# Interleukin-3 and Granulocyte-Macrophage Colony-Stimulating Factor Receptor Signal Transduction (43760)

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*Abstract.* **The cytokines, interleukin-3 (IL-3) and granulocyte-macrophage colony-stimulating factor (GM-CSF), share many similar activities on cells of the hemopoietic system. Cloning of the receptors for IL-3 and GM-CSF revealed that these two cytokines utilize receptors consisting of a ligand-specific α unit and a β subunit which is shared. Neither subunit contains intrinsic tyrosine kinase activity, but deletion analysis of the β subunit cytoplasmic domain has defined certain regions which are important for signal transduction.** [P.S.E.B.M. 1994, Vol 206]

Hemopoiesis, the process of blood cell formation, is tightly regulated by a complex network of stromal interactions as well as soluble polypeptide factors called cytokines (1). These cytokines exert varying actions on a wide range of target cells and are produced, either constitutively or in response to hematological stress, by many different cell types. Interleukin-3 (IL-3) was one of the earliest characterized cytokines, as it has profound effects at many stages of hemopoietic development, ranging from the early, multipotential progenitor compartment to the more mature, lineage-committed cells. Another cytokine, granulocyte-macrophage colony-stimulating factor (GM-CSF), exhibits many actions similar to that of IL-3 on their common target cells. In fact, in the human system, IL-3, GM-CSF, and a third cytokine, IL-5, were reported to cross-compete with each other for binding to their receptors (2–4). Molecular cloning of the receptors for IL-3, GM-CSF, and IL-5 revealed that they share a common subunit that is required for formation of a high-affinity receptor, and thus provided a biochemical basis for the observed ligand cross-competition (5, 6). However, since this shared subunit is also essential for signal transduction, a molecular basis for the observed functional redundancy of these two cytokines in common target cells was also suggested.

## Structure of the Receptors for IL-3, GM-CSF, and IL-5

In the human system, each of the receptors for IL-3, IL-5, and GM-CSF consists of a ligand-specific α subunit and the shared, common β subunit termed βc (Fig. 1). In isolation, the α subunit binds its ligand with only low affinity (7) and is unable to transduce a signal (8). In association with the βc subunit, however, a high-affinity receptor which is capable of signaling is formed. As analogous situation exists in the mouse, except that in addition to the βc subunit (originally referred to as AIC2A) that is shared among the IL-3, IL-5, and GM-CSF receptors, a second β subunit exists which associates only with the α subunit for IL-3 (9). This second β subunit, called $\beta_{IL\text{-}3}$ (originally AIC2B), is able by itself, to bind IL-3 with low affinity, although, it is unable to transduce signals when expressed in cells in the absence of the α subunit (9). No functional differences have yet been detected between the two different mouse β subunits. They are highly homologous and probably arose through gene duplication after the divergence of mouse and man (10, 11).

Both the α and β subunits of the IL-3, IL-5, and GM-CSF receptors belong to the Class I cytokine receptor family (12). Receptors of this family are characterized by a domain of approximately 200 amino acids in the extracellular region, containing two tandemly arranged Type III fibronection repeats of 90

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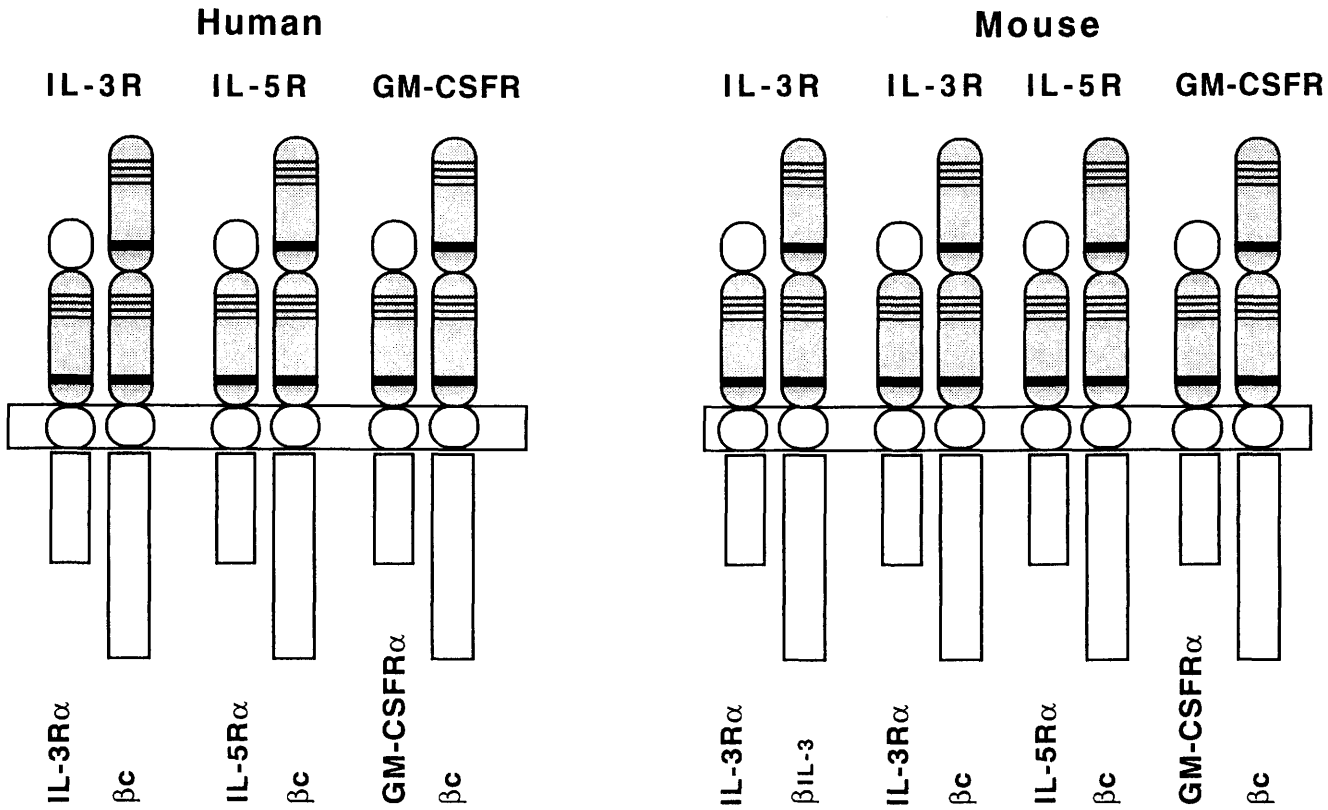


**Figure 1.** Structure of the receptors for IL-3, GM-CSF, and IL-5. The shaded region designates a hemopoietic receptor family domain. Inside this region, the thin lines position the conserved cysteines and the thick bar represents the trp-ser-X-trp-ser motif.

amino acids each. The amino terminal half of this domain contains four spatially conserved cysteines, while the a trp-ser-X-trp-ser motif is found near the carboxy terminal region. Each fibronection Type III module consists of seven antiparallel β strands, and together they are predicted to fold into a barrel structure (13). The α and β subunits each contain one and two copies, respectively, of this structural motif.

In contrast, the intracellular domains of these receptors are less well defined. The cytoplasmic domains of the α subunits are relatively short, consisting of approximately 50 amino acids, while the β subunits are substantially longer with about 450 residues, and deletion of either domain abrogates signaling (14). Neither contains sequences predictive of enzymatic activities such as protein tyrosine kinase, however, cytoplasmic truncations of the β subunit have defined a membrane proximal region which is essential for supporting a mitogenic signal (Sato *et al.*[2]). Similar investigation of other members of the Class I cytokine family (i.e., erythropoeitin receptor [Epo-R] [15], IL-2Rβ [16], and gp130 [17], the signaling subunit of the IL-6 receptor) has also shown the membrane proximal regions of these receptors to be important in mitogenic signaling. Closer scrutiny of these regions has revealed some sequence similarity among these different receptors (17).

## Intracellular Signaling Events Induced by IL-3 and GM-CSF

In spite of not possessing an intrinsic tyrosine kinase receptor, one of the earliest events to occur after IL-3 or GM-CSF stimulation is induction of protein tyrosine phosphorylation (18–23). The importance of tyrosine kinase action in the signaling cascade of IL-3/GM-CSF was first indicated by the ability of activated tyrosine kinases to abrogate the factor requirement of IL-3-dependent cell lines (24–28). Furthermore, tyrosine kinase inhibitors inhibit (29) while tyrosine phosphatase inhibitors (30) potentiate IL-3/GM-CSF-driven growth. IL-3-induced tyrosine phosphorylations occur very rapidly, even at 4°C, suggesting that the receptor, a tyrosine kinase, and its initial substrates are closely associated before ligand binding.

Several tyrosine kinases have been reported to become activated in IL-3- or GM-CSF-stimulated cells, including Fyn (31, 32), Lyn (33), Fps (34), and Janus kinase 2 (JAK2) (35). The kinases Fps and JAK2 have

[2] Sato N, Sakamaki K, Terada N, Arai K, Miyajima A. Signal transduction by the high-affinity GM-CSF receptor: Two distinct cytoplasmic regions of the common β subunit responsible for differentiation. Embo J 12(11):4181–4189, 1994.

been detected in co-immunoprecipitates of the human GM-CSF receptor and thus may be the initial tyrosine kinases activated in ligand-stimulated cells. However, although Fps is attractive as an IL-3 or GM-CSF receptor-associated kinase, because of its myeloid restricted pattern of expression, not all investigators have been able to observe its receptor association. Perhaps the role of Fps depends on cell type. For example, although the promyelocyte cell line, HL60, expresses human GM-CSF receptors, it does not respond to GM-CSF until dimethylsulfoxide (DMSO)-induced differentiation (36). The intracellular factor(s) in DMSO-treated HL60 which allow GM-CSF responsiveness may also couple the receptor to Fps. The role of JAK2 and the JAK family of kinases in IL-3/GM-CSF signaling, on the other hand, is more universally accepted. The JAK family kinases include at least three members (37); all have been found to function in at least one cytokine system and many Class I cytokine receptors, including growth hormone, prolactin, Epo (38), IL-6/ciliary neurotrophic factor (39), and IL-3 (35), are physically associated with a JAK family member. One member of the JAK family, tyk2, is though to be involved in α-interferon signaling through the phosphorylation and activation of a latent, cytoplasmic transcription complex, ISGF3α (40). Phosphorylation of this complex results in nuclear translocation of this factor and transcription of IFN-α-specific genes. Thus, the discovery of JAK kinases in IL-3/GM-CSF action (35) is exciting, as it predicts the presence of a similar transcription factor downstream of the IL-3/GM-CSF receptor. Other tyrosine kinases that become activated in IL-3/GM-CSF-stimulated cells are the Src family kinases Fyn and Lyn. The usage of particular members of the Src family kinases appears to depend on whether each is expressed in the particular cell type studied.

Initially, the search for an IL-3/GM-CSF receptor-associated kinase focused on the Src family kinases because these kinases associate with other nontyrosine kinase type receptors, specifically the B and T cell antigen receptors. However, although Src family kinases become activated in IL-3/GM-CSF stimulation, there is no evidence for physical association with the receptor. Thus, the JAK and Src family kinases may serve different functions in the signaling cascade; further evidence for this hypothesis can be derived from analysis of the signaling capability of various truncations of the human GM-CSFβ subunit (14; Sato *et al.*, submitted). Truncation up to amino acid 626 (β626) had no effect on the spectrum or intensity of bands observed in α-phosphotyrosine Western blots of GM-CSF-stimulated cell lysates. Interestingly, although GM-CSF receptors with deletions longer than β626 were still able to transmit a herbimycin A (a tyrosine kinase inhibitor) sensitive proliferative signal, no tyrosine phosphoproteins could be detected by Western analysis. These data suggest that at least two tyrosine kinases function in signaling which may interact, directly or indirectly, with different regions of the β subunit; investigation of their roles will be important in dissecting the many events that occur in stimulated cells.

In addition to the β subunit itself (14), JAK2 (35) and Fps (34), many intracellular substrates (i.e., Vav [41], Shc [Sato *et al.*, submitted], Raf [42], and MAP kinase [MAPK] [43–45]) become tyrosine phosphorylated in response to IL-3/GM-CSF. The significance of phosphorylation of the β subunit is not clear since deletion of the putative, phosphorylated tyrosine does not affect the ability of the GM-CSF receptor to transmit a mitogenic signal (14), however, phosphorylation of Vav, Shc, Raf, and MAPK correlate with activation of these proteins. These proteins are also related in that they all function in the Ras activation pathway.

Ras is a low molecular weight, GTP binding protein that switches between GTP-bound, active and GDP-bound, inactive states in response to extracellular signals (46–48). This conversion can be mediated by either stimulation of the intrinsic GTPase activity of Ras, or by activation of a nucleotide exchange factor which exchanges Ras-bound GDP for GTP. Many cytokines, including IL-3 and GM-CSF have been shown to activate Ras (48), perhaps through Vav or Shc. Vav (49) is an SH2 (Src homology Domain 2: 100 amino acid domains which interact with specific phosphotyrosines [50]) containing protein with Ras GTP exchange activity (51), that is expressed only in hemopoietic cells. Shc (52), on the other hand, consists almost entirely of SH2 and SH3 domains, but tyrosine phosphorylated Shc forms a bridge between activated growth factor receptors and the nucleotide exchange factor, Sos (46). The tyrosine phosphorylation of Vav and Shc implicates them in IL-3/GM-CSF action, but the way in which either of these is coupled to receptor activation remains to be determined.

One downstream consequence of Ras activation is stimulation of the serine/threonine kinase Raf (53). Active Raf kinase then activates another serine/threonine kinase, MAP kinase (MAPK), through at least one intermediate, resulting in c-*fos*/c-*jun* induction. This cascade of activation, first described for the intrinsic tyrosine kinase receptors, appears to exist among the IL-3/GM-CSF signaling pathways since Ras, Raf, MAPK activation and c-*fos*/c-*jun* induction all map to the same region of the GM-CSF β subunit (Sato *et al.*, submitted).

In contrast, other regions of the GM-CSF β subunit are required for phosphoinositol 3′ kinase activation, Pim-1 and c-*myc* induction. PI3K is an enzyme that becomes associated, through its SH2 domains with tyrosine phosphorylated proteins such as acti-

vated receptors or kinases, in ligand-stimulated cells (50). Pim-1 is a serine/threonine kinase, expressed mainly in hemopoietic tissues, which can synergize *in vivo* with c-*myc* in producing lymphoma in mice (54). Pim-1 and c-*myc* induction and to some extent, PI3K activation appears to be related to the membrane proximal domain of the β subunit (Sato *et al.*, submitted).

## Conclusion

The receptor for IL-3 and GM-CSF does not possess intrinsic tyrosine kinase activity, or any other feature of better characterized receptors with intrinsic enzyme activities. However, study of truncations of the β subunit has provided not only clues as to the structure/function relationship of the β subunit itself, but also has helped in dissecting the various pathways activated in ligand-stimulated cells. It is important to remember, however, that although most attention has been focused on the longer β subunit, the α subunit of the IL-3, GM-CSF, and IL-5 receptors is also essential for signal transduction (14, 55) and that these cytokines do exert ligand-specific effects on certain cells (1). Thus, it is likely that the β subunit is responsible for signals which are common to IL-3/GM-CSF and IL-5 action while the α subunit contributes a ligand-specific function. Examination of the signaling pathways emanating from the α subunit is essential in understanding the ligand-specific functions of IL-3, GM-CSF, and IL-5.


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