Mutations in the gene for the IL-7 receptor result in T⁻B⁺NK⁺ severe combined immunodeficiency disease

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Recently, two SCID (severe combined immunodeficiency disease) patients with greatly diminished T cells but normal or increased numbers of B and NK cells (T⁻B⁺NK⁺ SCID) were found to have mutations in the gene for the IL-7 receptor. This has established a major role for IL-7-receptor-dependent signaling in T cell development in humans and probably explains the diminished T cell numbers seen in patients with X-linked SCID or SCID that results from Jak3-deficiency.

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Abbreviations

IL-7R	IL-7 receptor
Jak3	Janus tyrosine kinase 3
PI 3-K	phosphatidylinositol-3′-OH kinase
SCID	severe combined immunodeficiency disease
Stat	signal transducer and activator of transcription
XSCID	X-linked SCID

Introduction

Severe combined immunodeficiency disease (SCID) represents the most severe form of primary immunodeficiency diseases, affecting one child in approximately every 80,000 live births [1]. These children exhibit profound defects in cellular and humoral immunity, with death occurring within the first year of life due to severe and recurrent opportunistic infections unless they receive a successful bone marrow transplant [2]. SCID is a syndrome with many causes and, although the genetic basis for many of the defects has now been elucidated, in approximately 30% of cases this basis remains unknown [1].

A common feature in SCID patients is a profound defect in T cell development and/or function. The range of defects in B- or NK-cell development and/or function is more variable [3]. Accordingly, it is possible to classify SCID into four groups: T⁻B⁻NK⁻, T⁻B⁻NK⁺, T⁻B⁺NK⁻ and T⁻B⁺NK⁺ SCID [4••]. In this review, we will focus on the T⁻B⁺NK⁻ and T⁻B⁺NK⁺ forms of SCID resulting from mutations in genes required for the function of the IL-7/IL-7R (IL-7 receptor) signaling pathway.

T⁻B⁺NK⁻ SCID: γ_c-deficient and Jak3-deficient patients

The most common form of SCID is X-linked SCID (XSCID), which accounts for almost 50% of cases of SCID [1,5]. In XSCID, affected males typically have few if any T or NK cells but have normal or increased numbers of B cells (T⁻B⁺NK⁻ SCID); however, the B cells are non-functional and exhibit defective class switching, due only in part to the absence of T cell help [5]. Earlier work localized the defective gene in XSCID (in the *SCIDX1* locus) to the chromosomal region between Xq11 and Xq13 [6]. Subsequently, the gene encoding the IL-2R γ chain was cloned [7] and localized to Xq13 [8], at the *SCIDX1* locus. DNA sequencing then established that mutations in *IL2RG* represent the basis for XSCID [8] (see Figure 1).

Because XSCID patients exhibit a more severe immunological phenotype than patients with IL-2 deficiency, where T- and NK-cell development are normal, it was hypothesized that IL-2Rγ was a component of more than one cytokine receptor [8], at least one of which was required for lymphoid development. Indeed, IL-2Rγ was shown to also be a shared component of the receptors for IL-2, IL-4, IL-7, IL-9 and IL-15, and was therefore renamed as the common cytokine receptor γ chain, γ_c (reviewed in [5,9,10]; see Figure 1).

In one family pedigree, affected males exhibit a more moderate form of X-linked combined immunodeficiency and live until adulthood [11]. These patients were found to exhibit partial T cell development resulting from a point mutation in the γ_c cytoplasmic domain that reduces the interaction between γ_c and its associated tyrosine kinase Jak3 (Janus tyrosine kinase 3) [11]. It was thus hypothesized that mutations in Jak3 might result in a similar phenotype to that found in XSCID but with an autosomal recessive mode of inheritance, as the *JAK3* gene is located on chromosome 19 [12]. Patients with mutations in *JAK3* were indeed reported, having a phenotype indistinguishable from that found in XSCID patients [13,14], indicating that most if not all γ_c-dependent signals require Jak3 and that Jak3 only contributes to γ_c-dependent signaling.

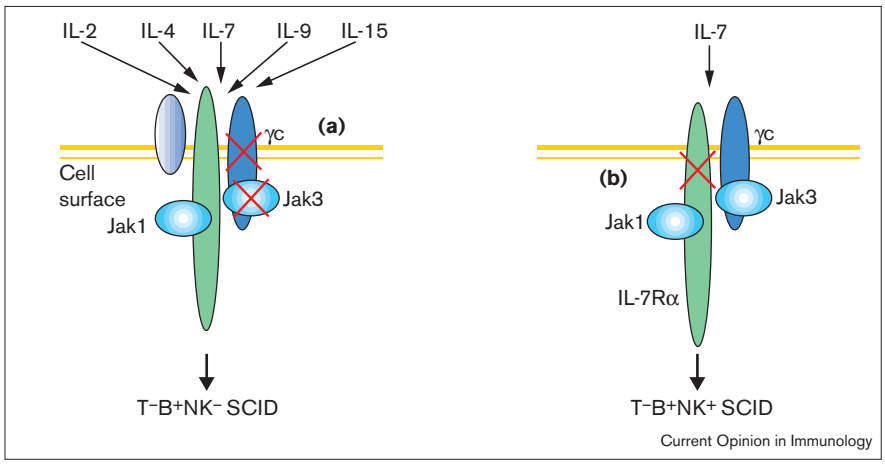
In patients with XSCID or with Jak3 deficiency, the severity of the phenotype is explained by the disruption of five signaling pathways: those for IL-2, IL-4, IL-7, IL-9 and IL-15 [5]. IL-2 and IL-4 do not appear to contribute to lineage development. However, defective IL-15 signaling may explain the defect in NK cell development (reviewed in [15]) whereas IL-7 (see below) and perhaps IL-9 [16] are critical for early T cell development.

T⁻B⁺NK⁺ SCID: relationship to the IL-7 signaling pathway

Il7/Il7r-deficient mice

IL-7 signals through a receptor containing the IL-7R α chain and γ_c [5]. Deletion of the *Il7* [17] or *Il7r* [18] genes in mice or treatment of mice with antibodies

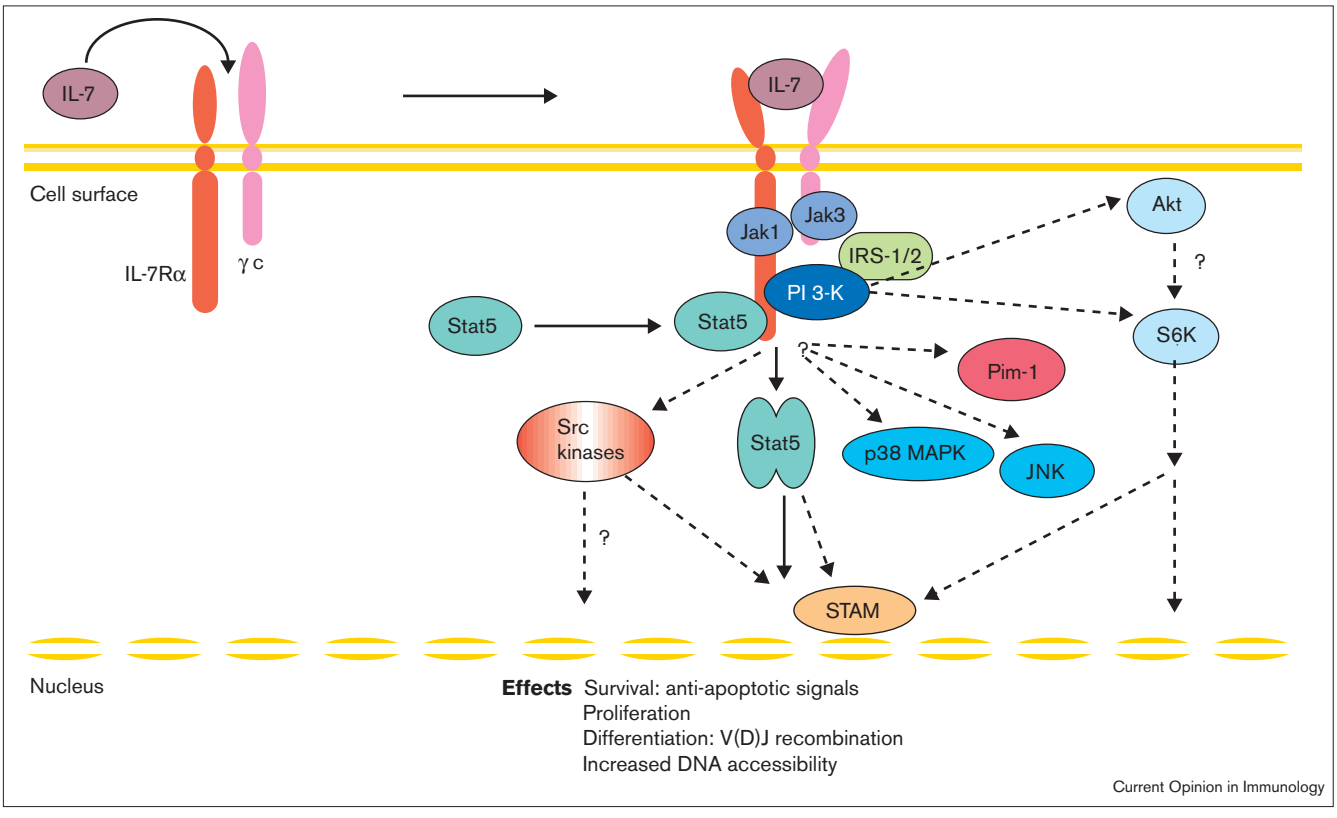
Figure 1



Causes of T⁻B⁺NK⁻ and T⁻B⁺NK⁺ SCID. (**a**) Mutations in the genes encoding γ_c or Jak3 result in T⁻B⁺NK⁻ SCID. The schematic shows that γ_c is shared by the receptors for IL-2, IL-4, IL-7, IL-9 and IL-15. Two receptor subunits other than the γ_c subunit are shown in the figure because the high affinity IL-2R and the IL-15R have three subunits; however, it should be noted that the IL-4, IL-7 and IL-9 receptors each only have two subunits. (**b**) Mutations in the *IL7R* gene cause T⁻B⁺NK⁺ SCID.

against IL-7 [19] or against IL-7Rα resulted in a profound B-cell and T-cell lymphopenia and absent γδ T cells; NK cell numbers and function were normal [20,21]. The reduced T and B cell development in these mice was comparable to that observed in γ_c-deficient [22,23] or Jak3-deficient mice [24,25]. *Il7r*$^{-/-}$ mice exhibit a block early in T-cell development at the pro-T2 stage (CD44⁺CD25⁺HSA⁺CD4⁻CD8⁻); some peripheral T cells are present but have impaired survival [26]. Regarding B cell development, whereas *Il7r*$^{-/-}$ mice exhibit a block at the transition between pre-pro-B and early pro-B stages, *Il7*$^{-/-}$ mice have a later

Figure 2



Schematic of signaling pathways used by IL-7. IL-7 signals are important in B cell and T cell development and differentiation. Stat5 denotes both Stat5a and Stat5b. Akt is a serine/threonine kinase. IRS, insulin-receptor substrate; JNK, c-Jun N-terminal kinase; MAPK, MAP kinase; S6K, ribosomal S6 kinase; STAM, signal transducer adaptor molecule.

block — at the transition between the late pro-B and the pre-B stages. Thymic stromal lymphopoietin (TSLP), which signals through a receptor containing IL-7Rα but not γ_c [27–29], may be the cytokine that explains this difference between *Il7*$^{-/-}$ and *Il7r*$^{-/-}$ mice.

Strikingly, whereas mice made deficient for γ_c, Jak3, IL-7 or IL-7Rα show a profound defect in B cell development and reduced peripheral B cells, humans with XSCID or SCID due to Jak3 deficiency have either normal or increased numbers of B cells. Therefore, IL-7 either does not contribute to B cell development in humans or its function in this regard is redundant.

IL-7R-deficient SCID patients

To investigate whether the defect in the IL-7 signaling pathway in XSCID and Jak3-deficient patients was responsible for defective T cell development, we sought to identify SCID patients with an autosomal recessive form of deficiency of unknown genetic origin, in which T cell development was selectively impaired.

In a study of 108 children with SCID [1], two children exhibited a selective defect in T cell numbers and function but retained normal or increased numbers of B cells and functional NK cells ($T^-B^+NK^+$ SCID). They were believed to have an autosomal recessive form of SCID of unknown genetic cause [1]. Although no defect in *IL7* mRNA levels or sequence was found in Epstein–Barr virus (EBV)-transformed B-cell lines established from either patient, *IL7R* mRNA levels were not detected or were greatly reduced compared to the levels expressed in EBV-transformed B cells from normal donors [30]. The patient with diminished *IL7R* mRNA levels had two mutations: on one allele, there was a splice-junction acceptor mutation in intron 4 (AG→AA) whereas the other allele contained a non-sense mutation with a premature stop codon (TGG→TGA: Trp^{217}→stop) in exon 5. Whereas his mother was heterozygous for the splice-junction acceptor mutation, the premature stop codon was a spontaneous mutation [30]. The second patient had no detectable *IL7R* mRNA and was found to be homozygous for a mutation located at the exon-2/intron-2 splice-donor site (GT→GG) [4••]. Both parents were heterozygous for the mutation and interestingly only expressed the wild-type allele [30].

Thus, both of these SCID patients had point mutations in their *IL7R* genes that prevented the production of a functional IL-7Rα protein as a basis for the absence of T cells (Figure 1). Moreover, these data suggest that the T cell defect observed in XSCID and in Jak3-deficient SCID patients can largely if not entirely be attributed to the defective IL-7 signaling. The normal or increased numbers of functional NK cells indicate that IL-7 signaling is not involved in NK cell development or function [30]. Instead, the disruption of the IL-15 signaling pathway in XSCID or Jak3-deficient patients probably explains the absence of NK cells. Finally, this study also excluded a major role for the IL-7/IL-7R signaling pathway in B cell development in humans, in contrast to the markedly defective B cell development in mice lacking expression of *Il2rg*, *Jak3*, *Il7* or *Il7r*.

Consistent with these findings, an atypical case of XSCID with a selective T cell defect has been described [31]. This patient had a mutation in the extracellular domain of γ_c (Ala156→Val) that affected IL-4 and IL-7 binding and signaling; IL-2 and IL-15 signaling were relatively normal. As IL-4 signaling does not seem to be required for T cell development, the selective T cell defect in this patient probably results from defective IL-7 signaling [31].

Signaling pathways activated by IL-7

Consistent with its role in lymphoid development, IL-7 is mainly produced by bone marrow and thymic stromal cells. Additionally, it is produced by the intestinal epithelium to help in the extrathymic development of γδ T cells [32,33] and also by monocytes/macrophages, follicular dendritic cells, keratinocytes and certain B-cell lines (reviewed in [34]). IL-7 signaling is involved in several processes, including cell survival, by protecting against cell death and by expanding cells during lymphoid development (for reviews, see [34,35•,36]).

IL-7 induces the activation of both Jak1 and Jak3, which interact with IL-7Rα [37,38] and γ_c [11,39,40] respectively, promoting the activation of signal transducer and activator of transcription (Stat)3, Stat5a and Stat5b [12,37] (Figure 2). Both *Jak1*$^{-/-}$ [41] and *Jak3*$^{-/-}$ [24,25] mice have profound defects in lymphoid development with a severe reduction in thymocyte numbers, showing the importance of Jak1 and Jak3 for IL-7-induced growth effects and proliferation. Mice lacking Stat5a, Stat5b or both Stat5 proteins have normal or only slightly reduced thymic cellularity [42–44]; nevertheless, Stat5 proteins are likely to be involved in T cell differentiation [45,46]. Notably, IL-7 is indispensable for γδ T cell development [20] and *Stat5a*$^{-/-}$ but not *Stat5b*$^{-/-}$ mice show a reduced number of γδ T cells; thus, Stat5a may be required for their development [42].

IL-7 has also been shown to activate the phosphatidylinositol-3′-OH kinase (PI 3-K) pathway. A direct interaction of PI 3-K with the phosphorylated tyrosine residue 429 on IL-7Rα has been demonstrated [47]; this same tyrosine mediates the docking of Stat5 proteins [48]. The activation of the PI 3-K has been shown to be essential for the IL-7-mediated survival and proliferation of T cell precursors [45]. Moreover, disruption of the p85α regulatory subunit of PI 3-K leads to impaired B cell development at the pro-B cell stage, with a reduced number of mature B cells [49,50]. Thus, PI 3-K appears to be involved both in T- and B-cell development. IL-7 has also been shown to induce tyrosine phosphorylation of insulin-receptor substrate (IRS)-1 and -2, which then associate with p85 [51]. IL-7 can also activate non-receptor protein tyrosine kinases from the Src family: $p59^{fyn}$ [52] and $p53^{lyn}$ in human

pre-B cells and p56^{lck} and p59^{fyn} in mature human T cells [53]; however, their role in IL-7 responses remains unclear.

In addition to Jak/STAT, PI 3-K and Src kinases, a number of other signaling molecules have been implicated in the IL-7/IL-7R signaling pathway. Signal transducing adaptor molecule (STAM) [54], MAP kinase family proteins (c-Jun N-terminal kinase [JNK] and the p38 kinase [55]) may be involved in T cell proliferation induced by IL-7. The *pim1* proto-oncogene — which encodes a serine/threonine kinase, whose expression is induced by IL-7 — is likely to play an important role in the IL-7 signaling pathway, as Pim-1 expression significantly restores thymic cellularity and proliferation in γ_c- or *Il7*-deficient mice [56].

IL-7 signaling is important for cell survival, acting in part by increasing and maintaining levels of the antiapoptotic protein Bcl-2 (and perhaps Bcl X_L) during lymphoid development [57,58]. Impaired Bcl-2 expression has been found in developing thymocytes and mature T cells in *Il7*$^{-/-}$ and *Il7r*$^{-/-}$ mice, and the expression of a *Bcl2* transgene in *Il7r*$^{-/-}$ or *Il2rg*$^{-/-}$ mice can partially rescue T lymphopoiesis (except for γδ T cells) [59–63]. It is conceivable that IL-7 might also induce cell survival by inhibiting proapoptotic proteins. In addition to these effects, IL-7 promotes V(D)J recombination [64,65] although its effect in this regard may at least in part be due to its effect as a survival factor [66]. Finally, IL-7 has been suggested to regulate DNA accessibility of target loci either by increasing levels of transcription factors [65] or through a demethylation process [67].

Towards the identification of other genes that when mutated will cause T⁻B⁺NK⁺ SCID

Although *IL7R* mutations can cause T⁻B⁺NK⁺ SCID, there are other possible genetic causes for this syndrome. The most obvious candidate gene whose mutation might cause T⁻B⁺NK⁺ SCID is the *IL7* gene. We hypothesize that such patients would have a similar phenotype to *IL7R*-deficient patients, except that they might fail to engraft transplanted bone marrow as the host stromal cells would be unable to secrete IL-7, which is necessary for the proper development and expansion of donor T cells.

Conclusions

We have discussed defective cytokine signaling as a cause of SCID. Mutations in *IL7R*, *IL2RG* (which encodes γ_c) or the *JAK3* genes abrogate T cell development in humans. We presume that mutations in the *IL7* gene will have a similar effect. However, it is unclear that inactivation of a single protein downstream of Jak3 would recapitulate the defect in T cell development observed in *IL7R*-deficient patients. Instead, a variety of signaling molecules including Stat5a, Stat5b, Pim-1, Bcl-2, PI 3-K and perhaps others may all contribute to IL-7-mediated T cell development. Clarification of this issue may be difficult to obtain but could at least partially be addressed by the eventual identification of patients with mutations in these individual genes. Although disruption of the IL-7 signaling pathway significantly accounts for the T cell defect in XSCID, it is disruption of the IL-15 signaling pathway that is likely to account for the NK cell defect in XSCID [68]. Again, clarification of this issue awaits the identification of patients with mutations in the *IL15* or *IL15R* genes.

In addition to γ_c-dependent signaling pathways, it is important to note that other cytokine signaling pathways (for review see [10]) and TCR signaling pathways also play major and perhaps overlapping roles during thymic development [69,70]. Several molecules involved in these signaling pathways have been shown to play a critical role in early T cell development in knockout mice and indeed defects in components of the TCR have been identified as causes of human SCID (for a review, see [71]). Interestingly, a male patient with SCID due to mutations in the tyrosine phosphatase *CD45* gene also has been reported [72]. This patient had greatly diminished and nonfunctional T cells, increased numbers of B cells and reduced but detectable numbers of NK cells. Thus, defective T cell development can occur due to a variety of defects. The identification of the full range of genetic defects that can cause SCID will enhance our knowledge of human immunology as well as have diagnostic and clinical implications for treating this group of patients.

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