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Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes

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The genetic dissection of various human infectious diseases has led to the definition of inborn errors of human STAT1 immunity of four types, including (i) autosomal recessive (AR) complete STAT1 deficiency, (ii) AR partial STAT1 deficiency, (iii) autosomal dominant (AD) STAT1 deficiency, and (iv) AD gain of STAT1 activity. The two types of AR STAT1 defect give rise to a broad infectious phenotype with susceptibility to intramacrophagic bacteria (mostly mycobacteria) and viruses (herpes viruses at least), due principally to the impairment of IFN- γ -mediated and IFN- α/β -mediated immunity, respectively. Clinical outcome depends on the extent to which the STAT1 defect decreases responsiveness to these cytokines. AD STAT1 deficiency selectively predisposes individuals to mycobacterial disease, owing to the impairment of IFN- γ -mediated immunity, as IFN- α/β -mediated immunity is maintained. Finally, AD gain of STAT1 activity is associated with autoimmunity, probably owing to an enhancement of IFN- α/β -mediated immunity. More surprisingly, it is also associated with chronic mucocutaneous candidiasis, through as yet undetermined mechanisms involving an inhibition of the development of IL-17-producing T cells. Thus, germline mutations in human *STAT1* define four distinct clinical disorders. Various combinations of viral, mycobacterial and fungal infections are therefore allelic at the human *STAT1* locus. These experiments of Nature neatly highlight the clinical and immunological impact of the human genetic dissection of infectious phenotypes.

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Current Opinion in Immunology 2012, 24:364–378

This review comes from a themed issue on **Host pathogens**

Edited by **Anne O'Garra** and **Eric Pamer**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 30th May 2012

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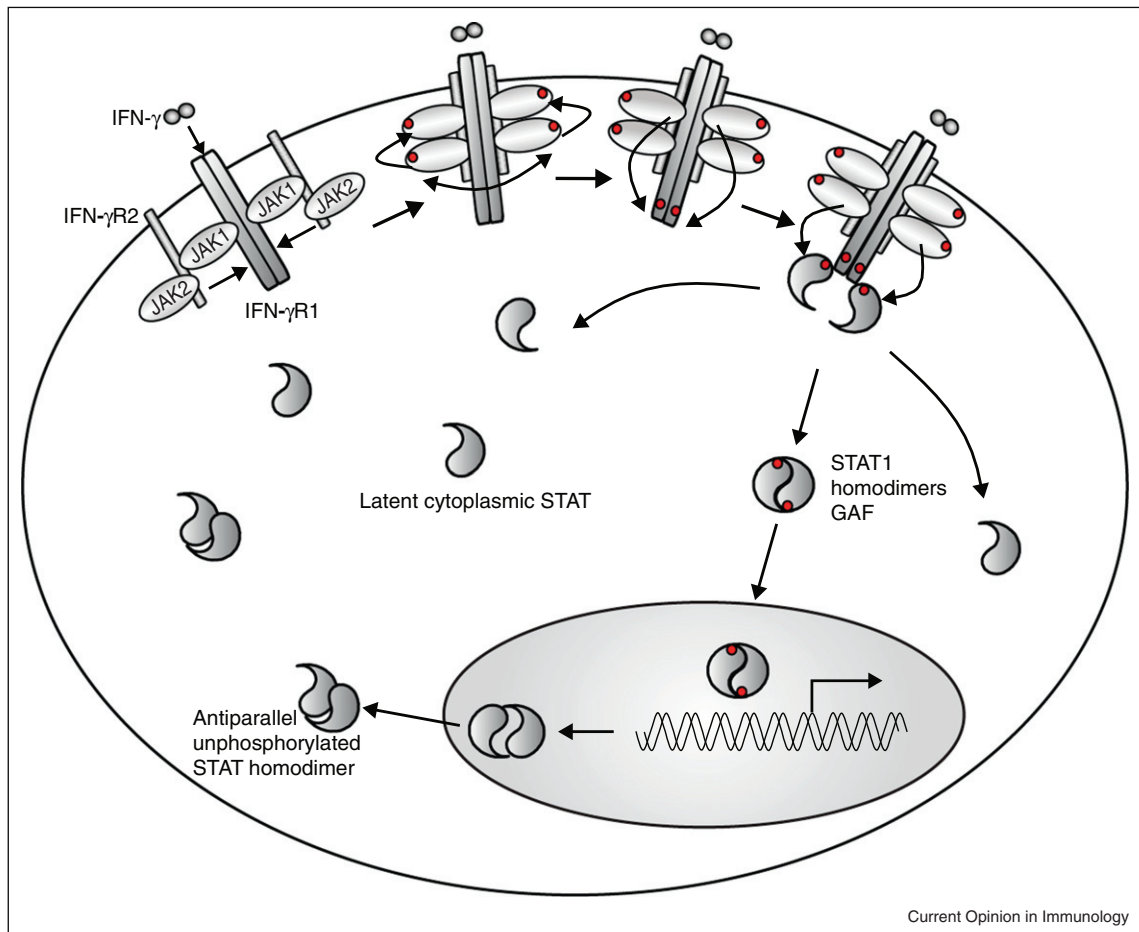
<http://dx.doi.org/10.1016/j.coi.2012.04.011>

Introduction: structure and function of STAT1

STAT1 was the first STAT to be identified, in 1989, and is a key transcription factor mediating IFN- α/β signaling [1–5]. In mice and humans, the *STAT1* gene encodes two STAT1 isoforms, generated by alternative splicing. STAT1- α is transcriptionally active and encodes a protein of 750 amino acids (91 kDa), whereas STAT1- β (84 kDa) acts as its dominant-negative inhibitor as it lacks part of the transactivation domain and the Ser phosphorylation site (Ser 727) [6]. STAT1- α (hereafter referred to as STAT1) is involved in various signaling pathways, including the IFN- α/β , IFN- γ , IFN- λ , IL-2, IL-3, IL-6, IL-9, IL-10, IL-11, IL-12, IL-15, IL-21, IL-22, IL-26, IL-27, EGF, VEGF, FGF, HGF, GH, angiotensin and OSM pathways [7]. STAT1 activation conforms to the same general pattern as for other STATs (Figure 1)[8–10]. Briefly, the binding of the soluble extracellular agonist to its specific cell surface receptor leads to the activation of specific JAKs constitutively associated with the receptor chains. The JAKs phosphorylate the intracellular domains of the receptors, thereby creating a docking site for latent cytoplasmic STAT1, which is recruited, undergoes Tyr 701 phosphorylation and is then released from the receptor complex. Phosphorylated STAT1 can form homodimers and heterodimers and multimers, which are then translocated to the nucleus, where they bind to conserved genetic boxes to activate or modulate the transcription of specific target genes [10]. STAT1 is subsequently dephosphorylated in the nucleus [11–13] and exported back to the cytoplasm, where it remains as a monomer or antiparallel unphosphorylated dimer [14,15]. A role for unphosphorylated STAT1 (U-STAT1) in the mediation of some transcriptional activity has been reported [16]. Other posttranslational modifications of STAT1, in addition to the phosphorylation of Tyr and Ser residues, have been reported to contribute the activity of this protein. These modifications include acetylation, methylation and sumoylation [17–20]. However, the specific roles of posttranslational modifications other than Tyr 701 and Ser 727 phosphorylation remain to be clarified.

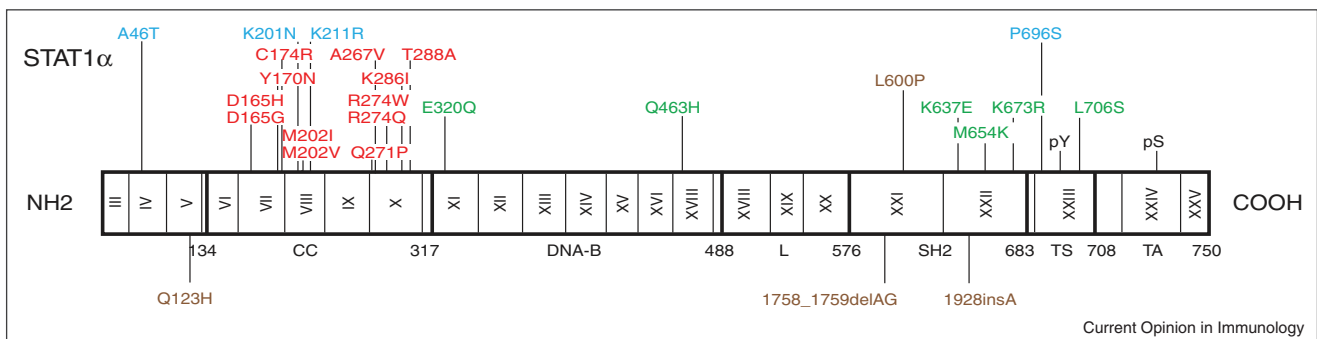
The N-terminal domain (NTD) of STAT1 is known to be involved in the interaction of the protein with its surface receptor [21], and in phosphorylation [21], nuclear translocation [22] and transcriptional activity, through the facilitation of tetramerization [23,24] and dephosphorylation (Figures 1 and 2) [22,25,26]. The coiled-coil domain

Figure 1



The STAT1 cycle: signaling pathway and recycling. Schematic diagram of STAT1 activation and de-activation following IFN- γ stimulation. Following the binding of the cytokine to its receptor, a series of tyrosine phosphorylation events (red circles) occur: first the JAKs autophosphorylate and transphosphorylate each other; they then phosphorylate the intracellular part of the receptor, creating a docking site for STAT1. Recruited STAT1 are also phosphorylated by the JAKs, leading to their removal from the receptor, dimerization and translocation to the nucleus to modulate target gene expression. STAT1 dephosphorylation occurs in the nucleus and STATs are then exported back to the cytoplasm.

Figure 2



Representation of the human *STAT1* gene and of the domains of the corresponding protein, with key residues and morbid mutations indicated. The human *STAT1 α* isoform is shown, with its known pathogenic mutations. Coding exons are numbered with roman numerals and delimited by a vertical bar. Regions corresponding to the coiled-coil domain (CC), DNA-binding domain (DNA-B), linker domain (L), SH2 domain (SH2), tail segment domain (TS), and transactivator domain (TA) are indicated, together with their amino-acid boundaries, and are delimited by bold lines. Tyr701 (pY) and Ser727 (pS) are indicated. Mutations in green are dominant and associated with partial *STAT1* deficiency and MSMD. Mutations in brown are recessive and associated with complete *STAT1* deficiency and intracellular and viral diseases. Mutations in blue are recessive and associated with partial *STAT1* deficiency and mild intracellular and/or viral disease. Mutations in red are dominant and associated with gain-of-activity of *STAT1* and CMCD.

(CC) has considerable potential for involvement in protein-protein interactions and plays a key role in the dimerization of unphosphorylated STAT1 and nuclear STAT1 dephosphorylation [10,14,26–30]. The DNA-binding domain (DNA-B) includes residues such as Asn 460 and Lys 336, which come into contact with the DNA major groove, and Glu 421, which comes into contact with the minor groove [28]. In addition, some residues contribute to the nuclear import of phosphorylated STAT1 dimers by binding to importin- α 5 [31–34], whereas others are involved in the nuclear export of the protein [12,35,36]. The linker domain (L) is involved in IFN- γ -driven transcription [37] and in the stability of DNA binding [38]. The SH2 domain (SH2) plays an essential role in binding to the phosphorylated surface receptor and to the phosphorylated tail of other STATs [28]. The tail segment (TS) includes the crucial Tyr 701 residue, which is phosphorylated by JAKs upon activation, thereby facilitating dimerization through interaction with the SH2 domain of another STAT [28]. The transactivation domain (TA) enables the protein to induce or modulate the transcription of target genes. It also contains the Ser 727 residue, the phosphorylation of which increases the transcriptional activity of STAT1 [10,39]. The structure-function relationship of various domains and residues of STAT1 has been characterized in detail.

Immunological and infectious phenotypes of STAT1-deficient mice

STAT1 knockout mice were generated in 1996 by two different groups [40,41]. Despite the demonstration of STAT1 activation by diverse cytokines and hormones *in vitro* [3,5,7], the knockout mice were born in Mendelian proportions, displayed no overt developmental abnormalities and their leukocyte counts were not low for the populations of cells tested (T cells, B cells, monocytes, macrophages and granulocytes), with the exception of CD4⁺CD25⁺ regulatory T cells [42]. However, these mice responded very poorly to IFN- α/β and IFN- γ , as demonstrated by the absence of detectable gamma activating factor (GAF; STAT1 homodimer) and interferon-stimulated gene factor 3 (ISGF3; STAT1/STAT2/IRF9 heterotrimer). The transcription of most of the genes usually induced by IFN- α/β and IFN- γ was abolished, highlighting a non-redundant role of STAT1 in the two corresponding pathways. Interestingly, residual STAT1-independent responses were subsequently reported [43,44]. It was not until 2004 and 2010 that STAT1 was also shown to be non-redundant for cellular responses to IFN- λ and IL-27, respectively [45–49]. Overall, correct cellular responses to at least four cytokines in the mouse model seem to be highly dependent on STAT1. Mouse STAT1 appears to be redundant for the responses to at least 11 other cytokines (IL-2, IL-3, IL-6, IL-9, IL-10,

Table 1

The infectious phenotype of STAT1 knockout mice

Pathogens	Classification	Additional information	S or N	Reference
Sindbis (SINV)	Virus	Togaviridae ss RNA (+)	S	[43]
Chikungunya virus (CHIKV)	Virus	Togaviridae ss RNA (+)	S	[50,51]
Mouse hepatitis virus (MHV)	Virus	Coronaviridae ss RNA (+)	S	[40]
Severe acute respiratory syndrome coronavirus (SARS-CoV)	Virus	Coronaviridae ss RNA (+)	S	[52]
Murine norovirus 1 (MNO1)	Virus	Caliciviridae ss RNA (+)	S	[53,54]
Dengue virus (DENV)	Virus	Flaviviridae ss RNA (+)	N	[63,64]
Vesicular stomatitis virus (VSV)	Virus	Rhabdoviridae ss RNA (–)	S	[40,41]
Influenza A virus	Virus	Orthomyxoviridae ss RNA (–)	S	[48]
Filoviruses (Ebola, Marburg, Reston Ebola)	Virus	Filoviridae ss RNA (–)	S	[56*,57*]
Machupo Virus (MACV)	Virus	Arenaviridae ss RNA (–)	S	[58*]
Crimean-Congo hemorrhagic fever virus (CCHFV)	Virus	Bunyaviridae ss RNA (–)	S	[59*]
Sendai virus (SeV)	Virus	Paramyxoviridae ss RNA (–)	S	[60]
Measles virus	Virus	Paramyxoviridae ss RNA (–)	N	[65,66]
Herpes simplex virus (HSV)	Virus	Herpesviridae ds DNA	S	[61,62*]
Mouse cytomegalovirus (MCMV)	Virus	Herpesviridae ds DNA	S	[43]
<i>Listeria monocytogenes</i>	Bacteria	Gram +	S	[40]
<i>Mycobacterium tuberculosis</i>	Bacteria	Acid fast Gram +	S	[67]
<i>Francisella novicida</i>	Bacteria	Gram –	S	[68]
<i>Chlamydia pneumoniae</i>	Bacteria	Gram –	S	[69]
<i>Borrelia burgdorferi</i>	Bacteria	Gram –	N	[70]
<i>Toxoplasma gondii</i>	Parasite		S	[71,72]
<i>Cryptosporidium parvum</i>	Parasite		S	[73]
<i>Leishmania major</i>	Parasite		S	[74]
<i>Leishmania donovani</i>	Parasite		N	[75]
<i>Candida albicans</i>	Fungus		N	[76]

S: susceptible. N: normal.

IL-11, IL-12, IL-15, IL-21, IL-22, IL-26), and seven hormones (EGF, VEGF, FGF, HGF, GH, angiotensin, OSM), at least in the experimental conditions tested.

STAT1 knockout mice have been challenged with at least 27 pathogens, including 17 viruses, five bacteria, four parasites and one fungus (Table 1). Unsurprisingly, STAT1-deficient mice are highly susceptible to most viruses, including (+) single-strand RNA viruses, such as Sindbis [43], chikungunya virus (CHIKV) [50,51], mouse hepatitis virus (MHV) [40], severe acute respiratory syndrome coronavirus (SARS-CoV) [52] and murine norovirus 1 [53,54], (–) single-strand RNA viruses, such as vesicular stomatitis virus (VSV) [40,41], influenza virus A [48,55], filoviruses (Ebola, Marburg, Reston Ebola) [56,57], Machupo virus (MACV) [58], Crimean-Congo hemorrhagic fever virus (CCHFV) [59], and Sendai virus (SeV) [60], double-strand DNA viruses, such as herpes simplex virus (HSV) [61,62] and mouse cytomegalovirus (MCMV) [43]. However, they seem to be normally resistant to the (+) single-strand RNA dengue virus [63,64] and to the (–) single-strand RNA measles viruses [65,66]. STAT1 knockout mice are less susceptible to some infections (MCMV and Sindbis viruses) than mice with a double knockout for IFN- γ R and IFN- α/β R, presumably owing to STAT1-independent responses [43]. STAT1 knockout mice are also susceptible to infection with intracellular Gram-positive bacteria, such as *Listeria monocytogenes* [40] and *Mycobacterium tuberculosis* [67], and intracellular Gram-negative bacteria, such as *Francisella novicida* [68] and *Chlamydia pneumoniae* [69], but not in the largely extracellular *Borrelia burgdorferi* [70]. STAT1-deficient mice are highly susceptible to the parasites *Toxoplasma gondii* [71,72], *Cryptosporidium parvum* [73] and *Leishmania major* [74], but are normally resistant to infection with *Leishmania donovani* [75]. Most of these bacteria and parasites infect macrophages, and the

susceptibility of STAT1-deficient mice probably closely resembles that of IFN- γ R-deficient mice. STAT1-deficient mice have also been challenged with the fungus *Candida albicans*; their response to this challenge was similar to that of wild-type mice [76]. To our knowledge, mice heterozygous for a null *STAT1* allele have not been tested. Transgenic mice overexpressing wild-type *STAT1* and mice carrying hypomorphic or hypermorphic *STAT1* alleles do not appear to have been described either.

Human AR complete STAT1 deficiency: life-threatening intramacrophagic bacterial and viral diseases

A new syndrome characterized by the association of infectious diseases caused by intracellular bacteria (typically mycobacteria) and viruses (typically herpes viruses) was clinically described and genetically elucidated in 2003 (Table 2, Figures 1–5) [77]. Some infections resemble those seen in patients with T-cell combined immunodeficiencies, except that the patients have normal T-lymphocyte counts and function [78]. The known patients carry biallelic loss-of-expression and loss-of-function (LOF) *STAT1* alleles, leading to a complete absence of the wild-type protein [77]. They have missense mutations (L600P and Q123H, leading to the in-frame splicing out of coding exon 3), small frameshift deletions (1758_1759delAG), and small frameshift insertions (1928insA). Only six patients from four unrelated families have been identified to date (Table 2) (Figure 2) [77,79,80] (unpublished data). This is a purely recessive disorder and no haplo-insufficiency at the *STAT1* locus has been reported for any of the known cellular or clinical phenotypes. The patients are susceptible to weakly virulent mycobacteria, such as BCG vaccines and *Mycobacterium kansasii*, and to herpes viruses, such as HSV-1 and CMV. The control of attenuated poliovirus type III vaccine, rhinovirus and parainfluenza virus type II in

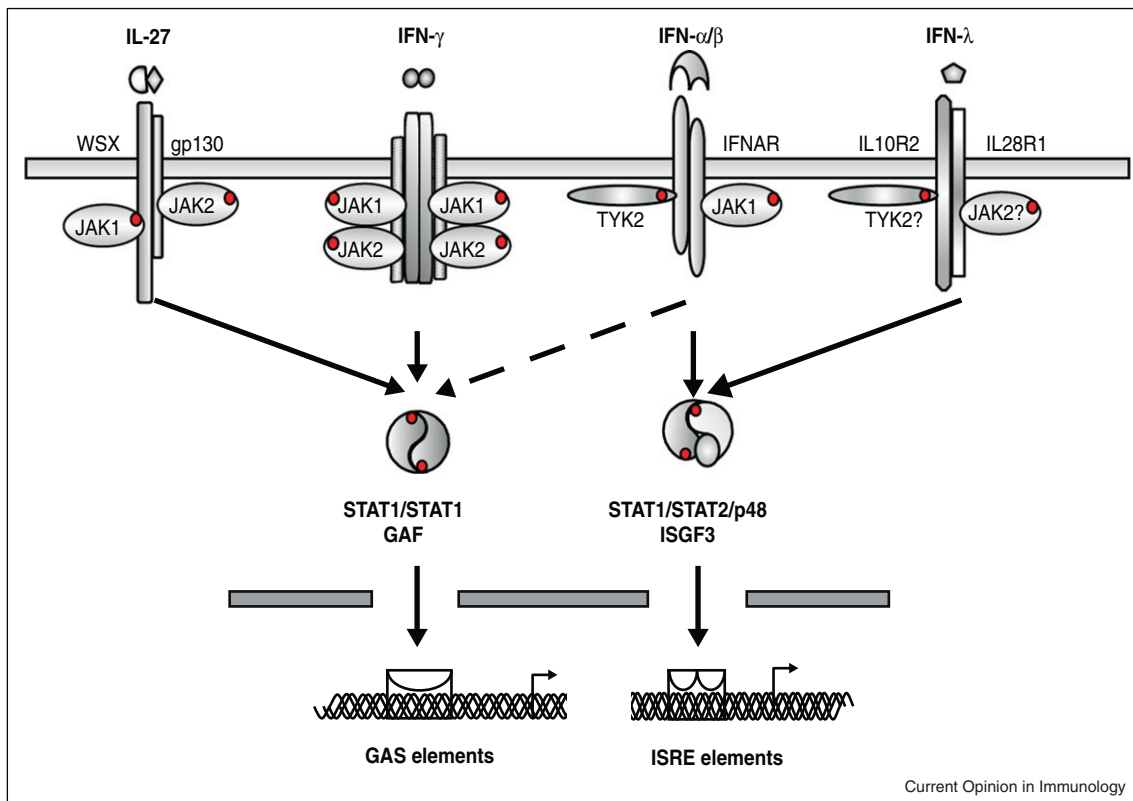
Table 2

Four types of inborn errors of human STAT1 immunity

	Number of patients described	Number of kindreds	STAT1 domain affected	Main cellular phenotype	Main clinical phenotype
AR complete STAT1 deficiency	6	4	NTD, SH2	No STAT1-dependent response to IFN- γ , IFN- α/β , IFN- λ and IL-27	Lethal intracellular bacteria (mainly mycobacteria) and viral (mainly herpes) diseases
AR partial STAT1 deficiency	5	3	NTD, CC, TS	Impaired STAT1-dependent response to IFN- γ , IFN- α/β , IFN- λ and IL-27	Curable intracellular bacteria (mainly mycobacteria) and viral (mainly herpes) diseases
AD LOF STAT1 deficiency	16	8	DNA-B, SH2, TS	Impaired STAT1-dependent response to IFN- γ and IL-27	Mycobacterial diseases
AD GOF STAT1 disorder	68	27	CC	Enhanced STAT1-dependent response to at least IFN- γ , IFN- α/β , IL-27, IL-6 and IL-21. Impaired IL-17 T-cell immunity	CMCD and autoimmunity

AR: autosomal recessive. AD: autosomal dominant. LOF: loss-of-function. GOF: gain-of-function. NTD: N-terminal domain. SH2: SH2 domain. CC: coiled-coil domain. DNA-B: DNA-binding domain. TS: tail segment domain. To date, incomplete clinical penetrance is only observed for AD LOF STAT1 deficiency. The unpublished identification of defects in AD LOF STAT1 deficiency (mutation Y701F in one kindred) and AD GOF STAT1 disorder (24 and 18 CMCD kindreds with mutations in the STAT1 DNA-B and CCD, respectively) are not taking into account in the table.

Figure 3



Schematic diagram of the role of STAT1 in antiviral and anti-mycobacterial immunity. Schematic representation of the STAT1-dependent signaling pathways in response to IL-27, IFN- γ , IFN- α/β and IFN- λ . In humans, STAT1-GAF dependent IFN- γ immunity is crucial for protection against mycobacteria (and other intramacrophagic microbes), and a role of STAT1-GAF-dependent IL-27 immunity in this process cannot be excluded. STAT1-ISGF3 dependent IFN- α/β immunity is crucial for protection against viruses (mainly herpes viruses), and a role of STAT1-ISGF3-dependent IFN- λ immunity cannot be excluded.

one patient suggests that STAT-1-independent innate antiviral mechanisms may be sufficient in humans [79,81]. Nevertheless, five patients died: two at 3 months of age from mycobacterial disease, two at 12 and 16 months of age from viral disease (including one from HSV-1 encephalitis, HSE) [82*] and another at 11 months of age from severe hepatitis in the course of hematopoietic stem cell transplantation (HSCT) [79]. The sixth patient is still alive one year after HSCT [80*]. Some key infectious phenotypes of STAT1-deficient patients have been seen in patients with other inborn errors of cytokine immunity. The TLR3-dependent induction of IFN- α/β and IFN- λ was shown to be impaired in other children with HSE [82*]. Moreover, mycobacterial disease in some other children has been shown to result from impaired IFN- γ -mediated immunity [83]. Both TLR3 and IFN- γ R deficiencies are also life-threatening disorders.

EBV-transformed B cells (EBV-B cells) and SV40-transformed fibroblasts (SV40-fibroblasts) from these patients were unresponsive to IFN- γ and IFN- α in terms of both

GAF and ISGF3 activity [77,79,80*]. They were also unresponsive to IL-27 and IFN- λ stimulation, in terms of GAF-DNA binding activity and the induction of target genes, such as *IFIT1*, respectively [84]. EBV-B cells and SV-40 fibroblasts from patients with complete STAT1 deficiency cannot control the replication of viruses, such as VSV, EMCV, or HSV-1, even after treatment with IFN- α [77,79]. In addition, induction of MxA after Influenza A infection was shown to require IFN- α/β -dependent or IFN- λ STAT-1-dependent signaling [85]. Moreover, leukocytes from these patients have an impaired response to IFN- γ in terms of the induction of IL-12 and other target genes. The STAT1-independent induction of IFN- γ has been documented in IFN- α -stimulated NK cells from a patient [80*]. In addition, STAT1 has been shown to be dispensable for T follicular helper (Tfh) cell differentiation [86*], memory B-cell formation and IL-21-induced Ig secretion in patients' cells *in vitro* [87*]. The overall susceptibility of patients to mycobacteria and other intracellular bacteria may be largely explained by the impairment of IFN- γ -GAF

immunity. Indeed, IFN- γ has already been shown to be essential for human antimycobacterial immunity (Figures 3–5) (see below [83]). A role for impaired IL-27 immunity, although unlikely [88], is possible, at least if we consider IL-27 as an IFN- γ -inducing cytokine (through a decrease in STAT1-independent IFN- γ responses). By contrast, the observed susceptibility to viruses is largely owing to the impairment of IFN- α/β responses, as inferred from the susceptibility of IFN- α/β R-deficient mice (Figure 3). A contribution of impaired IFN- λ immunity is plausible, at least for some viral infections, as inferred from both the mouse model [89,90] and the role of human IFN- λ in the clearance of hepatitis C virus [91,92,93,94]. Patients lacking IL-10R2 (one of the two chains of the receptor for IFN- λ) have not been reported to be particularly susceptible to viral diseases [95]. However, these rare patients died or underwent HSCT early in life, possibly preventing the expression of a viral phenotype. In any case, the cellular and clinical penetrance of complete STAT1 deficiency appears to be complete, as all homozygous patients have an equally severe cellular and clinical phenotype. HSCT appears to be the only curative treatment for these patients. The identification and investigation of a larger number of patients is required to improve delineation of the redundant and non-redundant roles of human STAT1 in cell signaling, host defense and beyond.

AR partial STAT1 deficiency: milder intramacrophagic bacterial and viral diseases

From 2009 onwards, five patients from three unrelated kindreds were identified with a partial, as opposed to complete form of AR STAT1 deficiency (Table 2) (Figure 2) [96,97,98]. The patients harbor biallelic *STAT1* mutations (homozygous in two kindreds and compound heterozygous in the third), which are hypomorphic (as opposed to amorphic). The four mutations are missense and all reduce but do not abolish STAT1 production. One mutation affects the NTD (A46T), two affect the CCD (K201N and K211R) and one affects the TSD (P696S). No precise functional data are available for the A46T mutation, but the other three mutations are unusual in being not only missense mutations, but also, primarily, splice mutations. Indeed, the two mutations in the CCD region cause the splicing-out of exon 8 [97,98], whereas that in the TSD region splices out exon 23 [96]. The P696S and K201N mutations have no effect on the function of the residual full-length STAT1 produced, accounting for the partial nature of the defect [96,97]. The K211R mutation has not been characterized in this respect [98]. By comparison with complete STAT1 deficiency, this disorder is thus associated with milder intramacrophagic bacterial (*Salmonella*, *M. avium*, BCG) and viral (CMV, VZV, HSV-1, RSV) diseases, most of which are cured by antibacterial or antiviral drugs [96,97,98]. Four of the five patients are alive and were aged 12, 14, 14 and 16 years at last follow-up. The fifth

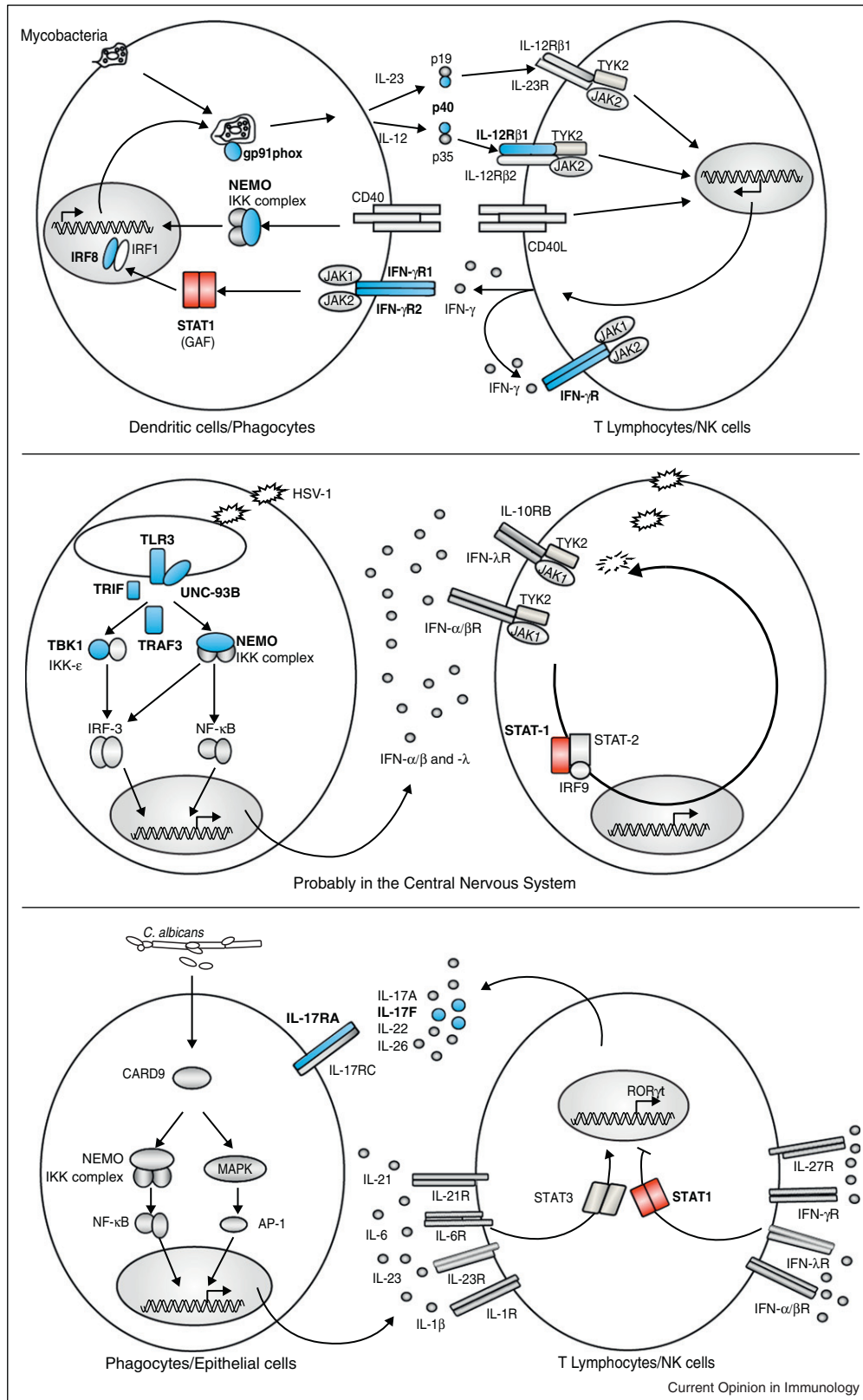
patient died of sepsis at the age three years, after an episode of disseminated mycobacterial disease. Two patients are seropositive for EBV and CMV and another is seropositive for EBV, CMV and VZV, so these patients were able to mount an effective immune response against at least these viruses, leading to their control [81,97,98]. As they are now in their teens, they probably have been exposed to and controlled other viruses as well.

Unlike EBV-B cells and SV40-fibroblasts from patients with complete STAT1 deficiency, cells from patients with a partial deficiency produce residual non-null amounts of functional STAT1, corresponding to between 10% and 25% normal levels (depending on the mutation). Consequently, their cells have an impaired, but not abolished STAT1-dependent response to IFN- γ and IFN- α treatment, in terms of both GAF and ISGF3 activity [96,97]. They also display an impaired response to stimulation with IL-27 and IFN- λ . The ability of the patients' cells to control viral infection (VSV and HSV) *in vitro* after treatment with IFN- α seems to depend on the mutation and, possibly, on the level of residual STAT1 activation after IFN- α stimulation. In any case, the impaired, but not abolished IFN- α/β and/or IFN- λ responses probably account for the viral infection phenotype being less severe than that in patients with complete STAT1 deficiency (Figures 3–5). Only a small number of patients with partial STAT1 deficiency have been identified, but it may be significant that none has had HSE [96,97,98]. Similarly, the residual response to IFN- γ (and perhaps IL-27) may well account for their mycobacterial infections being curable. A thorough investigation of the cellular phenotype conferred by one of these *STAT1* mutations (K201N/K201N) suggested that the expression of genes induced by IFN- γ during the early response phase was particularly impaired, at least in SV-40 fibroblasts, identifying this group of genes as important for antimycobacterial immunity [97]. Overall, the defect being partial, these patients display less severe clinical diseases than patients with a complete defect. However, the degree of severity of the disease has been shown to vary between patients, even within a given family. The amount of functional residual STAT1 produced may differ between siblings with the same mutation (a splicing mutation) [96]. Nevertheless, the clinical penetrance of partial STAT1 deficiency also appears to be complete. Overall, levels of STAT1 production and activity are correlated with the severity of bacterial and viral infections in patients with AR STAT1 deficiency. There are clearly two different forms of AR STAT1 deficiency, studies of the natural history of which provide different and complementary information about the role of STAT1 in host defense.

AD STAT1 deficiency: Mendelian susceptibility to mycobacterial disease

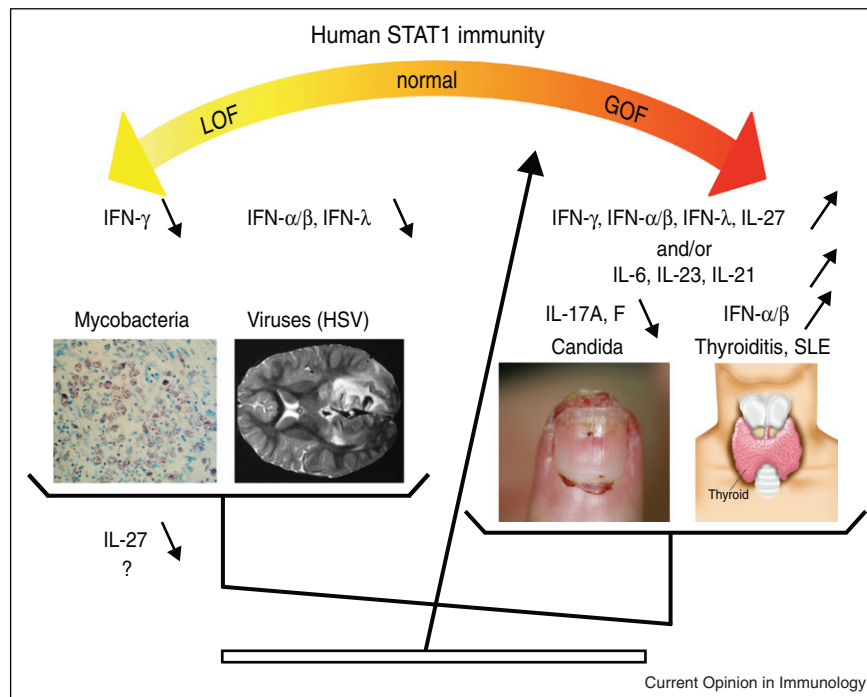
Mendelian susceptibility to mycobacterial disease (MSMD) is a rare syndrome characterized by infections

Figure 4



Schematic diagrams of the role of STAT1 in antimycobacterial, antiviral and antifungal immunity. In the three panels, proteins for which mutations in the corresponding genes have been identified and associated with MSMD, HSE and CMC, respectively, are shown in blue. STAT1 is shown in red. Top panel:

Figure 5



Clinical consequences of low or high levels of STAT1 activity. A narrow range of STAT1 activity should be maintained to ensure health. Biallelic and even monoallelic loss-of-function (LOF) alleles, including not only null but also hypomorphic alleles, confer a predisposition to mycobacterial disease, owing to impaired IFN- γ immunity. The concomitant impairment of IFN- α/β and IFN- λ signaling further predisposes patients to viral illnesses. The severity of the clinical phenotype depends on the severity of the cellular phenotype. The impact of IL-27 hypo-responsiveness is unclear. By contrast, heterozygosity for gain-of-function (GOF) alleles owing to a gain of phosphorylation through a loss of nuclear dephosphorylation, predisposes patients to chronic mucocutaneous candidiasis (CMC) and autoimmunity (typically thyroiditis and, more rarely, other conditions, such as systemic lupus erythematosus). The mechanism underlying CMC involves an impairment of the development of IL-17 T cells, owing to enhanced STAT1-dependent responses to the IL-17 inhibitors IFN- γ , IFN- α/β , IFN- λ and IL-27, or weak STAT3-dependent responses, owing to enhanced STAT1-dependent responses to the IL-17 inducers IL-6, IL-21, and IL-23. The mechanism underlying autoimmunity probably involves enhanced IFN- α/β responses.

with weakly pathogenic mycobacteria (such as the BCG vaccine and environmental mycobacteria) in otherwise healthy individuals [83,99]. The patients are also susceptible to the more virulent *Mycobacterium tuberculosis* and half of them also suffer from non-typhoidal salmonellosis [100,101]. Since the discovery in 1996 of its first genetic etiology, eight morbid genes (*IFNGR1*, *IFNGR2*, *STAT1*, *IRF8*, *IL12B*, *IL12RB1*, *NEMO* and *CYBB*) have been found (Figure 4) [99,102^{**},103^{**}]. They collectively

define up to 15 genetic disorders affecting IL-12-dependent, IFN γ -mediated immunity. In this context, the first human patients with any form of inherited STAT1 deficiency were discovered in 2001, with the identification of two patients from unrelated kindreds, both heterozygous for the L706S LOF dominant-negative *STAT1* allele [104]. These two patients suffered only from relatively mild MSMD (disseminated BCG disease and *M. avium*, both curable without recurrence). Two

(Figure 4 Legend Continued) The phagocytosis of mycobacteria leads to cytokine production and cooperation between phagocytes/dendritic cells and NK/T cells. The IL-12/23/IFN- γ loop, the CD40/CD40L pathway and the oxidative burst (mediated by *CYBB*, a component of NADPH oxidase) are crucial for protective immunity to mycobacteria in humans. STAT1 deficiency is associated with an impaired IFN- γ response. Middle panel: The recognition of dsRNA by TLR3 induces activation of the IRF-3 and NF- κ B pathways via TRIF, leading to IFN- α/β and/or IFN- λ production. TLR3, UNC-93B, TRIF, TRAF3, TBK1 and NEMO deficiencies are associated with impaired IFN- α/β and/or IFN- λ production, particularly during herpes virus infection. The binding of IFN- α/β or IFN- λ to its receptor induces the phosphorylation of JAK1 and TYK2, activating the signal transduction proteins STAT1, STAT2 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. STAT1 deficiency is associated with impaired IFN- α , IFN- β and IFN- λ responses. Bottom panel: Following the recognition of *C. albicans*, the CARD9 adaptor molecule mediates the induction of pro-inflammatory cytokine production by myeloid and epithelial cells. These pro-inflammatory cytokines, including IL-6 and IL-23, activate T lymphocytes via STAT3, inducing the differentiation of these cells into IL-17-producing T cells; these cells constitute a major component of immune defenses against *C. albicans*. Gain-of-function mutations in STAT1 inhibit this differentiation in response to IFN- α/β , IFN- γ , IFN- λ and IL-27 or the impairment of normal IL-6, IL-21 and/or IL-23 signaling, through an as yet undetermined mechanism.

children of the first patient were also heterozygous and, in the absence of BCG vaccination, have remained healthy [84,104]. None of the four patients identified had ever displayed any unusually severe viral illness at least until their most recent check-up visits at the ages of 10, 14, 21 and 44 years (unpublished data). Since 2001, up to six other kindreds have been found to carry dominant-negative *STAT1* mutations associated with MSMD (Figure 2). All the mutations are missense, two mutations affect the DNA-B (E320Q and Q463H) [84], three others the SH2D (K637E, M654K and K673R) [105,106] and a fifth mutation affects Tyr 701 itself (Y701C) (Hirata *et al.*, in preparation). Most patients from the eight kindreds suffered from MSMD (BCG-osis or *M. avium* disease). One patient suffered only from *bona fide* tuberculosis, caused by *M. tuberculosis* [84]. For several mutations, clinical penetrance is incomplete, as up to five genetically affected relatives of index cases, two of whom are known not to have been vaccinated with BCG, have remained clinically healthy.

The transfection of fibrosarcoma cells lacking *STAT1* owing to a somatic event with MSMD-causing *STAT1* alleles has shown some of these alleles to be LOF (in a broad sense, including amorphic and hypomorphic alleles) owing to loss-of-phosphorylation (L706S, M654K and K673R) for both the IFN- γ -GAF and IFN- α -ISRE signaling pathways [104–106]. Others (E320Q and Q463H) were found to be deleterious owing to impaired DNA-binding [84]. One mutation (K637E) affects both Tyr 701 phosphorylation and DNA-binding activity [105]. However, in the cells of heterozygous patients, the mutant alleles were shown to be dominant for IFN- γ -GAF activity but recessive for IFN- α -ISRE activity. In other words, the response to IFN- γ was impaired in heterozygous cells, whereas the response to IFN- α/β was unaffected. This provided the first example of a human allele intrinsically null for two cellular phenotypes but recessive for one and dominant for the other in heterozygous cells [104]. We also know that this dichotomy applies at the level of the whole organism, as patients with AD *STAT1* deficiency have MSMD, whereas those with AR *STAT1* deficiency are susceptible to both mycobacterial and viral diseases. The mechanisms of dominance and recessiveness, for GAF and ISGF3 activation, respectively, have been deciphered [84]. There is no haploinsufficiency for *STAT1*, as assessed by GAF and ISGF3 DNA-binding activity, in cells heterozygous for a loss-of-expression *STAT1* allele [84]. The mutant proteins are also intrinsically able to associate with phosphorylated IFN- γ -R1 and to form dimers with mutant or WT *STAT1*. The lack of phosphorylation of the mutant proteins or their inability to bind DNA therefore destroys the activity of dimers containing them. As a result, only dimers combining two phosphorylated wild-type *STAT1* molecules are functional, accounting for the detection of about 25% the normal level of GAF activity

(for null alleles) in response to IFN- γ in the patients' cells. Conversely, some mutated *STAT1* molecules (like L706S) do not bind to phosphorylated *STAT2* recruited to and activated at the IFN- α/β receptor complex. Only WT *STAT1* molecules are therefore recruited in heterozygous cells. Other mutated *STAT1* molecules (in the DNA-B) bind phosphorylated *STAT2* but do not impair the binding of ISGF3 with its DNA target. This results, in a normal response to IFN- α and the formation of ISGF3, albeit in sufficient quantities because there is no haploinsufficiency for the *STAT1* locus. The ability of the patients' cells to respond correctly to IFN- α/β and to control viral infections *in vitro* accounts for the lack of a clinical phenotype *in vivo*. The patients' cells also respond well to IFN- λ in terms of *IFIT1* mRNA induction [105]. As discussed above, the poor cellular response to IFN- γ accounts for the patients' susceptibility to mycobacteria (Figures 3–5). In *STAT1*-deficient recipient cells, the transfected mutant *STAT1* alleles are null for GAF activation in response to IL-27 [105]. Moreover, the patients' cells also respond poorly to IL-27, potentially contributing to their clinical phenotype, given that IL-27 has been implicated in IFN- γ -dependent antibacterial immunity in the mouse [88]. The identification of patients carrying mutations in the genes encoding IL-27 or its receptor would facilitate assessments of the contribution of this molecule to antimycobacterial immunity. In any event, the dominant-negative *STAT1* alleles identified do not confer a predisposition to viral disease, but they may underlie AD MSMD in rare patients, because although null or severely hypomorphic for both signaling pathways, these alleles impair IFN- γ responses, but not IFN α/β responses in heterozygous cells.

AD gain of *STAT1* activity: CMCD and autoimmunity

Heterozygous gain-of-function *STAT1* alleles were discovered in 2011, in patients with chronic mucocutaneous candidiasis (CMC) [107^{*},108^{*}]. *Candida albicans* is a fungus that causes invasive or chronic mucocutaneous disease in immunocompromised patients [109]. CMC is common in patients with other clinical signs carrying various inborn errors of immunity, including mutations in *STAT3* [110–114], *IL12B* [111], *IL12RB1* [111] and *AIRE* [115^{*},116^{*}]. All these defects are associated with impaired IL-17 immunity, whether owing to the impaired development of IL-17-producing T cells (mutations in *STAT3* and, to a lesser extent, *IL12RB1* and *IL12B*) or to high titers of neutralizing auto-Abs against IL-17 cytokines (*AIRE*) [115^{*}]. This suggests that IL-17A, IL-17F and/or IL-22 play an important role in mucocutaneous immunity to *C. albicans* (Figure 4) [117]. Consistent with this hypothesis, genetic predisposition to CMC disease (CMCD) in rare patients without the clinical features associated with the aforementioned defects was attributed to a specific hypomorphic heterozygous mutation of

IL17F in a kindred with AD CMCD, and to biallelic amorphic mutations of *IL17RA* in a kindred with AR CMCD [117,118^{••}]. Surprisingly, heterozygous mutations of *STAT1* were discovered in this context by whole-exome sequencing [107^{••}] or genome-wide linkage analysis [108[•]] in patients with CMCD, including some patients with autoimmune signs (Figures 2 and 5) [107^{••},108[•]]. A first report described 12 mutations in 47 patients from 20 kindreds [107^{••}]. Another report identified two mutations in 14 patients from five families [108[•]]. A third report subsequently identified two other families and seven patients with CMCD carrying a known mutation [119]. Altogether, 68 patients with CMCD from 27 kindreds have been reported to be heterozygous for *STAT1* mutant alleles (Table 2). Remarkably, all these mutations affect the CCD of STAT1. Moreover, all are missense mutations, including six found in several unrelated kindreds (R274Q, M202V, R274W, T288A, M202I, and A267V), and they appear to be due to mutational hotspots [107^{••}] rather than a founder effect [108[•]]. The mutations segregate with clinical phenotype, and clinical penetrance appears to be complete, although clinical severity varies between and even within families [107^{••},108[•]]. In addition, we recently identified 24 and 18 new CMCD patients from 15 and 13 families heterozygous for mutations affecting the DNA-B and CCD of STAT1, respectively (Okada S. *et al.*, in preparation). Heterozygous *STAT1* mutations account for approximately half the patients enrolled in our CMC cohort.

These CMCD-causing mutant *STAT1* alleles were shown to be gain-of-function (GOF) [107^{••}]. At the cellular level, this gain of function results from a gain of phosphorylation [107^{••}]. Following the transfection of STAT1-deficient fibrosarcoma cells with these alleles, the response to IFN- γ , IFN- α , IL-27, IL-6 and IL-21 was reproducibly two to three times stronger than that in control cells, in terms of STAT1 phosphorylation, GAS-binding activity, reporter gene induction, and the induction of some endogenous target genes. The mechanism underlying the GOF has been analyzed with inhibitors of kinases and phosphatases, and has been shown to be largely, if not exclusively, associated with an impairment of nuclear STAT1 dephosphorylation [107^{••}] (Okada S. *et al.*, in preparation). Several residues close to those affected by CMCD-causing mutations in the CCD and DNA-B have been shown, by site-directed mutagenesis, to be essential for STAT1 dephosphorylation [10,12,14,26–30,35,36]. Heterozygous cells from patients also display a stronger response to IFN- γ , IFN- α and IL-27, demonstrating that the GOF alleles are dominant at the cellular level. These cells also displayed defective nuclear STAT1 dephosphorylation. Heterozygosity for GOF *STAT1* alleles therefore accounts for AD CMCD with autoimmunity. The autoimmunity seen in these patients probably reflects an enhancement of the cellular response to IFN- α/β [120^{••}]. What is the immunological

mechanism underlying CMC? The analysis of IL-17-producing T cells *ex vivo* and *in vitro* highlighted a profound defect in the development of these cells in the patients [107^{••}]. This observation provided a cellular basis for CMC in patients heterozygous for GOF *STAT1* alleles, but also raised questions about the underlying mechanism. It is possible that an excessive response to one or several of the cytokines known to inhibit IL-17 T-cell development, such as IFN- γ , IFN- α and IL-27 (Figures 4 and 5) [121–123] (whether leading to a decrease or an increase in the transcription of key target genes with respect to controls) impairs the development of these cells in the patients, rendering them susceptible to CMC. Alternatively, enhanced STAT1 activation may divert the response to IL-6, IL-21 and IL-23 from the normal preferential use of STAT3 for signaling, which favors the development of IL-17 T cells [124–128] (Figures 4 and 5). These two hypotheses are not mutually exclusive. Other mechanisms may also operate. Further work is required to investigate the mechanisms by which the heterozygous *STAT1* GOF alleles impair IL-17 T-cell development, at both the molecular and cellular levels. However, recent studies have clearly established that CMC develops in patients heterozygous for GOF *STAT1* alleles because of the impaired development of IL-17 T cells.

Conclusion and perspectives

STAT1 is, to our knowledge, the first human gene identified for which LOF and GOF heterozygous alleles are apparently associated with a relatively narrow set of distinct infectious diseases. Heterozygotes for LOF dominant-negative alleles display MSMD, whereas heterozygotes for GOF dominant alleles display CMCD. The mutations may even affect the same domain of STAT1. *STAT1* is not the first host defense gene to harbor LOF or GOF mutations in different patients, as this situation has already been demonstrated for the X-linked *WASP* gene, for which LOF mutations underlie XR Wiskott–Aldrich syndrome whereas GOF mutations underlie XR severe congenital neutropenia [129,130]. The range of infections seen in these two X-linked traits is, however, broader and there is some overlap. Moreover, there are not two, but four distinct disorders of *STAT1*, each of which is apparently associated with a specific set of infectious diseases. Heterozygous morbid alleles of *STAT1* are associated with AD MSMD or AD CMCD, whereas biallelic LOF mutations (whether amorphic or hypomorphic) are associated with AR predisposition to both mycobacterial and viral diseases. Intriguingly however, two patients heterozygous for GOF *STAT1* alleles were recently shown to display recurrent herpes virus infections [131], which is reminiscent of STAT3-deficient patients and might involve the same mechanism of impaired T cell memory [132]. Finally, the severity of the infectious phenotype is more pronounced in patients with AR complete STAT1 deficiency than in patients

with a partial form of STAT1 deficiency. The set of bacterial and viral diseases may be broader in patients with complete STAT1 deficiency, although the better prognosis of patients with a partial defect may reveal infections not seen in those with complete deficiency, who die in early childhood unless treated by HSCT.

The discovery and characterization of the various human *STAT1* morbid alleles has built on elegant studies on human and mouse cell lines *in vitro* and the mouse model *in vivo*. Human studies have helped to elucidate the function of STAT1 in host defense *in natura*, in the context of a natural ecosystem governed by natural selection [133,134]. The range and nature of viral infections controlled by IFN α / β -dependent and IFN- λ -dependent STAT1 immunity are gradually being deciphered. Clearly, human STAT1-dependent IFN- γ immunity is crucial for protection against mycobacteria and a relatively limited set of intramacrophagic microbes. More surprisingly, a gain of STAT1 activity impairs the development of IL-17-producing T cells and impairs mucocutaneous immunity to *C. albicans*. Too little STAT1 immunity, whether owing to monoallelic dominant-negative or biallelic LOF mutations, is associated with a predisposition to viral and/or mycobacterial diseases. Conversely, too much STAT1 immunity, owing to monoallelic GOF mutations, is associated with CMC and autoimmunity (Figure 5). There is therefore probably a strong evolutionary pressure in favor of the maintenance of optimal STAT1 activity [135^{••}], as even heterozygous mutations increasing or decreasing the activity of this protein outside a particular range would be subject to strong counterselection during the evolution of the population. Evolutionary genetic studies in human populations would probably reveal a strong purifying selection operating at the *STAT1* locus, as recently shown for the human genes encoding several IFNs, including IFN- α / β and IFN- γ [136^{••}].

Acknowledgements

We thank Yelena Nemirovskaya and Eric Anderson for secretarial assistance, Shen-Ying Zhang for the HSE figure, Emmanuelle Jouanguy and Amandine Crequer for critical reading and all the Laboratory of Human Genetics of Infectious Diseases for helpful discussions. The Laboratory of Human Genetics of Infectious Diseases is supported partly by grants from the St. Giles Foundation, the Jeffrey Modell Foundation, The Rockefeller University Center for Clinical and Translational Science grant number 5UL1RR024143, the National Institute of Allergy and Infectious Diseases grant numbers 5R01AI089970-02 and 1R37AI095983-01, The Rockefeller University, the Agence Nationale de la Recherche (ANR), and the European Research Council (ERC). X.F.K. was supported by a Choh-Hao Li Memorial Fund Scholar Award and the Shanghai Educational Development Foundation, and S.C. is supported by the AXA Research Fund.

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