# CYTOKINES AND IMMUNODEFICIENCY DISEASES

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Severe combined immunodeficiency disease (SCID) refers to a spectrum of inherited immunodeficiencies that together represent the most severe forms of primary immunodeficiency in humans. Recent work has shown that many of these diseases, as well as other forms of immunodeficiency, result from defects in cytokine signalling pathways. Such defects can prevent normal development of lymphoid lineages and/or compromise cytokine signalling by these cells. These natural 'experiments' in human genetics have shown the non-redundant role for several cytokines or cytokine signalling molecules. Moreover, a comparison of the phenotypes of humans with SCID to analogous mouse-knockout models has shown not only expected similarities, but also unexpected differences in cytokine signalling between humans and mice.

NATURAL KILLER CELLS (NK cells). Lymphocytes that confer innate immunity. They were originally defined on the basis of their cytolytic activity against tumour targets, but it is now recognized that they have a broader role in host defence against invading pathogens.

XSCID
X-linked severe combined immunodeficiency disease. This is a profound immunodeficiency that accounts for approximately half of the cases of SCID. It is characterized by an absence of T cells and natural killer cells. B cells are normal in number but are non-functional.

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Severe combined immunodeficiency diseases (SCIDs) represent a spectrum of illnesses with similar clinical manifestations[1–4], which can be subdivided into several categories on the basis of the presence or absence of T cells, B cells and NATURAL KILLER (NK) cells. These are relatively rare diseases, collectively occurring in ~1 in 80,000 live births[1–4]. Affected individuals have defects in both T- and B-cell function. Without effective treatment, patients typically die of opportunistic infections before 1 year of age. Fortunately, SCID can be cured by bone marrow transplantation in most instances[3]. In addition, there is active work on the development of gene therapy, particularly for the most common form of SCID, X-linked SCID (XSCID)[5–7].

In 1993, it was shown that XSCID results from mutations in the COMMON CYTOKINE RECEPTOR γ-CHAIN, $\gamma_c$ (REF. 8). This observation immediately established that defective cytokine signalling was the underlying cause of many cases of human SCID. Here, I review the forms of SCID that result from defects in cytokine signalling, as well as the cytokines and relevant signalling pathways that are affected. In addition, several other forms of immunodeficiency that result from defective cytokine signalling will be discussed.

## X-linked SCID

As mentioned above, XSCID is the most common form of SCID, accounting for approximately half of all cases[1–4]. XSCID, formally designated as SCIDX1, is generally known to the lay public as the 'Bubble Boy Disease', named after a boy who lived in a protective sterile 'bubble' for more than a decade before his death after an unsuccessful bone marrow transplant. XSCID is the main form of $T^-B^+NK^-$ SCID, in which T cells and NK cells are absent or profoundly diminished in number, whereas B-cell number is normal. However, consistent with this being a 'combined' immunodeficiency, the B cells do not function; presumably this is owing, in part, to the lack of T-cell help combined with an intrinsic defect in B-cell signalling.

Many investigations were carried out to identify the genetic cause of XSCID, and the gene was mapped to Xq13 (REFS 9,10). Eventually, the genetic basis was identified, not by positional cloning, but by studies on the interleukin-2 receptor (IL-2R)[8]. One component of this receptor, a protein that was originally designated as the IL-2Rγ chain, was cloned[11], and its gene was found to be located on chromosome Xq13, at or near the *SCIDX1* locus[8]. It was then shown that patients with XSCID had mutations in the gene that encodes IL-2Rγ (the gene

COMMON CYTOKINE RECEPTOR γ-CHAIN ($\gamma_c$). A type I cytokine receptor chain that is shared by the receptors for interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15 and IL-21.

JAK
Janus-activated kinase. There are four JAKs — JAK1, JAK2, JAK3 and TYK2 — which are activated by cytokines and interferons, inducing the phosphorylation of the cytokine/interferon receptors and other cellular substrates, including STAT proteins.

designation is *IL2RG*), establishing the basis for the disease[8]. However, this discovery presented researchers with a major dilemma, as mice[12] and humans[13,14] that lack IL-2 expression had normal T-cell and NK-cell development. Because the clinical/immunological deficits that result from a defect in the cytokine (IL-2) were less severe than those that result from mutation in a component of the cytokine receptor (IL-2Rγ), it was proposed that the γ-chain must be part of additional cytokine receptors[8]. Indeed, it was subsequently shown that the γ-chain was also a component of the receptors for IL-4 (REFS 15,16), IL-7 (REFS 17,18), IL-9 (REFS 19,20), IL-15 (REF. 21) and IL-21 (REF. 22) (FIG. 1), consistent with its current name $\gamma_c$, for the common cytokine receptor γ-chain[23].

## Cytokine signalling

To understand the basis for the defects in XSCID, it is important that several aspects of cytokine signalling are introduced. Cytokines are broadly defined as molecules that are made by one cell and act on another[24]. Two main classes of cytokines, type I and type II, have been defined (see BOX 1 and TABLE 1)[24].

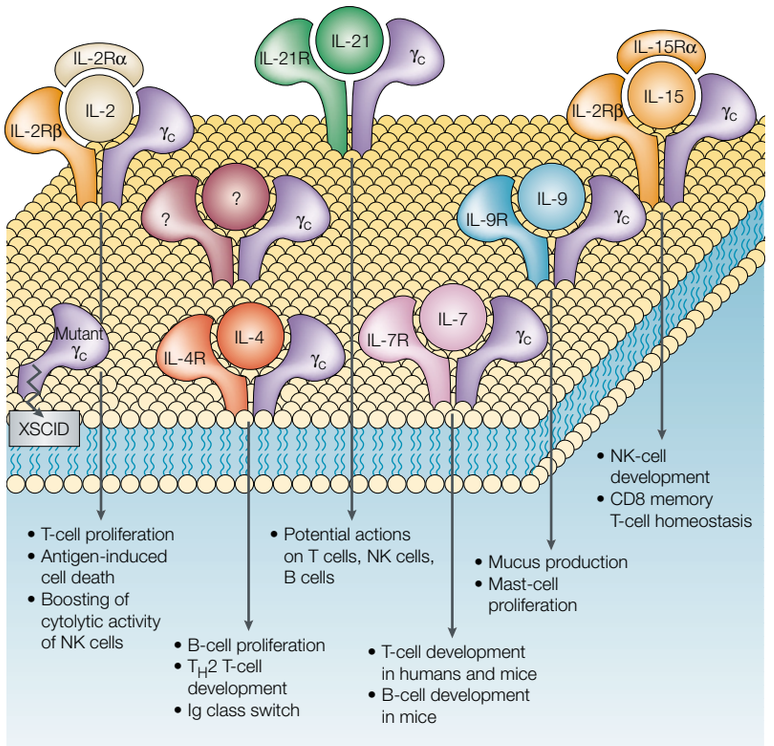



Figure 1 | **Actions of cytokines whose receptors share $\gamma_c$.** Mutation of the common cytokine receptor γ-chain ($\gamma_c$) results in X-linked severe combined immunodeficiency disease (XSCID). $\gamma_c$ is a component of the receptors (R) for interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15 and IL-21. It is conceivable that additional cytokine receptors might also share $\gamma_c$, as indicated by '?'. $\gamma_c$ can be individually targeted to the cell membrane and can exist independently of associated chains. $\gamma_c$ can be recruited into different cytokine receptor complexes. If $\gamma_c$ is limiting, it is conceivable that different cytokines might compete for a limited 'resource', whereas under conditions in which $\gamma_c$ is in excess, cells might be able to respond simultaneously to several $\gamma_c$-dependent cytokines. The main actions of each of the cytokines are shown — these are potentially disrupted in patients with XSCID. NK, natural killer; $T_H2$, T helper 2.

A common feature of type I and type II cytokines is that their receptors lack intrinsic tyrosine kinase activity (with rare exceptions, such as stem-cell factor, a type I cytokine whose receptor is c-kit) and that they signal, at least in part, by the Janus-activated kinase (JAK)/signal transducer and activator of transcription (STAT) pathway.

***The JAK/STAT pathway.*** The JAK/STAT pathway was originally discovered in the context of interferons (IFNs), but was subsequently also found to be broadly used by type I cytokines[25–28]. JAKs are cytoplasmic tyrosine kinases that are either constitutively associated with cytokine receptors or, in some instances, recruited to receptors after ligand binding. In either case, stimulation with the ligand results in the catalytic activation of the receptor-associated JAKs. This activation results, in turn, in the tyrosine phosphorylation of cellular substrates, including the JAK-associated cytokine receptor chains. Some of these phosphorylated tyrosines can serve as docking sites for STAT proteins, which bind to the phosphotyrosines by their SRC-homology 2 (SH2) domains[25–27]. STAT proteins are also phosphorylated on a conserved tyrosine residue, resulting in their dimerization and acquisition of high-affinity DNA-binding activity, which facilitates their action as nuclear transcription factors (FIG. 2). However, STAT proteins can function as transcription factors even in the absence of cytokine/IFN-mediated activation, participating in the constitutive expression of some genes[29]. Along with nuclear factor-κB (NF-κB)[30,31], nuclear factor of activated T cells (NF-AT)[32] and SMAD[33]-related pathways, the JAK/STAT pathway serves as one of the most rapid cytoplasmic-to-nuclear signalling mechanisms[25–27]. The JAK and STAT proteins that are activated by the various cytokines and IFNs are summarized in TABLE 1.

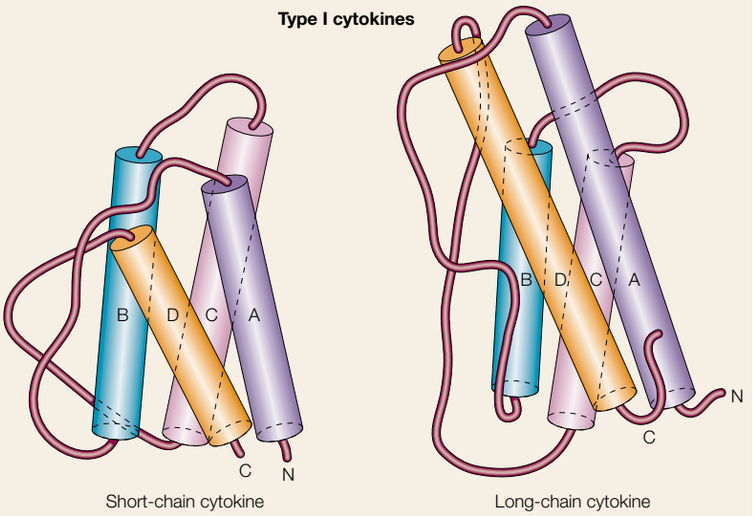
There are a total of four JAK (JAK1–3 and tyrosine kinase 2; TYK2) and seven STAT proteins (STAT1–4, STAT5A, STAT5B and STAT6)[24–27]. JAKs are relatively large cytoplasmic kinases (see BOX 2 for structural details) ~1,100 amino acids in length, and range in size from ~116 kDa to 140 kDa. Whereas JAK1, JAK2 and TYK2 are ubiquitously expressed, expression of JAK3 is inducible and restricted to haematopoietic cells[34,35].

Several negative regulators of STAT proteins have been described. For example, a set of proteins variably known as CIS (cytokine-inducible SH2-containing protein), SOCS (suppressor of cytokine signalling) and SSI (STAT-induced STAT inhibitor)-family proteins can negatively regulate JAK/STAT signalling. CIS, the first such protein to be identified, can negatively regulate signalling in response to IL-2, IL-3 and erythropoietin, and can bind to receptors. Some other members of the family, such as SOCS1, SSI-1 and JAB (JAK-binding protein), directly bind to and negatively regulate JAKs[36,37].

## JAK3-deficient SCID

As summarized in TABLE 1, all six $\gamma_c$-dependent cytokines (IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21) can activate both JAK1 and JAK3 (REFS 19,34,35). Although many other cytokines can also activate JAK1, the $\gamma_c$-dependent cytokines are the only ones that activate JAK3.

Box 1 | **Type I and type II cytokines**




**The type I/type II cytokine classification relates to the three-dimensional structure formed by these proteins. Type I cytokines have a four α-helical bundle structure, with an 'up-up-down-down' configuration[24,102,103]. These cytokines can be further divided into short-chain and long-chain four α-helical bundle cytokines[24,93,94] on the basis of the length of the α-helices as well as some other structural/topological considerations (see figure)[24,102,103]. In the short-chain cytokines, the helices are typically ~15 amino acids in length versus 25 amino acids for the long-chain cytokines. In the short-chain cytokines, the AB loop is 'under' the CD loop, whereas it is 'over' the CD loop in the long-chain cytokines. Another distinctive feature is that only short-chain cytokines have β-sheet structures within the AB and CD loops. Interleukin (IL)-5 and macrophage colony-stimulating factor (M-CSF) are distinctive in that they bind as dimers, whereas other type I cytokines bind as monomers. IL-5 and M-CSF nevertheless differ from each other in that only IL-5 'exchanges' helix D so that each monomer contributes helix D to the other monomer.**

**Type II cytokines have different structures. For example, interferon (IFN)-β has an extra helix in place of the CD strand[104], IFN-γ binds as an α-dimer of six helices/dimer[105], and IL-10 binds to its receptor as two sets of dimers, with each IL-10 domain consisting of six α-helices assembled from two intertwined peptide chains, with helices A–D being derived from one chain, and helices E and F derived from the twofold related chain[106].**

This $\gamma_c$–JAK3 connection was explained by the fact that JAK3 directly associates with $\gamma_c$, and is therefore immediately 'downstream' of $\gamma_c$[19,38,39]. Accordingly, it was proposed that mutations in JAK3 might cause a syndrome that was clinically and immunologically indistinguishable from that found in patients with XSCID[19]. This, hypothesis was subsequently confirmed; JAK3-deficient patients also have a $T^-B^+NK^-$ SCID phenotype[40,41]. The principal difference between XSCID and JAK3-deficient SCID is that the mode of inheritance in the latter is autosomal recessive, which is consistent with the location of JAK3 on human chromosome 19 (REF. 42). So, mutations in either $\gamma_c$ or in JAK3 result in $T^-B^+NK^-$ SCID. Numerous mutations in both XSCID and JAK3-deficiency have been identified (see online links to the X-Linked SCID Mutation Database and JAK3base). The identification of several mutations in each protein has provided insights into structure–function relationships; for example, helping to define residues in $\gamma_c$ that are important for ligand binding and residues in JAK3 that are important for catalytic activity. Corresponding to the similarity in humans, mutations in either $\gamma_c$ or JAK3, the phenotypes of mice lacking *Il2rg*[43–45], *Jak3* (REFS 46,47), or *Il2rg* and *Jak3* (REF. 48) are also similar.

Given that patients with XSCID and JAK3-deficient SCID have defects in both T-cell and NK-cell development, it was important to determine the identity of the cytokine(s), the simultaneous inactivation of which would result in this phenotype. As noted above, the absence of IL-2 signalling did not explain the lack of development of these lineages. Patients with mutations in the IL-7Rα chain were found to have a $T^-B^+NK^+$ form of SCID[49], and mice that lack either IL-15 (REF. 50) or IL-15Rα[51] were devoid of NK cells. So, the IL-7 and IL-15 signalling pathways, respectively, seemed to be essential for T-cell and NK-cell development. Consistent with the importance of IL-15 for NK-cell development, mice that lack expression of IL-2Rβ, which is a component of both the IL-2 and IL-15 receptors, also lack NK cells[52]. However, these mice, which effectively represent an IL-2/IL-15 'double knockout', show substantial T-cell development, indicating that IL-2 and IL-15, even in combination, are not crucial for T-cell development. So far, patients with mutations in IL-15, IL-15Rα or IL-7 have not been identified. Regarding IL-4 and IL-9, the phenotypes of mice that lack IL-4 (REF. 53) or IL-9 (REF. 54) indicate that these cytokines are not essential for T-/NK-lineage development. However, *Il9* transgenic mice develop thymic lymphomas[55], which indicates the presence of IL-9 receptors in the thymus and suggests that IL-9 might contribute to T-cell development, albeit in a redundant way.

The most notable immunological difference between humans and mice with mutations in $\gamma_c$ or JAK3 is within the B-cell compartment. Although humans with XSCID and JAK3 deficiency develop $T^-B^+NK^-$ SCID, mice that lack expression of either $\gamma_c$ or Jak3 have a $T^-B^-NK^-$ phenotype. These findings underscore the fact that $\gamma_c$ and JAK3-dependent signalling are not required for B-cell development in humans, whereas in mice they are essential. This striking observation extends to the IL-7 system, in which IL-7Rα-deficient patients have a normal B-cell number[49], whereas the corresponding IL-7Rα knockout mice are essentially devoid of B cells[56]. Therefore, IL-7 signalling is essential for B-cell development in mice, but in humans it either does not contribute or instead has a redundant role.

### The *in vivo* role of JAKs and STATs

As we have discussed, there is compelling evidence for the role of IL-7 and IL-15 signalling pathways in T-cell and NK-cell development, respectively. Although $\gamma_c$ and JAK3 are known to be essential components of these developmental pathways in humans, the role of JAK1 and other downstream molecules is less clear. SCID patients with defects in such molecules have not been identified, but the generation and analysis of knockout mice has provided valuable clues on the role of Jak1 and downstream signalling molecules (see TABLES 2 and 3).

STAT
Signal transducer and activator of transcription. These are proteins that are recruited to cytokine and interferon receptors following ligand binding to the receptor. STAT proteins are 'activated' by tyrosine phosphorylation so that they can form dimers and translocate to the nucleus, where they function as transcription factors.

Table 1 | **JAKs and STATs activated by type I and type II cytokines**

| Cytokines | Activated JAKs | Activated STATs |
|---|---|---|
| **Type I cytokines** | | |
| ***Short-chain cytokines*** | | |
| Cytokines that share $\gamma_c$ | | |
| IL-2, IL-7, IL-9, IL-15, IL-21 | JAK1, JAK3 | STAT5A, STAT5B, STAT3 |
| IL-4 | JAK1, JAK3 | STAT6 |
| IL-13* | JAK1, JAK2, TYK2 | STAT6 |
| TSLP‡ | None | STAT5A, STAT5B |
| Cytokines that share $\beta_c$ | | |
| IL-3, IL-5, GM-CSF | JAK2 | STAT5A, STAT5B |
| Other short-chain type I cytokines | | |
| M-CSF§ | JAK1, TYK2 | STAT1, STAT3, STAT5A, STAT5B |
| SCF‖ | | STAT5A, STAT5B |
| ***Long-chain cytokines*** | | |
| Cytokines that share gp130 | | |
| IL-6, IL-11, OSM, CNTF, LIF, CT-1 | JAK1, JAK2, TYK2 | STAT3 |
| Other long-chain type I cytokines | | |
| IL-12 | JAK2, TYK2 | STAT4 |
| Growth hormone | JAK2 | STAT5A, STAT5B, STAT3 |
| Prolactin, EPO, TPO | JAK2 | STAT5A, STAT5B |
| Leptin | JAK2 | STAT3 |
| G-CSF | JAK1, JAK2, TYK2 | STAT1, STAT3, STAT5A,STAT5B |
| **Type II cytokines** | | |
| IFN-α/β | JAK1, TYK2 | STAT1, STAT2, STAT4¶ |
| IFN-γ | JAK1, JAK2 | STAT1 |
| IL-10 | JAK1, TYK2 | STAT3 |
| IL-20 | ? | STAT3 |
| IL-22 | ? | STAT3 |

*IL-13 does not share $\gamma_c$ (common cytokine receptor γ-chain), but is related to IL-4 and shares IL-4Rα. ‡The thymic stromal lymphopoietin (TSLP) receptor consists of TSLPR and IL-7Rα; it is closely related to IL-7, the receptor of which contains $\gamma_c$ and IL-7Rα. §Macrophage colony-stimulating factor (M-CSF) and ‖stem-cell factor (SCF) are unusual in that they are short-chain cytokines, but their receptors contain intrinsic tyrosine kinase domains. Some $\gamma_c$-dependent cytokines also activate STAT1. ¶STAT4 is activated by IFN-α in humans, but not in mice. $\beta_c$, common cytokine receptor β-chain, which is shared by IL-3, IL-5 and granulocyte-M-CSF receptors; EPO, erythropoietin; gp130, a signal-transducing molecule that is part of the receptors for IL-6, IL-11, oncostatin M (OSM), CNTF (ciliary neurotrophic factor), LIF (leukaemia-inhibitory factor) and CT-1 (cardiotrophin 1); JAK, Janus-activated kinase; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TYK2, tyrosine kinase 2.

***Which JAK mutations result in SCID?*** Consistent with the importance of JAK1 for signalling in response to $\gamma_c$-dependent cytokines, type 1 and type 2 IFNs and cytokines the receptors of which contain gp130 (IL-6, IL-11, ciliary neurotrophic factor, oncostatin M, leukaemia-inhibitory factor and cardiotrophin 1), Jak1 knockout mice show perinatal lethality (see TABLE 2)[57]. Similar to Jak3, Jak1 seems to be important for T-cell and NK-cell development. However, mutations in Jak1 lead to such a severe phenotype in mice that JAK1-deficient humans would probably die, rather than merely manifest SCID. JAK2 deficiency is even more severe, resulting in fetal rather than perinatal lethality[58,59]. This primarily results from the profound anaemia due to defective erythropoietin signalling. In humans, the lack of JAK2 would be predicted to diminish signalling by IFN-γ and other cytokines, but such immunological defects are unlikely to develop given the prenatal lethality. The phenotype of humans with JAK3-deficient SCID[40,41] is largely recapitulated in Jak3-deficient mice[46,47], which have a very small thymus and absent NK cells. Consistent with the activation of Tyk2 by IFN-α/β and IL-12, signalling in response to these cytokines is diminished, albeit not abrogated, in Tyk2-deficient mice[60,61]. Unexpectedly, it is primarily Stat3 activation that is affected, even though IFN-α/β primarily activate Stat1 and Stat2, and IL-12 primarily activates Stat4. Moreover, signalling by IFN-γ is also diminished in these animals. So, although Tyk2 was found to be essential for certain responses, such as the ability to clear vaccinia virus, it is possible that other JAKs can serve a partially redundant function to compensate for the absence of Tyk2.

Given the phenotypes of the various Jak knockout mice, it seems unlikely that mutations in JAK1, JAK2 or TYK2 will result in SCID in humans — the former two because the mutations would probably be too severe; the latter one because it would not be severe enough. However, it is conceivable that certain mutations in JAK1 might selectively interfere with the ability of JAK1 to be recruited to IL-7R, but not to other cytokine receptors. If such a mutant JAK1 existed, it could cause a selective T-cell defect that might mimic an IL-7Rα-deficient $T^-B^+NK^+$ form of SCID.

## Role of molecules downstream of JAKs

As noted above, STAT proteins are activated by the JAKs after stimulation with appropriate cytokines. Mice deficient in Stat1, Stat2, Stat4 or Stat6 show phenotypes that

correspond with selective inactivation of specific cytokine pathways (TABLE 3). Although Stat1 is activated in cell lines by many different cytokines, including IL-6-family cytokines, IL-10, and epidermal growth factor, the defects in Stat1-deficient mice can be explained by defective signalling in response to IFN-α/β and IFN-γ[62,63]. This indicates that the Stat1 activation by other cytokines might not be essential *in vivo*. A naturally occurring STAT1 mutation was found in two individuals that showed increased susceptibility to mycobacterial, but not viral, disease (see below)[64]. The defects in Stat2-deficient mice are related to defects in IFN-α/β signalling[65], consistent with these being the only cytokines that activate Stat2. Stat4 and Stat6 are activated by IL-12 and IL-4/IL-13, respectively. Furthermore, Stat4-deficient mice show defective T helper ($T_H$)1 cell development[66,67], whereas Stat6-deficient mice have a defect in $T_H$2 cell differentiation[68,69]. On the basis of these observations, although mutations in Stat1, Stat2, Stat4 or Stat6 in humans could result in immunodeficiency, it is unlikely to be a full SCID phenotype.

Stat3, Stat5a and Stat5b are activated by IL-2, IL-7, IL-9 and IL-15, and therefore are candidate genes that, when mutated, might result in a SCID phenotype. However, consistent with the broad range of cytokines that activate Stat3, Stat3 knockout mice show perinatal lethality[70] (TABLE 3), making it unlikely that humans with mutations in Stat3 will be identified.

Mice that lack Stat5a[71], Stat5b[72] or both Stat5a and Stat5b[73] have all been generated. Stat5a and Stat5b are more than 90% identical at the amino-acid level[74–76], and the extent to which their actions are redundant versus distinctive has been the basis of considerable discussion. On the basis of knockout models, there are both overlapping and distinctive roles for these proteins *in vivo*. However, it remains unclear whether these differences are due to different specific actions or instead to differences in the relative abundance of these proteins in certain cell types.

Within the immune system, both Stat5a- and Stat5b-deficient mice show defective IL-2-induced IL-2Rα expression and defective IL-2-induced proliferation *in vitro*[77,78], a finding now well understood in view of the identification of two IL-2 response elements in the *IL2RA* gene[79–82]. Moreover, in Stat5a-deficient mice, there is a defect *in vivo* in the expansion of Vβ8$^+$ T cells in response to superantigen[77]. The Stat5b-deficient mice show a major defect in NK cytolytic activity[78]. Stat5a/Stat5b double-knockout mice completely lack NK-cell development[73], presumably reflecting a crucial role for Stat5 proteins in IL-15 signalling, and show a greater defect in T-cell proliferation, which is associated with defective induction of cyclin D2, cyclin D3 and cyclin-dependent kinase 6 (Cdk6) after stimulation with anti-CD3 (REF. 82). It is unclear whether the individual loss of STAT5A or STAT5B would result in a SCID phenotype, but the simultaneous deletion of both *STAT5A* and *STAT5B* genes, which are tandem genes on human chromosome 17 (REF. 76), would be more likely to be a cause of SCID. However, such a mutation would be predicted to cause severe anaemia, as has been observed in Stat5a/Stat5b double-knockout mice[83], so that affected infants might have key problems beyond the immune system. In addition to the lymphocyte-related effects of Stat5a and Stat5b, it has been shown in an antigen-induced asthma model that these STAT proteins are important for eosinophil recruitment into the lung[84].

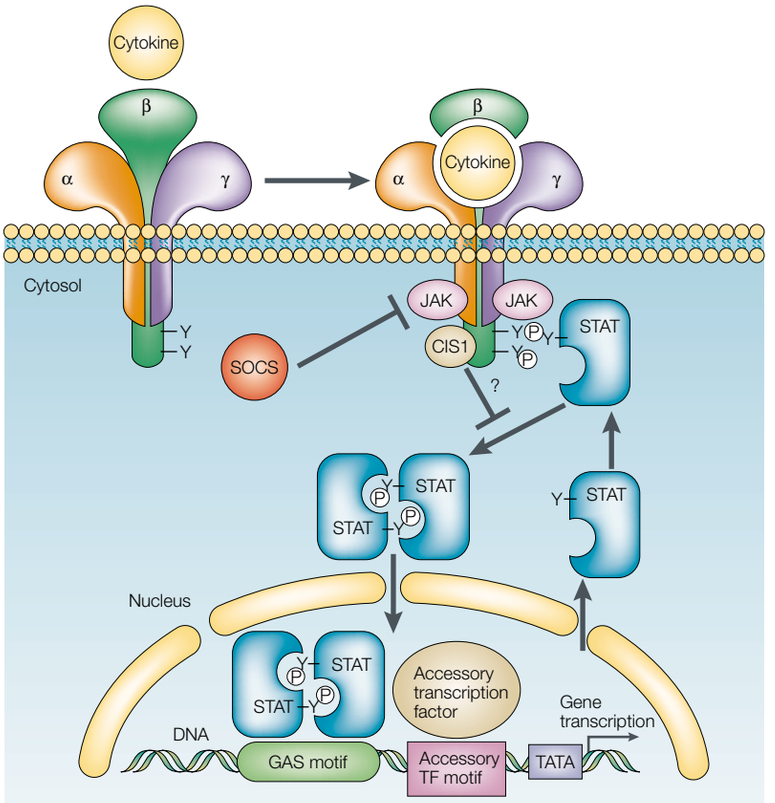


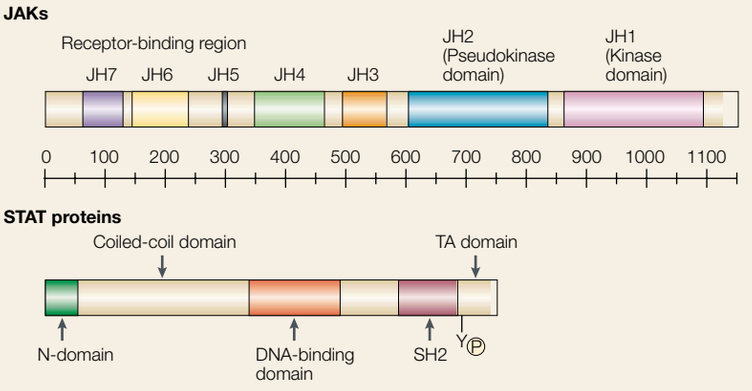

Figure 2 | **Signalling by the JAK/STAT pathway for a typical type I cytokine.** In this schematic, the receptor is a three-subunit receptor (α, β and γ); for example, interleukin (IL)-2 or IL-15. Many other cytokines have receptors that are homodimers or heterodimers. Binding of the cytokine induces the activation of JAKs (Janus-activated kinases), which then can phosphorylate cellular substrates, typically including at least one of the receptor chains. This allows the recruitment of STAT (signal transducer and activator of transcription) proteins to the phosphorylated receptor by their Src-homology 2 (SH2) domains, which, in turn, are also phosphorylated. The STAT proteins can dimerize, translocate to the nucleus and bind DNA. The TATA box allows the binding of basal transcription machinery by the transcription factor TF-IID. The 'accessory' transcription factor is shown to indicate that STAT proteins do not necessarily act alone, but that STAT-dependent responses can be differentially influenced by other transcription factors. Shown are SOCS (suppressor of cytokine signalling) family proteins, denoted as SOCS and CIS1 (cytokine-inducible SH2-containing protein 1), which can negatively regulate JAK/STAT signalling. CIS1 is shown as bound to the receptor, inhibiting STAT activation, and SOCS is shown as a JAK inhibitor[36,37]. GAS motif, γ-interferon activated sequences (see BOX 2); P, phosphorylated tyrosine (Y).

*Animated online*

### T-cell and NK-cell development in XSCID

As we have discussed, in XSCID and JAK3-deficient SCID, defective IL-7Rα-dependent signalling accounts for the disrupted T-cell development, whereas defective IL-15-dependent signalling accounts for disrupted NK-cell development. This is consistent with the finding that mice[85] and humans[86] lacking IL-2Rβ, which is a

Box 2 | **Structural features of JAKs and STATs**




**The Janus-activated kinases (JAKs) are divided into JAK homology (JH) regions (see figure). JH1 is the catalytic true kinase domain, whereas JH2 is a pseudokinase domain. The amino-terminal JH6 and JH7 regions are important for the interaction of JAKs with cytokine receptors[107,108].**

**Signal transducer and activator of transcription (STAT) proteins contain several functional regions. At the N-terminus, there is a region known as the N-domain, which can mediate oligomerization of STAT proteins[109–111]. This region forms a hook-like structure consisting of eight α-helices. Within this region, a tryptophan residue that is conserved in all STAT proteins is engaged in crucial polar interactions between the interacting helices. Oligomerization allows the dimerization of STAT dimers to form STAT tetramers, which results in augmented DNA-binding affinity and possibly provides greater target-sequence selectivity for different STAT proteins. This is followed by a coiled-coil domain, the DNA-binding domain, a linker region, the Src-homology 2 (SH2) domain and a carboxy-terminal transactivation (TA) domain that contains a conserved tyrosine the phosphorylation of which is important for STAT dimerization[25–27]. STAT dimerization is mediated by a bivalent SH2–phosphotyrosine interaction between the SH2 domain of one STAT monomer and the phosphotyrosine of a second STAT monomer. Most cytokines induce the formation of STAT homodimers or heterodimers. These dimers bind to palindromic or semi-palindromic binding sites known as γ-interferon activated-sequence (GAS) motifs (TTCN3–4GAA)[112]. Each STAT monomer is related to the other by a twofold axis of symmetry that passes through the centre of the DNA. The DNA-binding domain contacts DNA in the major groove of DNA. IFN-α/β are somewhat different in this regard: although they activate STAT1 and STAT2, which can dimerize, these STAT1–STAT2 heterodimers only potently bind DNA when combined with a DNA-binding protein, p48, to form a complex known as ISGF3 (REF. 26). Instead of binding to GAS motifs, ISGF3 binds to motifs known as interferon-stimulated response-element (ISRE) motifs (AGTTTNCNTTTCC)[26]. The carboxy-terminal region also contains the transactivation domain that can interact with transcriptional co-activators and that, in some STATs, such as STAT1, STAT3 and STAT4, contains a conserved serine the phosphorylation of which is required for maximal activity.**

component of both the IL-2 and IL-15 receptors, show defective NK-cell development. Our analysis of the phenotypes of STAT-deficient mice strongly indicates that the defect in NK-cell development and cytolytic function can be further attributed to a defect in IL-15-dependent Stat5a and Stat5b activation. One of the relevant Stat5 target genes might be perforin, a gene the expression of which is dependent on Stat5 due to the presence of at least two independent Stat5-dependent response elements in the gene[87] and is diminished in Stat5b knockout mice[78]. For T-cell development, the picture remains less clear. IL-7 also activates Stat5a and Stat5b. However, although the Stat5-deficient mice show diminished numbers of lymphocytes[77,78], substantial T cells are still produced even in Stat5a/Stat5b double-knockout mice[88]. So, Stat5 proteins are important signalling molecules activated by IL-7, but other IL-7-activated pathways/molecules, such as phosphatidylinositol 3-kinase (PI3K), Bcl-2 and Pim-1 might also contribute[89]. Indeed, transgenic expression of Bcl-2 increases the number of cells in IL-7 or $\gamma_c$ knockout mice[90–93], indicating the importance of this survival factor for the optimal number of cells. Similarly, transgenic expression of Pim-1 has been shown to increase the number of T cells in such mice[94]. Therefore, several pathways activated by IL-7 might contribute to normal T-cell development.

Table 2 | **Mouse phenotypes that result from defective Jak expression**

| Jak | Phenotype | References |
|---|---|---|
| Jak1 | Perinatal lethality; defective signal by gp130-dependent cytokines (IL-6, IL-11, CNTF, OSM, LIF and CT-1); defective signalling by $\gamma_c$-dependent cytokines, including IL-2 and IL-7 | 57 |
| Jak2 | Fetal lethality; profound anaemia due to defective erythropoietin signalling | 58,59 |
| Jak3 | Defective signalling by IL-2, IL-4, IL-7, IL-9, IL-15 and presumably IL-21; absent NK cells; greatly diminished T cells in thymus and spleen, but increasing $CD4^+$ T cells with a memory-activated phenotype that develop in an age-dependent fashion; phenotype is indistinguishable from $\gamma_c$-deficient mice; unlike humans with *JAK3*-deficient SCID[40,41], the *Jak3*-deficient mice lack B cells, consistent with a defect in IL-7 signalling | 46,47 |
| Tyk2 | Diminished, but not abrogated, signalling in response to IFN-α/β and IL-12; unexpectedly, it is primarily Stat3 activation that is affected, even though IFN-α/β primarily activate Stat1 and Stat2 and IL-12 primarily activates Stat4; diminished IFN-γ responses; defective clearing of vaccinia virus | 60,61 |

CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin 1; $\gamma_c$, common cytokine receptor γ-chain; IFN, interferon; IL, interleukin; Jak, Janus-activated kinase; LIF, leukaemia-inhibitory factor; NK, natural killer; OSM, oncostatin M; SCID, severe combined immunodeficiency disease; STAT, signal transducer and activator of transcription; Tyk2, tyrosine kinase 2.

### Defective signalling by IL-2R

As noted above, mutations in $\gamma_c$ cause XSCID in humans and a broad spectrum of abnormalities in mice. Defective expression of the other components of IL-2R also result in severe phenotypes. Mice that lack IL-2Rβ show defective NK-cell development, as well as severe autoimmunity and haemolytic anaemia, dysregulated T-cell activation and B-cell differentiation[85]. The one human patient with diminished IL-2Rβ expression was also identified with $T^+B^+NK^-$ SCID[86]. IL-2Rα-deficient mice show massive enlargement of peripheral lymphoid organs,

Table 3 | **Mouse phenotypes that result from defective STAT expression**

| Stat | Phenotype | References |
|---|---|---|
| Stat1 | Defective signalling in response to IFN-α/β and IFN-γ; defective responses to bacterial antigens and certain viruses | 62,63 |
| Stat2 | Defective IFN-α/β signalling; Stat2-deficient fibroblasts more severely affected than Stat2-deficient macrophages | 65 |
| Stat3 | Perinatal lethality, consistent with the broad range of cytokines that activate Stat3 | 70 |
| | Stat3-deficient T cells show defective IL-2-induced proliferation, correlating with a defect in IL-2-induced IL-2Rα expression | 113 |
| | and defective responses to IL-6 | 114 |
| | Stat3-deficient neutrophils and macrophages show defective IL-10 signalling | 115 |
| | Stat3 is also essential for normal involution of the mammary epithelium, and for wound healing and normal hair cycle processes | 115,116 |
| Stat4 | Defective $T_H1$-cell development | 66,67 |
| | Defective IL-12-mediated augmentation of NK-cell function | |
| Stat5 | Mice that lack Stat5a, Stat5b, or both Stat5a and Stat5b have all been generated | 71–73 |
| Stat5a | Defective prolactin signalling | 71 |
| | Defective IL-2-induced IL-2Rα expression and defects in IL-2-induced proliferation *in vitro* | 77 |
| | Defective *in vivo* expansion of Vβ8$^+$ T cells in response to superantigen | 77 |
| | Defective antigen-induced recruitment of eosinophils into the lung and decreased antigen-induced production of IgG1 | 85 |
| Stat5b | Defective growth hormone signalling | 72 |
| | Defective IL-2-induced IL-2Rα expression and severe defects in IL-2-induced proliferation *in vitro* | 78 |
| | Defective NK cytolytic activity | 78 |
| | Defective antigen-induced recruitment of eosinophils into the lung | 85 |
| Stat5a and 5b | Defective prolactin and growth hormone signalling | 73 |
| | Defective NK-cell development | 73 |
| | Major defect in T-cell proliferation | 83 |
| | Severe anaemia | 117 |
| Stat6 | Defective $T_H2$ cell differentiation | 68,69 |
| | Defective B-cell proliferation | 68,69 |

IFN, interferon; IL, interleukin; NK, natural killer; Stat, signal transducer and activator of transcription; $T_H$ cell, T helper cell.

polyclonal T-cell expansion and impaired antigen-induced cell death[95]. Autoimmunity, characterized in part by haemolytic anaemia, was also observed. Humans that lack IL-2Rα expression show lymphocytic infiltration of many tissues, diminished apoptosis in the thymus, failure to downregulate Bcl-2 and multiple autoreactive clones in the tissues[96,97]. These defects, coupled with those observed for $\gamma_c$, underscore the importance of each of the IL-2R components for normal immune function.

### Defects in clearing mycobacterial infections

Several immunodeficiencies have defects relating to the clearance of mycobacterial infections. In different individuals with these problems, mutations in the genes that encodes the IL-12 p40 subunit (*IL12B*)[98], the IL-12 receptor β1 chain (*IL12RB1*)[99], in the components of the IFN-γ receptor (*IFNGR1* and *IFNGR2*)[100,101] and *STAT1*[64] have all been identified. The similar phenotypes of patients with mutations in these different genes indicates that IL-12-induced IFN-γ-dependent signalling by STAT1 is important for anti-mycobacterial defence in humans. Interestingly, the *STAT1* mutation that was identified is a heterozygous dominant mutation that causes greatly diminished binding of STAT1 dimers to γ-interferon activated-sequence (GAS) motifs, whereas the binding of IFN-stimulated transcription factor 3γ (ISGF3) is relatively unaffected.

### Concluding comments

This review has focused primarily on SCID as a syndrome with many causes, some of which are based on defective cytokine signalling. The cytokines that are clearly important are IL-7 and IL-15 for T-cell and NK-cell development, respectively. Certain JAK/STAT-related proteins, such as JAK1, JAK3, STAT3, STAT5A and STAT5B, probably contribute to the development of these lineages. It is evident, however, that many cytokines activate the same JAKs and/or STAT proteins, despite the fact that they exert different functions *in vivo*. This, presumably, is at least partly explained by the fact that cytokines use many pathways apart from the JAK/STAT pathway for signalling. In addition, different cytokines can exert different effects owing to the differential regulation of their production, as well as the temporal expression and tissue distribution of their receptors. Mouse knockout models are useful in potentially predicting the defects that would be observed when certain genes are mutated in humans. However, caution is also required, as important differences can exist between these animal models and human disease. For example, in humans that lack expression of $\gamma_c$, JAK3 or IL-7Rα, B-cell numbers are normal, whereas mice that lack expression of the same proteins have virtually no B cells. Despite these differences, the studies in both humans and mice indicate the crucial role of cytokines for both lineage development and signalling in cells as a means of achieving normal immune function.


1. Leonard, W. J. The molecular basis of X-linked severe combined immunodeficiency: defective cytokine receptor signaling. *Annu. Rev. Med.* **47**, 229–239 (1996).
2. Buckley, R. H. *et al.* Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. *J. Pediatr.* **130**, 378–387 (1997).
3. Buckley, R. H. *et al.* Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. *N. Engl. J. Med.* **340**, 508–516 (1999).
4. Fischer, A. *et al.* Naturally occurring primary deficiencies of the immune system. *Annu. Rev. Immunol.* **15**, 93–124 (1997).
5. Lo, M. *et al.* Restoration of lymphoid populations in a murine model of X-linked severe combined immunodeficiency by a gene-therapy approach. *Blood* **94**, 3027–3036 (1999).
6. Cavazzana-Calvo, M. *et al.* Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. *Science* **288**, 669–672 (2000).
7. Fischer, A., Hacein-Bey, S., Le Deist, F., de Saint Basile, G. & Cavazzana-Calvo, M. Gene therapy for human severe combined immunodeficiencies. *Immunity* **15**, 1–4 (2001).
8. Noguchi, M. *et al.* Interleukin-2 receptor γ chain mutation results in X-linked severe combined immunodeficiency in humans. *Cell* **73**, 147–157 (1993).
**The discovery of mutations in IL-2Rγ as the genetic basis of XSCID.**
9. de Saint Basile, G. *et al.* Close linkage of the locus for X chromosome-linked severe combined immunodeficiency to polymorphic DNA markers in Xq11-q13. *Proc. Natl Acad. Sci. USA* **84**, 7576–7579 (1987).
10. Puck, J. M., Nussbaum, R. L., Smead, D. L. & Conley, M. E. X-linked severe combined immunodeficiency: localization within the region Xq13.1–q21.1 by linkage and deletion analysis. *Am. J. Hum. Genet.* **44**, 724–730 (1989).
11. Takeshita, T. *et al.* Cloning of the γ chain of the human IL-2 receptor. *Science* **257**, 379–382 (1992).
12. Schorle, H., Holtschke, T., Hunig, T., Schimpl, A. & Horak, I. Development and function of T cells in mice rendered interleukin-2 deficient by gene targeting. *Nature* **352**, 621–624 (1991).
13. Pahwa, R. *et al.* Recombinant interleukin 2 therapy in severe combined immunodeficiency disease. *Proc. Natl Acad. Sci. USA* **86**, 5069–5073 (1989).
14. Weinberg, K. & Parkman, R. Severe combined immunodeficiency due to a specific defect in the production of interleukin-2. *N. Engl J. Med.* **322**, 1718–1723 (1990).

15. Kondo, M. *et al.* Sharing of the interleukin-2 (IL-2) receptor γ chain between receptors for IL-2 and IL-4. *Science* **262**, 1874–1877 (1993).
16. Russell, S. M. *et al.* Interleukin-2 receptor γ chain: a functional component of the interleukin-4 receptor. *Science* **262**, 1880–1883 (1993).
17. Noguchi, M. *et al.* Interleukin-2 receptor γ chain: a functional component of the interleukin-7 receptor. *Science* **262**, 1877–1880 (1993).
18. Kondo, M. *et al.* Functional participation of the IL-2 receptor γ chain in IL-7 receptor complexes. *Science* **263**, 1453–1454 (1994).
**References 15–18 were the first to show that IL-2Rγ is shared by the IL-4 and IL-7 receptors, leading it to be renamed as the common cytokine receptor γ, $\gamma_c$.**
19. Russell, S. M. *et al.* Interaction of IL-2R β and $\gamma_c$ chains with Jak1 and Jak3: implications for XSCID and XCID. *Science* **266**, 1042–1045 (1994).
**Predicted that mutations in Jak3 would cause autosomal-recessive SCID.**
20. Kimura, Y. *et al.* Sharing of the IL-2 receptor γ chain with the functional IL-9 receptor complex. *Int. Immunol.* **7**, 115–120 (1995).
21. Giri, J. G. *et al.* Utilization of the β and γ chains of the IL-2 receptor by the novel cytokine IL-15. *EMBO J.* **13**, 2822–2830 (1994).
22. Asao, H. *et al.* Cutting edge: the common γ-chain is an indispensable subunit of the IL-21 receptor complex. *J. Immunol.* **167**, 1–5 (2001).
23. Leonard, W. J., Noguchi, M., Russell, S. M. & McBride, O. W. The molecular basis of X-linked severe combined immunodeficiency: the role of the interleukin-2 receptor gamma chain as a common γ chain, $\gamma_c$. *Immunol. Rev.* **138**, 61–86 (1994).
24. Leonard, W. J. in *Fundamental Immunology* **(eds?)** 771–774 (Lippincott Raven, Philadelphia, 1999).
25. Darnell, J. E. Jr. STATs and gene regulation. *Science* **277**, 1630–1635 (1997).
26. Horvath, C. M. & Darnell, J. E. The state of the STATs: recent developments in the study of signal transduction to the nucleus. *Curr. Opin. Cell Biol.* **9**, 233–239 (1997).
27. Leonard, W. J. & O'Shea, J. J. Jaks and STATs: biological implications. *Annu. Rev. Immunol.* **16**, 293–322 (1998).
28. Multiple reviews of STAT proteins in *Oncogene* **19**, 2466–2656 (2000).
29. Ramana, C. V., Chatterjee-Kishore, M., Nguyen, H. & Stark, G. R. Complex roles of Stat1 in regulating gene expression. *Oncogene* **19**, 2619–2627 (2000).
30. Ghosh, S., May, M. J. & Kopp, E. B. NF-κB and Rel proteins: evolutionarily conserved mediators of immune responses. *Annu. Rev. Immunol.* **16**, 225–260 (1998).
31. May, M. J. & Ghosh, S. Signal transduction through NF-κB. *Immunol. Today* **19**, 80–88 (1998).
32. Kiani, A., Rao, A. & Aramburu, J. Manipulating immune responses with immunosuppressive agents that target NFAT. *Immunity* **12**, 359–372 (2000).
33. Massague, J. & Wotton, D. Transcriptional control by the TGF-β/Smad signaling system. *EMBO J.* **19**, 1745–1754 (2000).
34. Johnston, J. A. *et al.* Phosphorylation and activation of the Jak-3 Janus kinase in response to interleukin-2. *Nature* **370**, 151–153 (1994).
35. Witthuhn, B. A. *et al.* Involvement of the Jak-3 Janus kinase in signalling by interleukins 2 and 4 in lymphoid and myeloid cells. *Nature* **370**, 153–157 (1994).
36. Kovanen, P. E. & Leonard, W. J. Inhibitors keep cytokines in check. *Curr. Biol.* **9**, R899–R902 (1999).
37. Kile, B. T., Nicola, N. A. & Alexander, W. S. Negative regulators of cytokine signaling. *Int. J. Hematol.* **73**, 292–298 (2001).
38. Boussiotis, V. A. *et al.* Prevention of T cell anergy by signaling through the $\gamma_c$ chain of the IL-2 receptor. *Science* **266**, 1039–1042 (1994).
39. Miyazaki, T. *et al.* Functional activation of Jak1 and Jak3 by selective association with IL-2 receptor subunits. *Science* **266**, 1045–1047 (1994).
40. Macchi, P. *et al.* Mutations of *Jak-3* gene in patients with autosomal severe combined immune deficiency (SCID). *Nature* **377**, 65–68 (1995).
41. Russell, S. M. *et al.* Mutation of Jak3 in a patient with SCID: essential role of Jak3 in lymphoid development. *Science* **270**, 797–800 (1995).
**References 40 and 41 showed that mutations in Jak3 cause SCID.**
42. Riedy, M. C. *et al.* Genomic sequence, organization, and chromosomal localization of human JAK3. *Genomics* **37**, 57–61 (1996).
43. DiSanto, J. P., Muller, W., Guy-Grand, D., Fischer, A. & Rajewsky, K. Lymphoid development in mice with a targeted deletion of the interleukin 2 receptor γ chain. *Proc. Natl Acad. Sci. USA* **92**, 377–381 (1995).
44. Cao, X. *et al.* Defective lymphoid development in mice lacking expression of the common cytokine receptor γ chain. *Immunity* **2**, 223–238 (1995).
45. Ohbo, K. *et al.* Modulation of hematopoiesis in mice with a truncated mutant of the interleukin-2 receptor γ chain. *Blood* **87**, 956–967 (1996).
46. Thomis, D. C. & Berg, L. J. The role of Jak3 in lymphoid development, activation, and signaling. *Curr. Opin. Immunol.* **9**, 541–547 (1997).
47. Nosaka, T. *et al.* Defective lymphoid development in mice lacking Jak3. *Science* **270**, 800–802 (1995).
48. Suzuki, K. *et al.* Janus kinase 3 (Jak3) is essential for common cytokine receptor γ chain ($\gamma_c$)-dependent signaling: comparative analysis of $\gamma_c$, Jak3, and $\gamma_c$ and Jak3 double-deficient mice. *Int. Immunol.* **12**, 123–132 (2000).
49. Puel, A., Ziegler, S. F., Buckley, R. H. & Leonard, W. J. Defective IL7R expression in $T^-B^+NK^+$ severe combined immunodeficiency. *Nature Genet.* **20**, 394–397 (1998).
**Identification of IL-7Rα-deficient SCID.**
50. Kennedy, M. K. *et al.* Reversible defects in natural killer and memory CD8 T cell lineages in interleukin 15-deficient mice. *J. Exp. Med.* **191**, 771–780 (2000).
51. Lodolce, J. P. *et al.* IL-15 receptor maintains lymphoid homeostasis by supporting lymphocyte homing and proliferation. *Immunity* **9**, 669–676 (1998).
52. Suzuki, H. *et al.* Deregulated T cell activation and autoimmunity in mice lacking interleukin-2 receptor β. *Science* **268**, 1472–1476 (1995).
53. Kuhn, R., Rajewsky, K. & Muller, W. Generation and analysis of interleukin-4 deficient mice. *Science* **254**, 707–710 (1991).
54. Townsend, J. M. *et al.* IL-9-deficient mice establish fundamental roles for IL-9 in pulmonary mastocytosis and goblet cell hyperplasia but not T cell development. *Immunity* **13**, 573–583 (2000).
55. Renauld, J. C. *et al.* Thymic lymphomas in interleukin 9 transgenic mice. *Oncogene* **9**, 1327–1332 (1994).
56. Peschon, J. J. *et al.* Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice. *J. Exp. Med.* **180**, 1955–1960 (1994).
57. Rodig, S. J. *et al.* Disruption of the *Jak1* gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. *Cell* **93**, 373–383 (1998).
58. Parganas, E. *et al.* Jak2 is essential for signaling through a variety of cytokine receptors. *Cell* **93**, 385–395 (1998).
59. Neubauer, H. *et al.* Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. *Cell* **93**, 397–409 (1998).
60. Karaghiosoff, M. *et al.* Partial impairment of cytokine responses in Tyk2-deficient mice. *Immunity* **13**, 549–560 (2000).
61. Shimoda, K. *et al.* Tyk2 plays a restricted role in IFNα signaling, although it is required for IL-12-mediated T cell function. *Immunity* **13**, 561–571 (2000).
62. Meraz, M. A. *et al.* Targeted disruption of the *Stat1* gene in mice reveals unexpected physiologic specificity in the JAK–STAT signaling pathway. *Cell* **84**, 431–442 (1996).
63. Durbin, J. E., Hackenmiller, R., Simon, M. C. & Levy, D. E. Targeted disruption of the mouse *Stat1* gene results in compromised innate immunity to viral disease. *Cell* **84**, 443–450 (1996).
64. Dupuis, S. *et al.* Impairment of mycobacterial but not viral immunity by a germline human *STAT1* mutation. *Science* **293**, 300–303 (2001).
**Impairment of mycobacterial infections associated with mutations in the *STAT1* gene.**
65. Park, C., Li, S., Cha, E. & Schindler, C. Immune response in Stat2 knockout mice. *Immunity* **13**, 795–804 (2000).
66. Kaplan, M. H., Sun, Y. L., Hoey, T. & Grusby, M. J. Impaired IL-12 responses and enhanced development of $T_H2$ cells in Stat4-deficient mice. *Nature* **382**, 174–177 (1996).
67. Thierfelder, W. E. *et al.* Requirement for Stat4 in interleukin-12-mediated responses of natural killer and T cells. *Nature* **382**, 171–174 (1996).
68. Kaplan, M. H., Schindler, U., Smiley, S. T. & Grusby, M. J. Stat6 is required for mediating responses to IL-4 and for development of $T_H2$ cells. *Immunity* **4**, 313–319 (1996).
69. Shimoda, K. *et al.* Lack of IL-4-induced $T_H2$ response and IgE class switching in mice with disrupted *Stat6* gene. *Nature* **380**, 630–633 (1996).
70. Takeda, K. *et al.* Targeted disruption of the mouse *Stat3* gene leads to early embryonic lethality. *Proc. Natl Acad. Sci. USA* **94**, 3801–3804 (1997).
71. Liu, X. *et al.* Stat5a is mandatory for adult mammary gland development and lactogenesis. *Genes Dev.* **11**, 179–186 (1997).
72. Udy, G. B. *et al.* Requirement of STAT5b for sexual dimorphism of body growth rates and liver gene expression. *Proc. Natl Acad. Sci. USA* **94**, 7239–7244 (1997).
73. Teglund, S. *et al.* Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses. *Cell* **93**, 841–850 (1998).
74. Azam, M. *et al.* Interleukin-3 signals through multiple isoforms of Stat5. *EMBO J.* **14**, 1402–1411 (1995).
75. Mui, A. L., Wakao, H., Harada, N., O'Farrell, A. M. & Miyajima, A. Interleukin-3, granulocyte-macrophage colony-stimulating factor, and interleukin-5 transduce signals through two forms of STAT5. *J. Leukoc. Biol.* **57**, 799–803 (1995).
76. Lin, J. X., Mietz, J., Modi, W. S., John, S. & Leonard, W. J. Cloning of human *Stat5B*. Reconstitution of interleukin-2-induced Stat5A and Stat5B DNA binding activity in COS-7 cells. *J. Biol. Chem.* **271**, 10738–10744 (1996).
77. Nakajima, H. *et al.* An indirect effect of Stat5a in IL-2-induced proliferation: a critical role for Stat5a in IL-2-mediated IL-2 receptor α chain induction. *Immunity* **7**, 691–701 (1997).
78. Imada, K. *et al.* Stat5b is essential for natural killer cell-mediated proliferation and cytolytic activity. *J. Exp. Med.* **188**, 2067–2074 (1998).
**References 77 and 78 show impaired immunological phenotype in Stat5a and 5b knockout mice, respectively.**
79. Sperisen, P. *et al.* Mouse interleukin-2 receptor α gene expression. Interleukin-1 and interleukin-2 control transcription via distinct *cis*-acting elements. *J. Biol. Chem.* **270**, 10743–10753 (1995).
80. John, S., Robbins, C. M. & Leonard, W. J. An IL-2 response element in the human IL-2 receptor α chain promoter is a composite element that binds Stat5, Elf-1, HMG-I(Y) and a GATA family protein. *EMBO J.* **15**, 5627–5635 (1996).
81. Lecine, P. *et al.* Elf-1 and Stat5 bind to a critical element in a new enhancer of the human interleukin-2 receptor α gene. *Mol. Cell. Biol.* **16**, 6829–6840 (1996).
82. Kim, H. P., Kelly, J. & Leonard, W. J. The basis for IL-2-induced IL-2 receptor α chain gene regulation: importance of two widely separated IL-2 response elements. *Immunity* **15**, 159–172 (2001).
83. Socolovsky, M., Fallon, A. E., Wang, S., Brugnara, C. & Lodish, H. F. Fetal anemia and apoptosis of red cell progenitors in *Stat5a*$^{-/-}$*5b*$^{-/-}$ mice: a direct role for Stat5 in Bcl-$X_L$ induction. *Cell* **98**, 181–191 (1999).
84. Kagami, S. *et al.* Both Stat5a and Stat5b are required for antigen-induced eosinophil and T-cell recruitment into the tissue. *Blood* **95**, 1370–1377 (2000).
85. Suzuki, H. *et al.* Deregulated T-cell activation and autoimmunity in mice lacking interleukin-2 receptor β. *Science* **268**, 1472–1476 (1995).
86. Gilmour, K. C. *et al.* Defective expression of the interleukin-2/interleukin-15 receptor β subunit leads to a natural killer cell-deficient form of severe combined immunodeficiency. *Blood* **98**, 877–879 (2001).
87. Zhang, J., Scordi, I., Smyth, M. J. & Lichtenheld, M. G. Interleukin 2 receptor signaling regulates the perforin gene through signal transducer and activator of transcription (Stat)5 activation of two enhancers. *J. Exp. Med.* **190**, 1297–1308 (1999).
88. Moriggl, R. *et al.* Stat5 is required for IL-2-induced cell cycle progression of peripheral T cells. *Immunity* **10**, 249–259 (1999).
89. Puel, A. & Leonard, W. J. Mutations in the gene for the IL-7 receptor result in $T^-B^+NK^+$ severe combined immunodeficiency disease. *Curr. Opin. Immunol.* **12**, 468–473 (2000).
90. Akashi, K., Kondo, M., von Freeden-Jeffry, U., Murray, R. & Weissman, I. L. Bcl-2 rescues T lymphopoiesis in interleukin-7 receptor-deficient mice. *Cell* **89**, 1033–1041 (1997).
91. Kondo, M., Akashi, K., Domen, J., Sugamura, K. & Weissman, I. L. Bcl-2 rescues T lymphopoiesis, but not B or NK cell development, in common γ chain-deficient mice. *Immunity* **7**, 155–162 (1997).
92. Maraskovsky, E. *et al.* Bcl-2 can rescue T lymphocyte development in interleukin-7 receptor-deficient mice but not in mutant *Rag-1*$^{-/-}$ mice. *Cell* **89**, 1011–1019 (1997).
93. Nakajima, H. & Leonard, W. J. Role of Bcl-2 in αβ T cell development in mice deficient in the common cytokine receptor γ-chain: the requirement for Bcl-2 differs depending on the TCR/MHC affinity. *J. Immunol.* **162**, 782–790 (1999).
94. Jacobs, H. *et al.* PIM1 reconstitutes thymus cellularity in interleukin 7- and common γ chain-mutant mice and permits thymocyte maturation in Rag- but not CD3γ-deficient mice. *J. Exp. Med.* **190**, 1059–1068 (1999).
95. Willerford, D. M. *et al.* Interleukin-2 receptor α chain regulates the size and content of the peripheral lymphoid compartment. *Immunity* **3**, 521–530 (1995).

96. Sharfe, N., Dadi, H. K., Shahar, M. & Roifman, C. M. Human immune disorder arising from mutation of the α chain of the interleukin-2 receptor. *Proc. Natl Acad. Sci. USA* **94**, 3168–3171 (1997).
97. Roifman, C. M. Human IL-2 receptor α chain deficiency. *Pediatr. Res*. **48**, 6–11 (2001).
98. Altare, F. *et al.* Inherited interleukin-12 deficiency in a child with Bacille Calmette–Guérin and *Salmonella enteritidis* disseminated infection. *J. Clin. Invest.* **102**, 2035–2040 (1998).
99. Altare, F. *et al.* Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. *Science* **280**, 1435–1438 (1998).
100. Jouanguy, E. *et al.* Partial interferon-γ receptor 1 deficiency in a child with tuberculoid Bacillus Calmette–Guérin infection and a sibling with clinical tuberculosis. *J. Clin. Invest.* **100**, 2658–2664 (1997).
101. Doffinger, R. *et al.* Partial interferon-γ receptor signaling chain deficiency in a patient with Bacille Calmette–Guérin and *Mycobacterium abscessus* infection. *J. Infect. Dis.* **181**, 379–384 (2000).
102. Bazan, J. F. Haemopoietic receptors and helical cytokines. *Immunol. Today* **11**, 350–354 (1990).
103. Davies, D. R. & Wlodawer, A. Cytokines and their receptor complexes. *FASEB J.* **9**, 50–56 (1995).
104. Senda, T. *et al.* Three-dimensional crystal structure of recombinant murine interferon-β. *EMBO J.* **11**, 3193–3201 (1992).
105. Ealick, S. E. *et al.* Three-dimensional structure of recombinant human interferon-γ. *Science* **252**, 698–702 (1991).
105. Josephson, K., Logsdon, N. J. & Walter, M. R. Crystal structure of the IL-10/IL-10R1 complex reveals a shared receptor binding site. *Immunity* **15**, 35–46 (2001).
107. Argetsinger, L. S. *et al.* Identification of JAK2 as a growth hormone receptor-associated tyrosine kinase. *Cell* **74**, 237–244 (1993).
108. Witthuhn, B. A. *et al.* JAK2 associates with the erythropoietin receptor and is tyrosine phosphorylated and activated following stimulation with erythropoietin. *Cell* **74**, 227–236 (1993).
109. Vinkemeier, U. *et al.* DNA binding of *in vitro* activated Stat1α, Stat1β and truncated Stat1: interaction between NH2-terminal domains stabilizes binding of two dimers to tandem DNA sites. *EMBO J*. **15**, 10743–10753 (1996).
110. Vinkemeier, U., Moarefi, I., Darnell, J. E. Jr & Kuriyan, J. Structure of the amino-terminal protein interaction domain of Stat4. *Science* **279**, 1048–1052 (1998).
111. John, S., Vinkemeier, U., Soldaini, E., Darnell, J. E. Jr & Leonard, W. J. The significance of tetramerization in promoter recruitment by Stat5. *Mol. Cell. Biol.* **19**, 1910–1918 (1999).
112. Lew, D. J., Decker, T., Strehlow, I. & Darnell, J. E. Overlapping elements in the guanylate-binding protein gene promoter mediate transcriptional induction by α and γ interferons. *Mol. Cell. Biol.* **11**, 182–191 (1991).
113. Akaishi, H. *et al.* Defective IL-2-mediated IL-2 receptor α chain expression in Stat3-deficient T lymphocytes. *Int. Immunol.* **10**, 1747–1751 (1998).
114. Takeda, K. *et al.* Stat3 activation is responsible for IL-6-dependent T cell proliferation through preventing apoptosis: generation and characterization of T cell-specific Stat3-deficient mice. *J. Immunol.* **161**, 4652–4660 (1998).
115. Akira, S. Roles of STAT3 defined by tissue-specific gene targeting. *Oncogene* **19**, 2607–2611 (2000).
116. Chapman, R. S. *et al.* Suppression of epithelial apoptosis and delayed mammary gland involution in mice with a conditional knockout of Stat3. *Genes Dev.* **13**, 2604–2616 (1999).
117. Socolovsky, M., Fallon, A. E., Wang, S., Brugnara, C. & Lodish, H. F. Fetal anemia and apoptosis of red cell progenitors in *Stat5a*$^{-/-}$*5b*$^{-/-}$ mice: a direct role for Stat5 in Bcl-$X_L$ induction. *Cell* **98**, 181–191 (1999).


## Online links

**DATABASES**

**The following terms in this article are linked online to:**

**LocusLink:** http://www.ncbi.nlm.nih.gov/LocusLink/
Bcl-2 | cardiotrophin 1 | CDk6 | ciliary neurotrophic factor | CIS | c-kit | cyclin D2 | cyclin D3 | epidermal growth factor | erythropoietin | $\gamma_c$ | gp130 | IFN-γ | *IFNGR1* | *IFNGR2* | IL-2 | IL-2R | *IL2RG* | IL-3 | IL-4 | IL-6 | IL-7 | IL-9 | IL-10 | IL-11 | *IL12B* | *IL12RB1* | IL-13 | IL-15 | IL-21 | ISGF3 | JAK1–3 | leukaemia-inhibitory factor | oncostatin M | Pim-1 | SOCS1 | SSI-1 | STAT1–4 | STAT5A | STAT5B | STAT6 | TYK2
**OMIM:** http://www.ncbi.nlm.nih.gov/Omim/
XSCID

**FURTHER INFORMATION**

**Encylopedia of Life Scienes:** http://www.els.net/
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**JAK3base:** http://www.uta.fi/imt/bioinfo/JAK3base/
**X-Linked SCID Mutation Database:** http://www.nhgri.nih.gov/DIR/GMBB/SCID/IL2RGbase.html
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