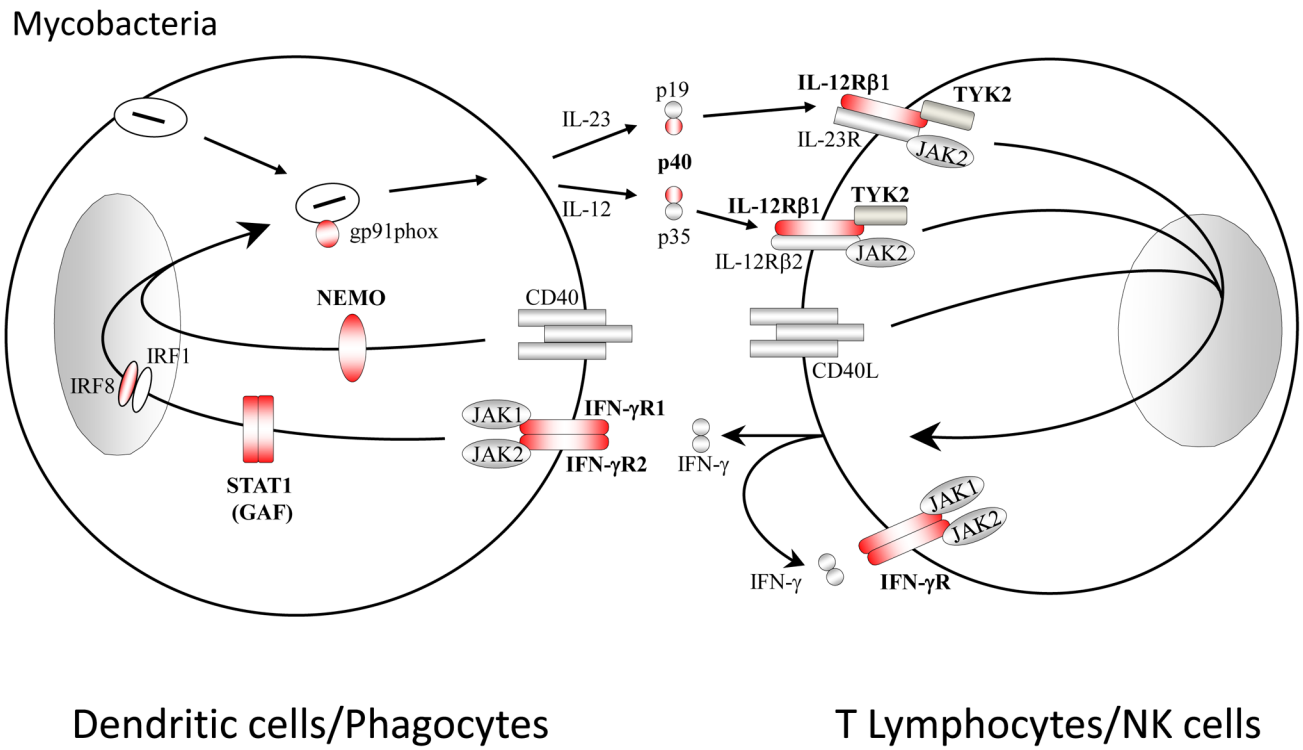

Figure 2. Inborn errors in the IL-12/23-IFN-γ pathway underlie Mendelian susceptibility to mycobacterial diseases (MSMD)

Schematic diagram of cytokine production and cooperation between phagocytes/dendritic myeloid cells and NK/T lymphocytes. The IL-12/IFN-γ circuit, the CD40/CD40L pathway and the oxidative burst (mediated in part by CYBB-encoded gp91, a component of the NADPH phagocyte oxydase) are crucial for protective immunity against mycobacterial infection in humans. Mutations in IFNGR1 or IFNGR2, encoding the ligand-binding and associated chains of the IFN-gR, impair cellular responses to IFN-g. Likewise, heterozygous dominant-negative mutations in STAT1 impair IFN-g but not IFN-a/b responses. Mutations in IL-12p40 or IL-12Rb1 impair IL-12-dependent induction of IFN-g. Mutations in CYBB that selectively impair the respiratory burst in monocyte-derived macrophages are associated with MSMD. Heterozygous dominant-negative mutations in IRF8 impair the development of IL-12-producing CD1cCD11c DCs. Proteins for which mutations in the corresponding genes have been identified and associated with MSMD, are shown in red. The allelic heterogeneity is described in Table 1.

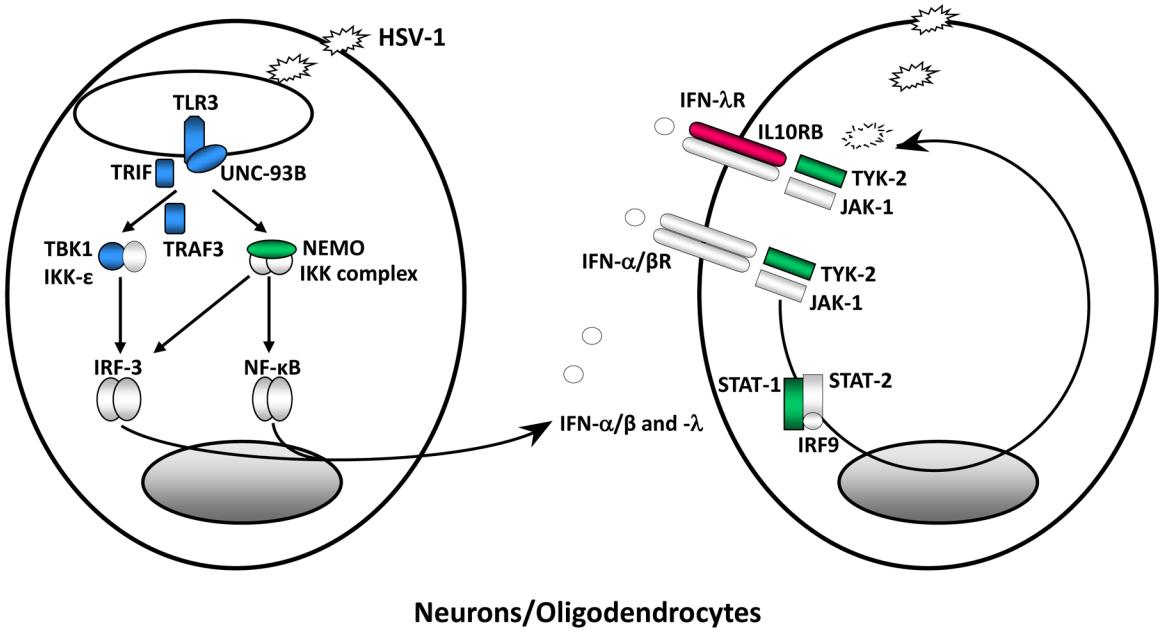

Figure 3. Inborn errors of TLR3-dependent, IFN-a/b and -l immunity underlie childhood herpes simplex virus 1 encephalitis (HSE)

Schematic representation of the production of and response to IFN-α/-β, and IFN-λ in anti-HSV-1 immunity in the central nervous system (CNS), based on the genetic dissection of children with HSE. Like most viruses HSV-1 produce dsRNA intermediates during its replication. TLR3 is an endosomal transmembrane receptor for dsRNA. The recognition of dsRNA by TLR3 induces activation of the IRF-3 and NF-kB pathways via TRIF, leading to IFN-α/-β and/or IFN-λ production. TLR3, UNC-93B, TRIF, TRAF3, TBK1 and NEMO deficiencies are all associated with impaired IFN-α/-β and/or IFN-λ production and predisposition to HSE in the course of primary infection by HSV-1. The binding of IFN-α/β and IFN-λ to their receptors induce the phosphorylation of JAK1 and TYK-2, activating the signal transduction proteins STAT-1, STAT-2 and IRF9. This complex is translocated as a heterotrimer to the nucleus, where it acts as a transcriptional activator, binding to specific DNA response elements in the promoter region of IFN-inducible genes. STAT-1 and TYK2 deficiencies are associated with impaired IFN-α/β responses and, for STAT1, impaired IFN-λ responses and predisposition to HSE. Proteins for which genetic mutations have been identified and associated with susceptibility to isolated HSE are shown in blue. Proteins for which genetic mutations have been identified and associated with susceptibility to mycobacterial, bacterial and viral diseases, including HSE, are shown in green. Proteins for which genetic mutations have been identified but not associated with susceptibility to infectious diseases are shown in red. This figure will be revised as new results are obtained with the genetic and immunological dissection of children with HSE and other viral diseases.

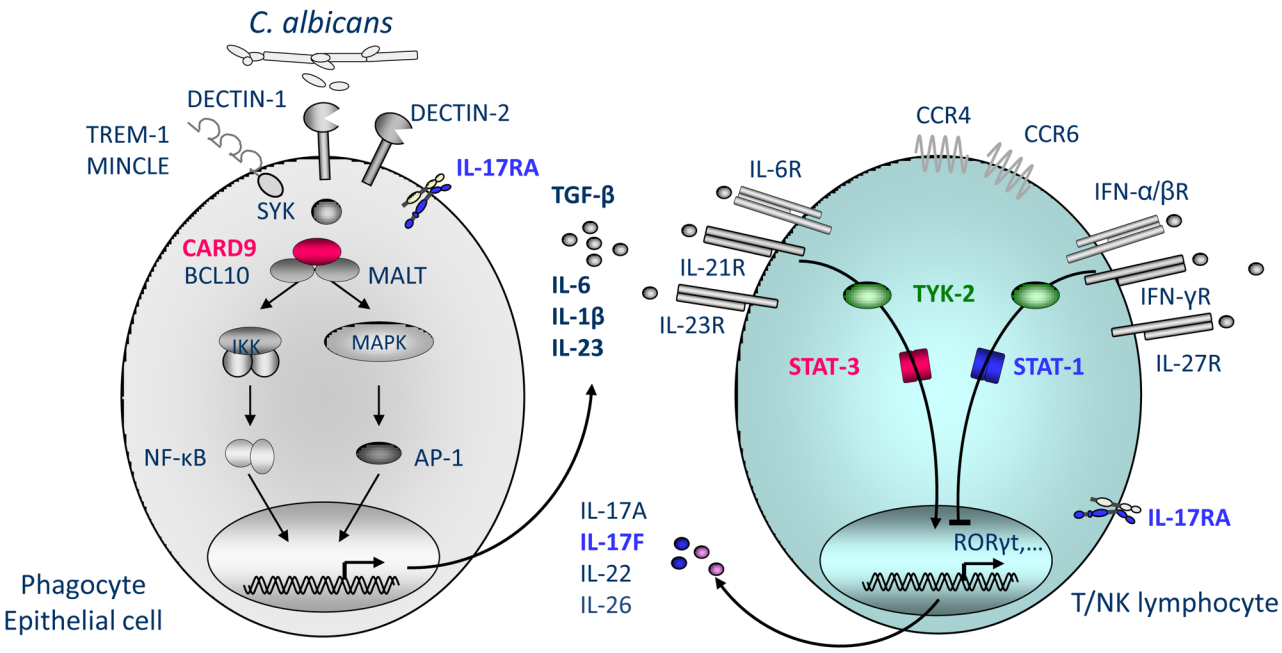

Figure 4. Inborn errors of IL-17 immunity underlie chronic mucocutaenous candidiasis (CMC)

Upon *C. albicans* recognition via various cell surface receptors, adaptor molecules SYK and CARD9 mediate the induction of pro-inflammatory cytokines by myeloid and epithelial cells. Pro-inflammatory cytokines, such as IL-6, IL-21 or IL-23, activate T lymphocytes via STAT3 resulting in their differentiation into IL-17-producing T cells. These cells constitute a major component of the immune defense against *C. albicans*, as mutations in IL-17F or IL-17RA underlie CMC. Gain of function mutations in STAT1 inhibit this differentiation by mechanisms that have remained elusive. Enhanced stimulation via IFN-a/b, IFN-g, IFN-d and IL-27 might be responsible for this phenotype. The molecule TYK2 is known to act upstream of STAT1 and STAT3. It is unclear whether patients with AR TYK2 deficiency display CMC. TYK2 deficient patients. Proteins represented in red are mutated in patients with CMC only. Proteins represented in blue are mutated in patients with CMC and other infections.

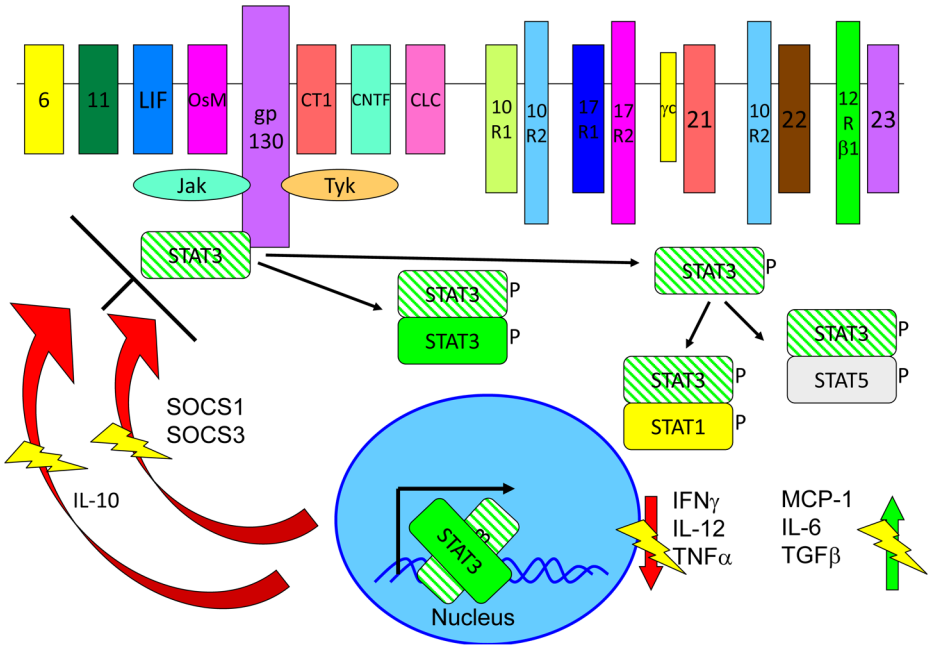

Figure 5. Multiple receptors activate the STAT3 signaling pathway

The signaling and inhibitions of STAT3 are shown, with areas of special emphasis for the dominant negative mutants shown. Crosshatched STAT3 depicts the AD-mutant form of the molecule, with each heterodimer in which it participates being inhibited from function. The thunderbolts are to indicate where a normal function is being inhibited. STAT3 is both involved in IL-10 signal transduction and in IL-10 expression, both of which are affected in Job's syndrome.

TABLE 1

Inborn errors of five human JAKs and STATs and their related defects

Gene	Inheritance	Allele	Cytokines	Hormones
JAK3	AR	LOF, HPO	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	
IL2RG	XR	LOF, HPO	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	
IL7R	AR	LOF	IL-7	
STAT5B	AR	LOF	IL-2, IL-7, IL-15	GH
IL2R	AR	LOF	IL-2	
GHR	AR	?		GH
	AD	?		GH
STAT1	AR	LOF, HPO	IFN-a/b, IFN-g, IFN-l, IL-27	
	AD	LOF	IFN-g	
	AD	HPR	IFN-a/b, IFN-g, IFN-l, IL-27	
IFNGR1	AR	LOF, HPO	IFN-g	
	AD	LOF	IFN-g	
IFNGR2	AR	LOF, HPO	IFN-g	
IRF8	AD	HPO		
IL12B	AR	LOF	IL-12, IL-23	
IL12RB1	AR	LOF	IL-12, IL-23	
NEMO	XR	HPO	Mulitple	
CYBB	XR	HPO		
TYK2	AR	LOF	IFN-a/b, IFN-l, IL-6, IL-10, IL-12, IL-23…	
IL12B	AR	LOF	IL-12, IL-23	
IL12RB1	AR	LOF	IL-12, IL-23	
IL-10	AR	?	IL-10	
IL10RB1	AR	LOF	IL-10	
IL-10RB2	AR	LOF	IL-10, IL-22, IFN-l	
STAT3	AD	LOF	IL-6, IL-10, IL-11, IL-21, IL-23, etc.	
IL11RA	AR	LOF	IL-11	
IL17F	AD	HPO	IL-17A/F, IL-17F/F[#]	
IL17RA	AR	LOF	IL-17A/A, IL-17A/F, IL-17F/F[#]	
STAT1	AD	HPR	IFN-a/b, IFN-g, IFN-l, IL-27[§]	
IL12B	AR	LOF	IL-12, IL-23	
IL12RB1	AR	LOF	IL-12, IL-23	
IL-10	AR	?	IL-10	
IL10RB1	AR	?	IL-10	
IL-10RB2	AR	?	IL-10, IL-22, IFN-l	

AR: Autosomal recessive

AD: Autosomal dominant

XR: X-linked recessive

LOF: Loss-of-function

HPO: Hypomorphic

HPR: Hypermorphic