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Cytokine Signaling Through Nonreceptor Protein Tyrosine Kinases

Tadatsugu Taniguchi

Cytokines are a family of soluble mediators of cell-to-cell communication that includes interleukins, interferons, and colony-stimulating factors. The characteristic features of cytokines lie in their functional redundancy and pleiotropy. Most of the cytokine receptors that constitute distinct superfamilies do not possess intrinsic protein tyrosine kinase (PTK) domains, yet receptor stimulation usually invokes rapid tyrosine phosphorylation of intracellular proteins, including the receptors themselves. It is now clear that these receptors are capable of recruiting or activating (or both) a variety of nonreceptor PTKs to induce downstream signaling pathways. Thus, the intracytoplasmic structure of cytokine receptors has evolved so as to allow the combined action of different PTK family members expressed in different cell types, which may ultimately determine the activity of cytokines.

Cell-to-cell communication is an essential aspect of many biological systems. Cytokines are a broad group of (mostly) soluble factors that mediate this communication and that have been extensively studied in the context of natural and acquired immunity, hematopoiesis, and inflammation (*1*). In addition, it is now widely appreciated that many cytokines act more broadly in many biological systems, including those regulating neural and embryonic development (*2*). Rapid progress has been made in the molecular characterization of cytokines and their receptors during the past 15 years, and the availability of recombinant cytokines has made it possible to study the function of each in its pure form. These studies have revealed two remarkable features of cytokines: their functional redundancy and extensive pleiotropy (*1*, *3*). In fact, a given biological function is often mediated by more than one cytokine, and each cytokine can display multiple functions. Typically, lymphocyte proliferation can be induced by a variety of interleukins in vitro, including interleukin-2 (IL-2), IL-4, IL-5, IL-6, IL-7, and IL-15 (*4*–*7*). Yet these interleukins can also induce distinct cellular responses such as lymphocyte differentiation and immunoglobulin class switching (*1*, *8*). Such diverse responses are mediated by a complex signaling system in which protein phosphorylation by nonreceptor PTKs appears to be critical. Here I summarize our current knowledge of the participation of such PTKs in cytokine signaling, primarily focusing on the IL-2–IL-2 receptor (IL-2R) system. Although the IL-2R has an unusual variety of intracellular signaling partners, all evidence suggests that a similarly heterogeneous array of signal transduction pathways can be invoked by other cytokine receptors.

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Structural and Functional Properties of Cytokine Receptors

Most of the cytokine receptors are type I membrane glycoproteins containing a single transmembrane domain and oriented with their NH_2-termini exterior to the plasma membrane. Cytokine receptors can be further divided into four subtypes, based on characteristic structural motifs found in their extracellular ligand binding domains (Fig. 1A). Regarding intracellular signal transduction, three important features of these receptors stand out. First, the COOH-terminal regions of these receptor molecules form cytoplasmic tails consisting of tens to hundreds of amino acids, yet they possess no motifs indicative of any known catalytic activity such as the PTK motifs that are the hallmark of many other growth factor receptors (*9*). Instead, two conserved motifs are found within the membrane-proximal regions of some receptors (referred to as box 1 and box 2 in Fig. 1A) (*6*, *10*). Second, many cytokine receptors consist of more than two subunits, although a few function as monomers. Third, one receptor subunit is often shared among different cytokine receptor complexes. For example, IL-2R consists of three subunits: the α, β, and γ chains (*11*), formally known as IL-2Rα, IL-2Rβc, and IL-2Rγc, respectively (Fig. 2). The small c denotes that these subunits are common to other cytokine receptors; IL-2Rβc is a subunit of IL-15R, whereas IL-2Rγc is a subunit of IL-4R, IL-7R, and IL-9R (*7*, *12*). Similarly, IL-3R shares its IL-3Rβc subunit with IL-5R and the granulocyte-macrophage colony-stimulating factor receptor (GM-CSFR), whereas the IL-6Rβc (gp130) subunit of IL-6R is also used by the leukemia inhibitory factor receptor (LIFR), the oncostatin M receptor (OSMR), and others (*3*). Thus, one envisages that the functional redundancy of certain cytokines may be partly explained by

this use of common receptor subunits.

Although the cytoplasmic regions of the type I cytokine receptors lack any intrinsic PTK domain, ligand engagement of these receptors typically results in the transmission of proliferative signals to the cell interior. For example, the murine IL-3–dependent pro–B cell line BAF-B03, which expresses endogenous IL-2Rα and IL-2Rγc but not IL-2Rβc, becomes responsive to the proliferative effects of IL-2 upon introduction and expression of human IL-2Rβc complementary DNA (cDNA). Systematic dissection of the IL-2Rβc by means of mutant cDNAs revealed that a membrane-proximal cytoplasmic region, termed the serine-rich region (S-region), is critical for this IL-2 proliferative response (*5*) (Fig. 2). The S-region includes the box 1 motif found in other receptors and is essential for proliferative signal transmission (*3*, *13*). The cytoplasmic region of the IL-2Rγc chain is also required for IL-2, IL-4, and IL-7 signaling although it lacks such a motif (*14*). Typically, receptor heteromerization (for example, IL-2R, IL-3R, or IL-5R) or homodimerization [for example, erythropoietin receptor (EpoR), IL-6Rβ, or granulocyte colony-stimulating factor receptor (G-CSFR)] results in triggering downstream signaling events (*14*, *15*). The G-CSFR contains, in addition to the box 1 motif, a membrane-distal region that delivers other signals required for cell differentiation (*16*). Thus, different cytoplasmic regions of this and other receptors appear to play distinct roles in mediating the diverse actions of cytokines, presumably by their recruitment of ancillary molecules necessary for signal transmission (see below).

Physical and Functional Interactions of Nonreceptor PTKs with Cytokine Receptors

The Src-family PTKs. Initially, the involvement of nonreceptor PTKs in cytokine signaling was shown for the Src-family PTK $p56^{lck}$ (Lck) (Fig. 1B). Lck is physically associated with the IL-2Rβc chain in the absence of IL-2 stimulation (*17*), and it is rapidly activated upon ligand binding to IL-2R (*17*, *18*). This intermolecular association occurs between the NH_2-terminal region of the kinase domain of Lck and a cytoplasmic region of the IL-2Rβc chain, termed the acidic region (A-region) (Fig. 2) and is critical for ligand-induced PTK activation (*17*, *19*). The mechanism of IL-2–induced Lck PTK activation is not clear at present; however, by analogy to its involvement with CD4 and CD8, it is possible that ligand binding causes IL-2R oligomerization or clustering and that this in turn allows associated Lck molecules to transphosphorylate each other, activating their intrinsic PTKs (*20*). Alternatively, Lck may be activated by other IL-2R–associated PTKs or by phosphatases (see below). In different cell types, IL-2Rβc can interact with and activate different Src family members (*21*, *22*) (Table 1). These observations have been followed by the discovery of physical and functional interaction of various Src-family PTKs with other cytokine receptors (*23*–*26*) (Table 1).

In the IL-2R system, Lck, Fyn, and Lyn are activated through their interaction with the A-region of IL-2Rβ (*19*, *21*, *22*). The A-region is also required, along with the S-region, for IL-2–mediated activation of Lck, and this activation is followed by the induction of the c-*fos* and c-*jun* genes, which suggests a role for Src-family PTKs in the induction of these proto-oncogenes (*19*, *27*, *28*) (Fig. 2). Lck phosphorylates the IL-2Rβ chain at either or both of two tyrosines (Tyr^{355} and Tyr^{358}) within the A-region (*17*) (Fig. 2), and phosphorylation of these residues may recruit other signaling molecules such as phosphatidylinositol-3 kinase (PI3 kinase) (*29*). IL-2 also induces the tyrosine phosphorylation and IL-2Rβ association of the adaptor Shc, which has been shown to act upstream of Ras (*30*). Cytokine-induced receptor binding of Shc

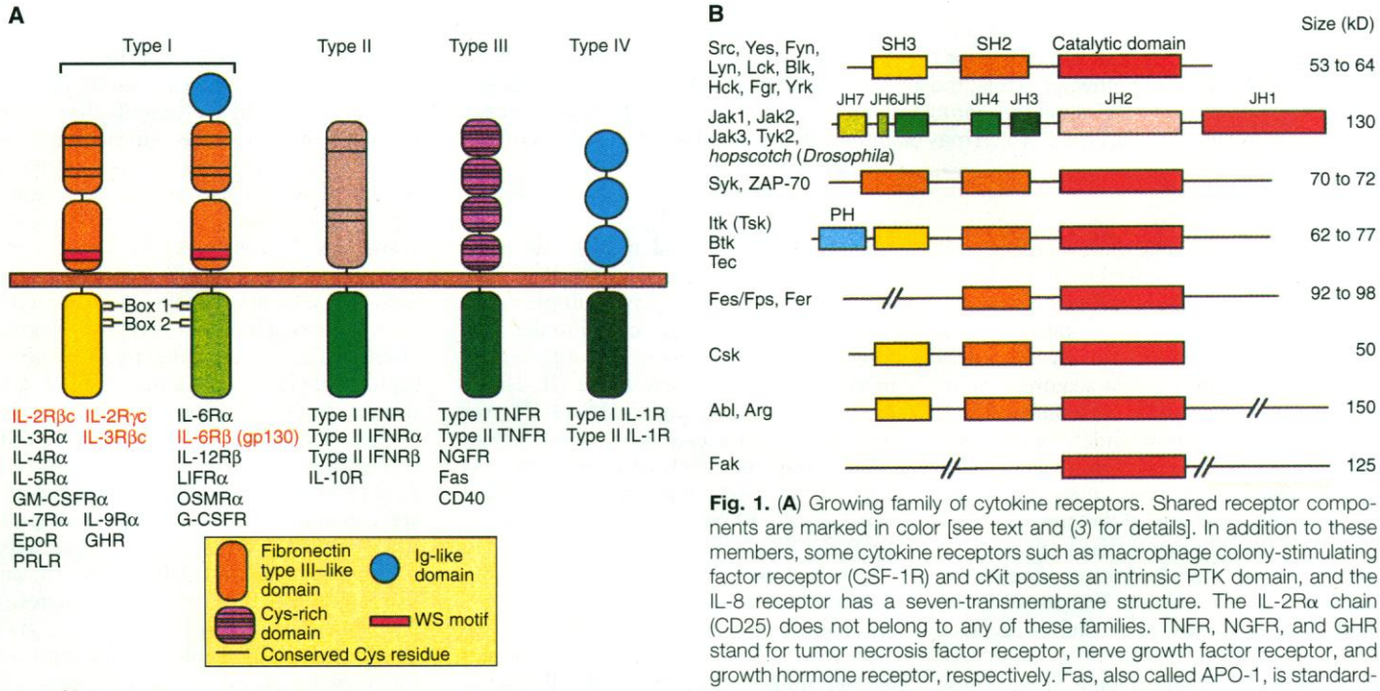

Fig. 1. (**A**) Growing family of cytokine receptors. Shared receptor components are marked in color [see text and (*3*) for details]. In addition to these members, some cytokine receptors such as macrophage colony-stimulating factor receptor (CSF-1R) and cKit posess an intrinsic PTK domain, and the IL-8 receptor has a seven-transmembrane structure. The IL-2Rα chain (CD25) does not belong to any of these families. TNFR, NGFR, and GHR stand for tumor necrosis factor receptor, nerve growth factor receptor, and growth hormone receptor, respectively. Fas, also called APO-1, is standardized as CD95. "Ig-like domain" denotes an immunoglobulin-like domain, and "WS motif" denotes a conserved WSXWS sequence (W, tryptophan; S, serine; X, nonconserved amino acid). (**B**) Diagrammatic structures of nonreceptor-type PTK members. The following abbreviations are used: SH, Src homology domain; JH, Jak homology region (JH1 constitutes a PTK domain); and PH, pleckstrin homology domain. SH2 and SH3 domains recognize short peptide motifs bearing phosphotyrosine and one or more proline residues, respectively. Both SH2 and SH3 domains mediate complex protein-protein interactions that can regulate many important signaling processes (*79*). JH1 and JH2 domains constitute a PTK and a PTK-like domain, respectively. PH domains have been found in a wide range of signaling molecules, yet their binding properties are less well understood. It has been reported that PH domains might associate with phospholipids or bind specific proteins and thereby facilitate the association of signaling proteins with membranes (*79*).

has also been reported for IL-3R and EpoR (*13*). Activation of cHa-Ras by IL-2 has been shown to require the A-region of the IL-2Rβc chain (*31*), although binding of Shc to this region has not been shown. The importance of Lck activation in mediating the IL-2–induced stimulation of PI3 kinase or cHa-Ras remains unclear.

BAF cells expressing the mutant IL-2Rβ lacking the A-region still respond to IL-2, albeit more weakly than those expressing the wild-type molecule (*28*). In primary T cells, deletion of the A-region affects the mitogenic function of the IL-2β cytoplasmic domain more severely (*32*). Evidence has now been provided showing that a constitutively active form of Lck can provide a mitogenic signal that cooperates with other proto-oncogene products, such as c-Myc or Bcl-2, to drive the BAF cell cycle in the absence of IL-2 or IL-3 (*33*). These observations suggest, but do not prove, a role for Lck in mitogenic signaling by IL-2.

Whether the redundancy of the Src-family PTKs engaged with IL-2R and other cytokine receptors has any physiological meaning in terms of the functional pleiotropism of cytokines is not clear at present; however, it may be worth pointing out that IL-2 increases the cytotoxic activity of $CD8^+$ T cells and natural killer cells, which predominantly express *lck*, whereas it induces immunoglobulin production in B cells, which express *lyn* (*8*, *34*). Evidence supporting a role for Lck in IL-2–induced cytotoxicity has been recently presented (*35*).

The Jak-family PTKs. Much attention has been focused on another PTK family involved in cytokine signaling: the Janus kinase (Jak) family (Fig. 1B). Both type I and type II cytokine receptors can activate one or more of the members of this PTK family (Table 1) (*13*). Evidence for the involvement of the Jak-family PTKs in cytokine signaling was first provided by genetic complementation experiments, in which a mutant cell line defective in the type I interferon (IFN) (IFN-α and -β) signaling pathway was rescued by transfection with a genomic DNA encoding Tyk2 (*36*). Similar genetic studies on the type I and type II IFN (IFN-γ) systems provided further compelling evidence for the involvement of Jak1 and Tyk2 in the former, and Jak1 and Jak2 in the latter, signaling processes (*37*). The critical role of the Jak-family PTKs has also been shown in the case of the growth-promoting, type I cytokine receptors (*13*) (Table 1). Each receptor selectively associates with distinct Jak members. Some receptors, such as EpoR, bind only one Jak-family member (*38*), whereas IL-6Rβ (gp130) is capable of recruiting three different members (*39*). In the case of IL-2R, the IL-2Rβc chain and IL-2Rγc chain selectively recruit Jak1 and Jak3, respectively (*40*). These interactions require the S-region of IL-2Rβc and the COOH-terminal 48–amino acid residues of IL-2Rγc, respectively, and both regions are indeed critical for Jak PTK activation and proliferative signal transmission (*40*, *41*) (Fig. 2). Jak3 mutants lacking the JH3-JH7 region, but not the JH1 PTK domain, do not interact with IL-2Rγc (*42*).

The mechanism of Jak PTK activation. How do these Jak-family PTKs become activated? It is likely that ligand-induced receptor dimerization or oligomerization brings about the local aggregation of these molecules, resulting in the activation of PTKs by cross-phosphorylation, a mechanism analogous to the well-established system of cross-activation of growth factor receptor PTKs resulting from ligand-induced receptor dimerization (*9*, *13*). Although use of Jak PTK family members by cytokine receptors may seem random prima facie, Jak1 and Jak3 (and perhaps Tyk2) always bind in combination with other members of the same family, whereas Jak2 often binds to receptors alone, particularly in the case of the monomeric receptors [such as EpoR and prolactin receptor (PRLR)] (Table 1). Hence, Jak2 molecules may be capable of

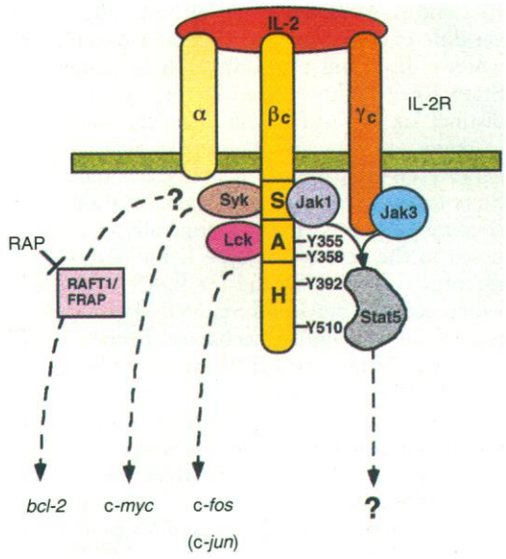

Fig. 2. Schematic illustration of multiple PTKs, downstream effector molecules, and target genes involved in IL-2 signaling. The tyrosine residues 355 (Y355) and 358 appear to be phosphorylated by Lck, whereas the residues 392 and 510 may recruit Stat5 upon phosphorylation by Jaks. Two other tyrosines of IL-2Rβ and four tyrosines of IL-2Rγ within their cytoplasmic regions are not indicated. This figure does not include other signaling and target molecules that have also been reported to function in the IL-2R system: Raf-1 kinase, mitogen-activated protein (MAP) kinase, p70 S6 kinase, $p34^{cdk2}$ and $p34^{cdc2}$, $p27^{Kip1}$, phosphatidylinositol-3 kinase (PI3 kinase), Shc, and glycosylphosphatidylinositol (GPI) (*8*, *11*). RAP denotes the drug Rapamycin, which is known to bind RAFT1-FRAP, a protein showing structural homology to lipid kinases (*31*). The interaction of these molecules with the PTKs remains unclear.

Table 1. Activation of nonreceptor-type PTKs and Stat proteins through cytokine receptors. The nonreceptor type PTKs that have been shown to associate with the respective type I or type II cytokine receptors (either constitutively or after cytokine stimulation) are indicated in bold. Molecules in parenthesis may be involved in signaling, but their PTK activation has not been confirmed. In mice, two highly related genes encoding Stat5 isoforms have been identified (*78*). Italic numbers in parentheses after names are reference numbers. NR, not reported.

Type I and type II cytokine receptors	Activated nonreceptor-type PTKs		Jak-activated Stat proteins
	General	Jak family	
IL-2R	**Lck** (*17*), **Fyn** (*22*), Lyn (*21*, *22*), **Syk** (*54*)	**Jak1** (*40*, *41*), **Jak3** (*40*, *41*)	Stat3 (*72*), Stat5 (*51*, *52*, *73*)
IL-3R	Lyn (*23*), (Fes) (*60*), Tec (*61*)	**Jak1** (*65*), **Jak2** (*65*)	Stat5 (*51*), Stat6 (*74*)
IL-4R		Jak1 (*41*), Jak3 (*41*)	Stat6 (IL-4 Stat) (*49*)
IL-5R	Btk (*62*), (Fyn) (*58*)	Jak1 (?) (*62*), **Jak2** (*62*)	NR
IL-6Rβ (gp130)	**Hck** (*26*), **Btk** (*63*), **Tec** (*63*)	**Jak1** (*39*), **Jak2** (*39*), **Tyk2** (*39*)	Stat1 (*75*), Stat3 (APRF) (*75*)
IL-7R	**Fyn** (*24*)	Jak1 (*66*), Jak3 (*66*)	NR
IL-12Rβ		Jak2 (*67*), Tyk2 (*67*)	Stat4 (*67*)
GM-CSFR	**Fes** (*60*)	Jak1 (?) (*68*), **Jak2** (*68*)	NR
G-CSFR	**Lyn** (*25*), **Syk** (*25*)	**Jak1** (*69*), **Jak2** (*70*)	Stat3 (*76*)
PRLR		**Jak2** (*71*)	Stat5 (MGF) (*77*)
EpoR	**Fes** (*64*)	**Jak2** (*38*)	NR
IFNα/βR		Jak1 (*37*), Tyk2 (*36*)	Stat1 (*50*), Stat2 (*50*), Stat3 (*47*)
IFNγR		Jak1 (*37*), Jak2 (*37*)	Stat1 (*48*)

cross-activating each other when they are brought into proximity by ligand-induced receptor dimerization, whereas other members may require a partner of the same family for optimal cross-activation to occur. In the NIH 3T3 fibroblast line 3T3αβγ, in which IL-2R has been reconstituted by cDNA expression and which expresses endogenous Jak1, Jak2, and Tyk2 but not Jak3, IL-2–induced activation of Jak1 is weak but is dramatically augmented upon ectopic expression of the Jak3 cDNA (*43*). Consistently, the combined overexpression of Jak1 and Jak3 in BAF-B03 cells, but of neither alone, results in the constitutive activation of these PTKs (*44*). Regarding the functional pleiotropism of cytokines, it may be particularly significant that in the IL-6Rβ (gp130)–LIFRβ system, where distinct receptors use the same receptor components, a particular cytokine can induce distinct phosphorylation patterns of the Jak-family PTKs in different cell lines (*39*).

Functional role of Jak PTKs. Several lines of evidence indicate that these Jak-family members also play critical roles in type I receptor signaling. The Jak recruitment sites of many type I receptors correspond to the box 1–containing regions required for proliferative signal transmission (*13*). In NIH 3T3–derived 3T3αβγ cells expressing the reconstituted IL-2R (and endogenous Jak1), IL-2–induced cell cycle progression to the S phase of DNA replication was achieved by the additional ectopic expression of Jak3 (*40*). When a mutant form of Jak3 that lacks the JH1 PTK domain but can still associate with IL-2Rγc was overexpressed in the BAF-B03–derived F7 cell line expressing reconstituted IL-2R, the IL-2 response but not the IL-3 response was strongly inhibited (*42*). Similarly, overexpression of a PTK-deficient form of Jak2 resulted in the inhibition of the Epo response (*45*). IL-6 responses are impaired in a cell line lacking Jak1 (*46*). However, the mechanisms by which these PTK members function to mediate cytokine-induced cellular responses are not fully understood. As described below, the best characterized molecular event following the stimulation of Jak PTKs thus far is the activation of a family of latent transcription factors, termed Stat proteins (signal transducers and activators of transcription) (*47*). In addition, tyrosine phosphorylation (direct or indirect) of cytokine receptors by Jak PTKs may create docking sites for SH2-containing signaling molecules, which include Shc, the 85 subunit of PI3 kinase, Vav, IRS-1, 4PS, PTP1C, and Syp (*13*).

Activation of Stat proteins. The Stat proteins usually reside in the cytoplasm and become activated when phosphorylated on specific tyrosine residues, presumably as a direct result of Jak PTK action. These phosphorylated Stats then form homo- or heterodimers, in which the phosphorylated tyrosine residue of each Stat interacts with the SH2 domain of its partner and they migrate to the nucleus, thereafter functioning as transcription factors (*13, 47*). The SH2 domain appears to play a critical role in the recruitment of a given Stat factor to each receptor upon receptor tyrosine phosphorylation, an early event required for the selective activation of Stats by cytokines (see below).

Different Stats become activated by different receptors (Table 1). This differential activation does not result from the use of different Jak PTKs by individual receptors: IL-2 and IL-4 activate both Jak1 and Jak3, yet different Stats are activated as a result; whereas IL-2 and prolactin both activate Stat5 (or a highly related factor) yet use distinct Jak PTKs (Table 1). It appears that in many cases the specificity of activation depends on the particular coupling of latent Stats to the intracellular domains of their cognate receptors, as was originally proposed in the case of the type II interferon receptor (IFNR) (*48*) and for IL-4R (*49*), which activate Stat1 and Stat6 (IL-4 Stat), respectively. A similar mechanism operates in the case of the type I IFNR which, unlike type II IFNR, activates Stat2; and this event is critical for subsequent heterodimerization with, and activation of, Stat1 (*50*).

In the case of IL-2R, two tyrosine residues within the IL-2Rβ chain, Tyr^{392} and Tyr^{510}, may be primarily required for Stat5 activation because receptor-derived peptide fragments harboring either of these tyrosines inhibit Stat5 activation (*51*). Consistently, in the BAF-derived cell line H-4, which expresses a mutant IL-2Rβ lacking the H-region (H-mutant) (Fig. 2) (*5*), the Jak1 and Jak3 PTKs are both activated by IL-2; however, Stat5 activation is almost completely abrogated (*52*). Although not clearly discernible in the primary sequence, one may envisage the existence of certain sequence motifs required for Jak-mediated phosphorylation and subsequent Stat recruitment. On the other hand, tyrosine phosphorylation of the growth hormone receptor, EpoR, and IL-3R chains may not be required for Stat activation (*53*). Specificity in these cases presumably resides within the higher-order conformation of the receptor cytoplasmic domains. It is also possible that the SH2 domains or other domains within Stat proteins may contribute to their selective interaction with Jak-receptor complexes (*13*).

The observation that Stat5 activation is abrogated in H-4 cells raises the intriguing issue of whether Stats play a role in cytokine-stimulated proliferative signal transmission. The IL-2Rβ H-mutant can transmit IL-2–induced proliferative signals in both BAF-B0 cells and primary T cells (*5, 32, 52*). A similar observation has been made with Stat6, whose activation is not required for the induction of mitogenesis after IL-3R or IL-4R stimulation (*53*). Although further work will be required before making any generalizations, these results suggest that Stat activation may participate in other aspects of cytokine responses, such as cell differentiation. It is also possible that Jak PTKs may participate in activating other nonreceptor PTKs (see below). It will be important to study the function of Jak PTKs in contexts other than Stat activation.

The Syk–ZAP-70 and other PTK members. In addition to the above two nonreceptor PTK families, other PTK family members have been shown to be associated with or activated by (or both) type I receptors: the Syk–Zap-70 family, Btk-Tec family, and Fes family (Fig. 1B and Table 1). As diagrammed in Fig. 2, the S-region of the IL-2Rβc chain can recruit Syk in addition to Jak1, and the Syk PTK is activated upon IL-2 stimulation (*54*). More recently, association of the related ZAP-70 kinase with IL-2R was also observed, a situation reminiscent of that observed with Src-family PTKs (*55*). The mechanism of Syk–ZAP-70 PTK activation by IL-2 is not known at present. One possibility involves Jak PTKs (discussed below). It is noteworthy that the IL-2Rβc S-region does not contain the ARAM (or TAM or ARH1) motif found in molecules of the T cell and B cell antigen receptor complexes, where it functions in the recruitment of these PTKs (*20*). Thus Syk–ZAP-70 PTK activation by IL-2 may represent a new example of an intermolecular association between the Syk–ZAP-70 family and a membrane receptor.

Syk activation by IL-2R requires the S-region, but not the A-region, of the IL-2Rβ chain, which indicates that Lck activation is not required for Syk activation (*54*), at least in this system (*56*). Antibody-mediated clustering and activation of Syk PTK in BAF cells results in the induction of the c-*myc* but not c-*fos* genes (*54*). Thus, the Lck and Syk pathways may be selectively linked to distinct proto-oncogenes. Another critical proto-oncogene, *bcl-2*, is linked to a Rapamycin-sensitive pathway (Fig. 2) (*33*). The above results suggest a role for Syk PTK (and probably ZAP-70 PTK) in IL-2 signaling, but the mechanisms by which these kinases are activated is unknown. It will be interesting to examine whether there exists any hierarchy of PTK activation during IL-2 signaling; that is, it is possible that Jak1 or Jak3 may function upstream of other PTK members. Supporting this view is the observation that in BAF-derived F7 cells overexpressing the dominant-negative form of Jak3, IL-2 induction of the c-*fos* and c-*myc* genes, but

not the *bcl-2* gene, is inhibited (*42*).

Although other nonreceptor PTK members (Fig. 1B) have not yet been extensively studied, genetic data suggest the importance of, for example, Btk in IL-5 signaling. The IL-5 response is compromised in B cells from X-chromosome–linked immunodeficient (*xid*) mice, which carry a mutation in *btk* (*57*). It is interesting that mice deficient for *fyn* also manifest a similar phenotype (*58*), because it has been reported that Btk interacts with Fyn (*59*). At present, it is not clear whether type III and IV receptors use any of the PTKs listed in Fig. 1B.

Conclusions and Perspectives

Different cytokines can act on the same cell type to mediate similar effects (redundancy), whereas many cytokines exhibit a wide range of biological effects in various tissues and cells (pleiotropy). This functional redundancy and pleiotropy in cytokine signaling can be explained in part by the existence of shared receptor subunits among the different cytokine receptor systems and the association of multiple distinct nonreceptor PTKs with different receptors. The specificity of cytokine signaling may be controlled at different levels: First, the intracellular structures of the receptor dictate which of the signaling molecules such as PTKs or Stats are to be recruited or activated. Second, the specificity of signaling by a given cytokine may also be dependent on the expression levels of signaling molecules in different cell types. The cooperation between different combinations of receptor subunits in distinct cell types would allow the generation of further diversity in the activation of overlapping or distinct signaling pathways.

Here, we start to notice the similarities and differences between cytokine receptors and other growth factor receptors containing an intrinsic PTK domain. Both control the recruitment of signaling molecules by tyrosine phosphorylation. On the other hand, the uniqueness of the cytokine receptors lies in the fact that their intracellular domains have structurally evolved to recruit multiple PTKs, presumably in order to increase the flexibility of cytokine action, allowing diverse responses in different cell types.

It will not be surprising if future studies unearth additional pathways, including some that do not include PTKs, which serve to link the cytokine receptors to a broad array of signal transduction systems.

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