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Interleukin-2 Signaling and Inherited Immunodeficiency

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Cytokines control the growth, differentiation, and survival of cells of the immune system. Since the identification of the genes for the T-cell growth factor interleukin-2 (IL-2) and its heterotrimeric receptor (IL-2R), the important role of cytokines in lymphocyte development and survival has become increasingly clear. The IL-2 family of cytokines—IL-2, IL-4, IL-7, IL-9, and IL-15—share both the common γ-chain (γc) receptor subunit and much of their intracellular signaling pathways. These cytokines are critical for normal lymphocyte development and peripheral-lymphocyte function. In recent years, important advances in understanding these receptors and their signaling pathways have contributed to and built upon the identification of naturally occurring mutations that underlie several inherited forms of immunodeficiency.

The discovery of both the Janus (Jak) family of tyrosine kinases and the family of signal transducers and activators of transcription (STAT) transcription factors has provided important insight into the biochemical mechanism of cytokine signal transduction. On IL-2 binding, Jak1 and Jak3—which are cytoplasmic tyrosine kinases that constitutively bind to the tails of cytokine receptor subunits—are activated to phosphorylate the IL-2R chains. Phosphotyrosine residues in these receptor chains provide docking sites for STAT proteins, which are phosphorylated by the Jaks. Once phosphorylated, the STAT proteins dimerize and translocate to the nucleus, where they activate target genes. This Jak/STAT mechanism is one of three known pathways through which IL-2 family members exert their intracellular effects (fig. 1). The activation of the proliferative and antiapoptotic PI3 kinase pathway and the well-characterized Ras pathway are not thought to be responsible for inherited immunodeficiencies and will not be discussed here, but they do play an important role in the control of IL-2 responses. In this review, we discuss the current understanding of these cytokine receptors and their signaling pathways, as well as the molecular basis of inherited severe combined immunodeficiencies (SCIDs) that arise from mutations in the genes for the common γc, the IL-2Rα, the IL-7Rα, and Jak3.

The IL-2R Complex

The discovery of an IL-2–binding, integral membrane protein (named "IL-2Rα") that exhibits low-affinity IL-2 binding (10 nM) but no signaling ability suggested the existence of a multisubunit IL-2–binding complex. Subsequently, two proteins that, in combination with the α-chain, constitute the fully functional, high-affinity (10 pM) IL-2R complex were identified (IL-2Rβ and IL-2Rγ). These proteins belong to the cytokine-receptor superfamily, which includes the receptors for many cytokines and interferons (Bazan 1990). Receptors of this superfamily share receptor subunits, which define specific subfamilies. For instance, receptors that contain the common β-chain (βc) bind IL-3, IL-5, or granulocyte macrophage–colony-stimulating factor, whereas the subfamily that contains gp130 includes the receptors for IL-6, oncostatin M, cardiotrophin, IL-11, and others (Bazan 1990). The IL-2R subfamily is defined by the presence of the IL-2Rγ, or γc (encoded by the *γc* gene), which is found in receptors for IL-4, IL-7, IL-9, and IL-15, as well as in IL-2R (Ihle et al. 1995). Members of each subfamily bind distinct multisubunit complexes that share many of their downstream signaling components and that, thus, have both pleiotropic and functionally redundant effects (O'Shea 1997).

Both IL-2Rβ and γc have four conserved cysteine residues, membrane-proximal WSXWS motifs in their extracellular domains, and cytoplasmic domains that couple the ligand-binding region of the receptors to intracellular effectors. Cytokine receptors, unlike receptor tyrosine kinases, lack intrinsic phosphotransferase activity, but their cytoplasmic domains contain a conserved membrane-proximal motif known as "box1/box2," which is critical for signal transduction from all known members of the family (fig. 1). The mechanism for signal transduction through cytokine receptors was first revealed by genetic complementation experiments using

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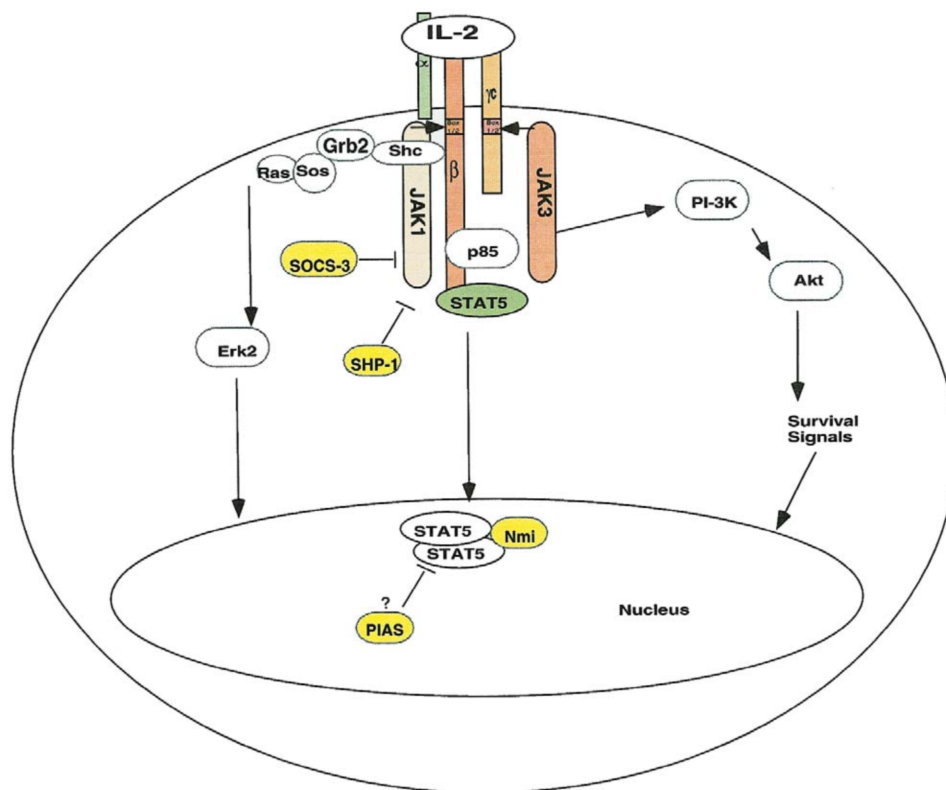

Figure 1 Signal transduction through the IL-2R complex. Binding of IL-2 to its high-affinity receptor induces the dimerization of IL-2Rβ and γc and activates at least three downstream signaling mechanisms. These mechanisms include a phosphorylation cascade that begins with the activation of Ras, a lipid kinase (PI-3K) pathway that is permissive for lymphocyte survival, and a third, cytokine-specific signal transduction pathway, the Jak/STAT pathway. Receptor ligation causes tyrosine phosphorylation and activation of Jak1 and Jak3 and triggers a series of biochemical events that drive gene transcription via STATs. Recently identified regulatory molecules are shown (*yellow*).

cells that lacked interferon responsiveness. These cells could be functionally complemented with the cDNA encoding members of the Jak family of kinases (Schindler and Darnell 1995). Signal transduction through all cytokine receptors depends on one or more Jak family members (fig. 1) (Ihle et al. 1995).

Four mammalian Jak family members that encode 120–135-kD proteins and that, as a family, exhibit a high degree of structural similarity, have been described. Outside of their catalytic domains, Jak proteins show little homology to other tyrosine kinases. Their catalytic domains (Janus homology domain 1, or JH1) are found at their C-termini, adjacent to a "kinase-like" domain, JH2, that has no detectable kinase activity but that probably performs a regulatory role (O'Shea 1997). The N-terminal half of the proteins (i.e., JH3–JH7) is unique to the Jak family and is thought to be important in receptor binding (Cacalano et al. 1999).

Three of the mammalian Jak family members—Jak1, Jak2, and Tyk2—are ubiquitously expressed, whereas Jak3 is expressed specifically in cells of the hematopoietic lineage and becomes tyrosine phosphorylated only in response to cytokines that use γc as a signaling component (O'Shea 1997). Jak1 and Jak3 physically associate with the IL-2Rβ chain and γc, respectively, and both are activated in response to IL-2, IL-4, IL-7, IL-9, and IL-15. Jak3 becomes tyrosine phosphorylated only in response to cytokines that use γc as a signaling component. The current dogma regarding signal transduction through these receptors is that oligomerization of the receptor components is required to initiate cross-phosphorylation and activation of Jak kinases, which lead to the activation of all downstream pathways.

X-Linked SCID

Formal genetic proof that the IL-2R components are critical for T-cell development came with the identification of patients lacking either γc or Jak3. These patients presented with phenotypically identical T^-/B^+/NK^- SCID (Noguchi et al. 1993; Macchi et al. 1995; Russell et al. 1995). A study of 108 patients with SCID later revealed that γc deficiency and Jak3 deficiency account for ~42% and ~6% of known

SCID cases, respectively (Buckley et al. 1997). Patients with Jak3 and γc deficiency have severe defects in T-cell development and lack peripheral T and NK cells. Affected infants are characterized by severe, persistent infections of the upper-respiratory and gastrointestinal tracts, which are caused by common viral (cytomegalovirus), fungal (*Candida*), and bacterial pathogens; such infants require allogeneic bone-marrow transplants in infancy to survive. These patients have normal to elevated levels of circulating B cells. However, the B cells are phenotypically immature and nonfunctional, presumably as a result of the lack of helper-T-cell activity, and the patients are usually hypo- or agammaglobulinemic. The presence of circulating B cells has made it possible to study signaling-pathway defects directly in Epstein-Barr virus–transformed B-cell lines derived from the patients.

Of $T^-/B^+/NK^-$ SCID cases, 60%–70% can be mapped to the Xq13 chromosomal region (Candotti et al. 1998). Among the criteria used to diagnose X-linked SCID (X-SCID) is nonrandom X-chromosome inactivation in lymphocytes from heterozygous female carriers of the disease. This criterion suggests that cells expressing the defective allele fail to develop normally, leading to a preferential expansion of cells that express the wild-type allele (Uribe and Weinberg 1998). When γc was also mapped to chromosome Xq13.1, it became an obvious candidate for X-SCID. This gene consists of eight exons and spans ~4.2 kb (Candotti et al. 1998).

Extensive genetic analysis of the molecular lesions in 135 unrelated patients with X-SCID provided some insight into the role of different regions of γc in signal transduction (Puck 1996). With the exception of two large deletions, the γc mutations are missense mutations involving one or a few nucleotides. Genetic analysis has revealed five mutational "hot spots" in exons encoding part of the extracellular domain, the transmembrane domain, and the membrane-proximal region of the γc cytoplasmic tail. Mutations in one hot spot near the highly conserved WSXWS residues of the extracellular domain are thought to interfere with proper folding and ligand binding (fig. 2). In addition, exon 6, which encodes the transmembrane domain, and exon 7, which encodes part of the cytoplasmic tail, also contain clusters of missense mutations that may disrupt surface expression or impair coupling to downstream signaling molecules (Puck 1996).

Three atypical cases of X-SCID, in which patients retain some peripheral T-cell function, have been described. In one case, a D17N mutation results in a fivefold decrease in high-affinity IL-2 cell-surface receptors, although it is unclear whether the mutation directly affects the surface expression or binding activity of the protein (DiSanto et al. 1994). The second case involves an L271Q mutation in γc box1, which impairs γc binding of Jak3, as demonstrated by immunoprecipitation experiments (Russell et al. 1994). This mutation most likely disrupts Jak3-dependent signaling through the receptor. Finally, Kumaki et al. (1999) recently described a case in which a splice-site mutation causes a 56-amino-acid substitution in the cytoplasmic tail and confers weak signaling in response to IL-2.

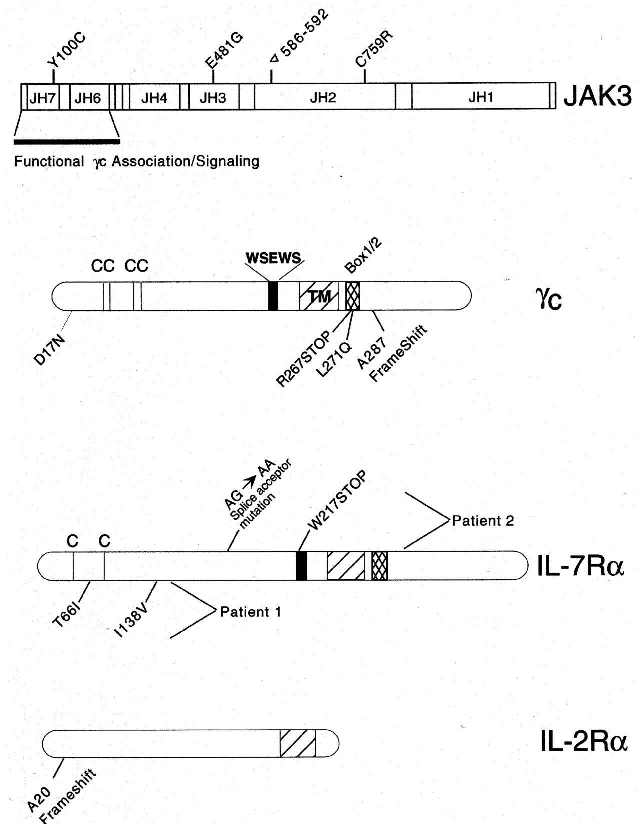

Figure 2 Schematic diagram of Jak3, γc, IL-7Rα, and IL-2Rα, with mutations that cause SCID. Jak3 mutations affect γc binding (Y100C), protein-expression levels, and basal or IL-2–inducible tyrosine phosphorylation. Mutations in γc also affect Jak3 binding and signal transduction (R267STOP, L271Q, and A287frameshift). The two patients with IL-7R defects lack significant mRNA and protein levels, and the IL-2Rα frameshift results in a nonfunctional protein.

Autosomal SCID

Jak3-deficient autosomal SCID is phenotypically identical to X-SCID, but it was identified by a "candidate gene" approach, after the discovery of the specific interaction between the γc and Jak3. The *Jak3* gene on chromosome 19p13.1 spans a region of ~15 kb and contains 22 exons in humans and 23 exons in mice (Candotti et al. 1998). Several families that include a female with SCID or a male with SCID, in whom γc mutations could be excluded, carry defects in *Jak3*, and transformed B-

cell lines derived from several of these individuals express little or no *Jak3* mRNA or protein (Macchi et al. 1995; Russell et al. 1995).

Several mutated alleles of *Jak3* have been isolated and characterized. Some nonsense or frameshift mutations result in premature chain termination and represent null alleles. Other, more subtle mutations still have profound effects on the function of the kinase (Candotti et al. 1997). Interestingly, Y100C, a missense mutation in *Jak3*, which prevents kinase-receptor interaction, resides in a short stretch of amino acids that are highly conserved in all members of the Jak family; this finding suggests an important function for this region in receptor interaction (Cacalano et al. 1999). The N-termini of Jak kinases bear homology to the erythrocyte structural-protein band 4.1. This domain has been found in a variety of protein kinases and phosphatases in addition to the ERMS (ezrin/radixin/moesin/schwannomin) proteins, which bind to the cytoskeleton and the plasma membrane. This portion of *Jak3* includes the entire JH7 and JH6 domains, which are critical for receptor binding (Cacalano et al. 1999). Therefore, the band-4.1 domain may provide a general mechanism for targeting a functionally diverse group of proteins or signaling molecules to transmembrane receptors (Girault et al. 1999). Disease alleles of *Jak3* may reduce the level of protein expression, disrupt kinase activity, or alter basal or IL-2–inducible tyrosine-phosphorylation levels. Two mutations in the JH2 domain (6-amino-acid deletion at position 586–592) and one JH3 point mutation (E481G) markedly decreased the basal and IL-2–inducible tyrosine phosphorylation, suggesting that kinase regulation may be mediated by several domains of Jak3. In contrast, a single point mutation, C759R, in the JH2 domain results in high, constitutive Jak3 phosphorylation in the absence of IL-2. However, in spite of its constitutive phosphorylation, this molecule fails to signal in response to IL-2 (Candotti et al. 1998).

In addition to the γc/Jak3 signal-transduction pathway, lymphoid development has been studied in humans and mice with defects in individual cytokine pathways. Several other forms of SCID have been identified, although their molecular lesions have not been characterized. Recently, two patients with autosomal recessive SCID of unknown etiology were reported; the patients lack T cells but retain both B and NK cells (von Freeden-Jeffry et al. 1995). The presence of NK cells in these patients indicated a defect distinct from γc or Jak3 deficiency. Guided by the phenotype of mice with a deficiency of IL-7 and/or IL-7R, Puel et al. (1998) identified multiple defects in the *IL-7R*α gene, as well as in very low IL-7Rα mRNA and protein expression in these individuals (fig. 2). Curiously, deficiency in IL-7R had a very specific effect on T-cell development, although it is dispensable in the development of NK cells. Thus, the defects in T-cell development seen in γc- and Jak3-deficient SCID are primarily due to loss of signaling through the IL-7R. NK-cell survival, on the other hand, depends on signaling through the IL-15R, a heterotrimeric complex that contains both γc and IL-2Rβ, as well as a ligand-specific binding chain. Survival signals through the IL-7R result in the activation of the antiapoptotic effects of bcl-2. Consistent with this idea, enforced expression of bcl-2 can rescue T-cell development in mice deficient for both IL-7 and γc, but it cannot rescue NK-cell development, thereby demonstrating the requirement for distinct signaling pathways in the development of different lymphocyte lineages (von Freeden-Jeffry et al. 1997).

Mice with a targeted disruption of the *Jak3* or γc gene have SCID, but crucial differences between their phenotypes and those seen in humans with SCID result from the different roles played by IL-7 in the species. Both $Jak3^{-/-}$ and $\gamma c^{-/-}$ exhibit marked reductions in thymus cellularity, but in contrast to the corresponding diseases in humans, the remaining thymic T cells in mice develop normally. Significant numbers of $CD4^{+}$ cells accumulate in the periphery of these animals as they age, perhaps because of a murine-specific thymus-derived growth factor that serves as an alternative ligand for the IL-7R. That thymic stromal lymphopoietin (TSLP) is a growth factor for T cells and can activate STAT5 in the absence of Jak1 or Jak3 activation suggests that it can sustain some T-cell development via a γc/Jak3-independent pathway. Furthermore, unlike humans with γc- and *Jak3*-linked SCID, these gene-targeted mice have defective B-cell development. B-cell development in these animals arrests between the pro–B- and pre–B-cell stages, indicating that IL-7 is a key factor in B-cell development in mice but not in humans. These mice also lack NK cells, intraepithelial $\gamma\delta$T cells, dendritic epidermal T cells, and peripheral lymph nodes, and they have a marked reduction in the size of their mesenteric lymph nodes as well. Interestingly, the surviving T cells in these mice, like those in the IL-2Rα and IL-2Rβ gene-targeted mice, have an activated phenotype, yet they fail to proliferate in response to concanavalin A or anti-CD3, and they produce very little IL-2 in response to mitogenic stimuli.

Genetic Analysis of the IL-2R

The role of both IL-2 and the IL-2–signaling pathway in lymphocyte function has been studied, by phenotypic analysis, both in gene-targeted mice that lack one of the components of the IL-2R and in humans with naturally occurring mutations in the IL-2R genes. Analysis of IL-2R mutations has revealed that the receptor components have a number of roles in lymphocyte function: in development, in proliferation, and in the control of sur-

vival, which can lead to down-regulation of the immune response.

Targeting the genes encoding IL-2, IL-2Rα, and IL-2Rβ has shown that IL-2 signaling is not essential for either B- or T-cell development, since each mutant strain develops normally for the first 3–4 wk of life. Thymi of the young mice contain the normal ratio of $CD4^+$ cells to $CD8^+$ cells, with normal cellularity. However, these mice develop very similar immune disorders, characterized by markedly elevated serum immunoglobulin levels and an often fatal hemolytic anemia. Surviving mice develop severe inflammatory bowel disease, splenomegaly, and lymphadenopathy. Lymph-node T cells from these mice exhibit a morphology and surface-marker–expression profile that are characteristic of activated/memory T cells. In spite of their activated phenotypes, lymph-node T cells from IL-2Rβ knockout mice do not respond to such polyclonal activators as PMA+, ionomycin, or concanavalin A.

The proliferative defect in IL-2R$\alpha^{-/-}$ mice is less severe, probably because of the presence of signaling-competent, cell-surface IL-2R$\beta\gamma$ heterodimers, but proliferation is decreased in these mice as well. T cells from IL-2Rβ knockout mice cannot mount normal antibody titers to challenge with vesicular stomatitis virus (VSV), nor do they generate normal cytotoxic responses to VSV-infected macrophages. The activated T-cell phenotype and inflammatory disease are thought to be due primarily to failure to trigger apoptosis in the activated cells, by maintenance of high levels of bcl-2 expression (O'Shea 1997). T cells apparently fail to delete after activation, resulting in exhaustive B-cell activation, hypergammaglobulinemia, and massive lymphocytic and granulocytic infiltration of such organs as the colon. In support of this idea is the finding that, in mice lacking the IL-2Rα chain, there is a striking lack of T-cell deletion in response to bacterial superantigens (O'Shea 1997).

In addition to the mouse models for IL-2 signaling deficiencies, a naturally occurring mutation in the *IL2RA* gene in humans has been identified. Its phenotype is similar to that of mice with a deficiency of IL-2Rα and is characterized by increased susceptibility to bacterial, viral, and fungal infections; massive lymphocytic infiltration of many organs; and severe colitis. In addition, bcl-2 expression in thymocytes was markedly enhanced in the IL-2Rα patient compared with normal controls, thereby supporting a model of defective apoptosis in activated T cells (Sharfe et al. 1997). This finding seems paradoxical, since it is known that IL-2 stimulation increases cellular levels of bcl-2. However, signaling through the IL-2R can induce molecules that inhibit cytokine responses and, perhaps, the inability to induce either inhibitors or apoptosis in the gene-targeted mice results in the severe autoimmune phenotypes. Clearly, the IL-2R affects the physiology of the immune response on many levels, acting as a regulator of the delicate balance between lymphocyte activation and deletion.

Interestingly, *IL-4Rα* mutations may predispose patients to an allergic disease known as "atopy." This disorder is characterized by an immediate hypersensitivity IgE-antibody response to specific allergens (hyper-IgE syndrome) and allergic inflammatory skin disease, a condition very similar to the phenotype of IL-4 transgenic mice. However, patients who have atopy have normal levels of IL-4, which suggests the presence of mutations of the IL-4R.

One patient with atopy was found to carry a G→A transition at nucleotide 1902 of *IL-4Rα*, which caused a Q576R substitution in the cytoplasmic domain of the IL-4Rα. This mutation results in enhanced signaling, possibly because the variant IL-4Rα chain fails to recruit SHP-1 (see the section on Recent and Forthcoming Discoveries in Cytokine Signal Transduction, below) efficiently (Hershey et al. 1997). The R576 allele was common among patients with allergic inflammatory disorders, and it segregated strongly in patients with atopy. The R576 allele was found in three of three patients with the hyper-IgE syndrome and in four of seven patients with severe atopic dermatitis. The mutation was also found in 13 of 20 subjects with elevated serum IgE levels, but it was seen in only 5 of 30 normal, asymptomatic individuals from a pool of 50 randomly chosen, unrelated adults. The overall allelic frequency of the Q576R mutation in the population of chromosomes was calculated to be 20%: 35% in patients with atopy and 10% in normal, asymptomatic subjects. The prevalence of this mutation suggests that it may contribute significantly to the high incidence of atopy, which affects $\leq$40% of the population.

Cytokine Signals and Transcriptional Regulation

Detailed functional and biochemical dissection shows that IL-2Rβ has six tyrosine residues that are phosphorylated on IL-2 stimulation. Y338 has been shown to stimulate proliferative signals via the MAP kinase pathway (fig. 1) (Friedmann et al. 1996), whereas Y392 and Y510 serve as docking sites for STAT5 proteins. These tyrosine residues are thought to be responsible for activation of the individual signaling pathways that are briefly outlined below.

Specificity of STAT-receptor interaction is determined by the sequence of the tyrosine-containing motif on the receptor (Hoey and Grusby 1999). STAT5a and STAT5b are recruited to the phosphorylated residues Y392 and Y510 of IL-2Rβ via their conserved SH2 domains. After Jak-mediated phosphorylation of the C-terminal STAT

tyrosine residues, the two STAT proteins interact reciprocally, by SH2-phosphotyrosine, to form a dimer that releases from the signaling complex and that translocates to the nucleus. There, the dimer binds specific, conserved promoter sequences that are collectively known as "GAS" (interferon-gamma–activated sequences).

Mice deficient for both STAT5a and STAT5b exhibit a profound defect in proliferation of peripheral T cells, although T-cell development proceeds normally (Teglund et al. 1998). In addition, *STAT5b*$^{-/-}$, but not *STAT5a*$^{-/-}$, knockout mice lack NK cells, a finding that is consistent with evidence that IL-15–induced STAT5b activation is required in NK-cell development (Teglund et al. 1998). The nonequivalence of STAT5a and STAT5b is surprising because these two proteins, which are encoded on closely linked genes on human chromosome 7q11.2, are 95% identical. Nonetheless, individual *STAT* gene knockouts have quite distinct effects on the immune system. Because of multiple defects that occur during development, *STAT3* gene disruption is embryonic lethal in mice; however, by use of the *cre-lox* system with expression of *cre* under the control of a T-cell–specific promoter, a conditional *STAT3* knockout has been generated, which lacks *STAT3* expression only in T cells. These animals show some loss of anti-CD3 and IL-2–induced proliferation, at least partially as a result of a defect in IL-2Rα–chain expression. This phenotype, which is also seen in *STAT5a*$^{-/-}$ mutants, can be overcome by treating the cells with high concentrations of IL-2, which suggests there is some functional overlap between STAT3 and STAT5a in IL-2–induced proliferation.

Recent and Forthcoming Discoveries in Cytokine Signal Transduction

Recent work has suggested that a number of proteins may be involved in the control of STAT-mediated transcriptional activation (fig. 1). A 45-kD Myc-binding protein, Nmi, can associate with STAT5 and may play a role in modulating many cytokine and interferon responses, including IL-2 (Zhu et al. 1999). Another family of proteins, PIAS (protein inhibitor of activated STAT), interacts with and specifically inhibits the DNA binding activity of STAT molecules. PIAS3 associates with STAT3 in response to IL-6, ciliary neurotrophic factor, and oncostatin M, and the interactions appear to be specific, since PIAS1 is not coprecipitated with STAT2 or STAT3 and since PIAS3 does not associate with STAT1 (Chung et al. 1997). The exact mechanism by which these proteins affect STATs requires further study.

Recently, the protein tyrosine phosphatase SHP-1 has been reported to be recruited to the IL-2R in a ligand-dependent manner. SHP-1 can dephosphorylate both Jak1 and IL-2Rβ, and its expression in IL-2–responsive cells markedly reduces the steady-state phosphorylation levels of both Jak1 and Jak3. Moreover, constitutive activation of the IL-2 signaling pathway has been observed in human T-cell leukemia virus-1–transformed T cells and in Sezary syndrome (O'Shea 1997), with an associated loss of SHP-1 expression (Migone et al. 1998). This is interesting, because peripheral T cells from SHP-1–deficient, "moth-eaten" mice exhibit enhanced proliferation to mitogens and IL-2, which further suggests that SHP-1 has an important role in the control of proliferation.

Another family of cytokine-induced inhibitory proteins, reported by several groups, includes variously named suppressors of cytokine signaling (SOCS), cytokine-induced SH2 proteins (CIS), or STAT-induced STAT inhibitors (SSI). SOCS-1 was cloned because of its ability to inhibit IL-6–mediated differentiation of a myeloid cell line, M1 (Endo et al. 1997; Starr et al. 1997). The mechanism of cytokine inhibition by SOCS family members is an area of intense investigation. CIS can inhibit IL-3 and erythropoietin responses by competing for a receptor phosphotyrosine residue that serves as a STAT docking site, which suggests that CIS is a direct competitive inhibitor of STAT activation. On the other hand, SOCS-1 and SOCS-3 inhibit cytokine responses by binding to that catalytic domain and inhibiting Jak activity. SOCS-3 expression is rapidly induced in lymphocytes in response to IL-2 (as are SOCS-1 and CIS) and has been shown to specifically inhibit IL-2–mediated STAT activation. Because these proteins may be important in the progression of T-cell–mediated inflammatory disease, they will no doubt be subject to intense investigation.

Despite these recent advances, our understanding of cytokine signaling remains sketchy in several respects. In particular, the pathways that control T-cell expansion and apoptosis are not understood in detail. The identification of novel families of proteins—such as SOCS, Nmi, and PIAS—that are induced by IL-2, points to an unexpected degree of complexity in downstream regulation of cytokine responses. The study of these proteins may shed some light on cross-talk that integrates the various signaling mechanisms within the cytoplasm, and it should help to pinpoint biochemical imbalances that manifest as autoimmune disorders or chronic inflammatory diseases.

Finally, the current understanding of cytokine signaling has identified targets for therapeutic intervention. For example, inhibitors of the Jak/STAT pathway may be valuable in the treatment of allergic disease, in transplantation therapy, and in the treatment of lymphomas in which constitutive Jak/STAT activity has been observed. Also, the identification of the genetic defects in several forms of SCID raises the possibility of therapeutic intervention with a gene-therapy approach. Studies in

mice have proved that retroviral-mediated transduction of the wild-type genes for γc and Jak3 rescues lymphocyte development and immune function in mice that are deficient for γc- and Jak3. Perhaps this approach will be feasible for human immunodeficiencies.

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