Cytokine and Cytokine Receptor Pleiotropy and Redundancy

by

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Cytokines represent a diverse group of molecules that collectively exert a wide range of actions (1). The term cytokine is rather general, technically referring to a molecule made by one cell that acts on another, but cytokines are primarily growth factors and hormones of the immune and hematopoietic systems. The term broadly encompasses many of the interleukins and colony stimulating factors (which are also referred to as type I cytokines) and interferons (which sometimes are referred to as type II cytokines) (1). Certain molecules, such erythropoietin, thrombopoietin, growth hormone, and prolactin, while not classically thought of as typical cytokines, have similar structures and signaling mechanisms to type I cytokines (1).

Many individual cytokines are themselves pleiotropic, exerting multiple actions, and particularly in vitro, many cytokines have overlapping actions (2, 3). There are multiple different possible mechanisms that can explain pleiotropic and overlapping actions for different cytokines. Pleiotropic actions can be explained by the presence of receptors for a cytokine on multiple lineages or by a cytokine having the ability to activate multiple signaling pathways wherein different signaling pathways differentially contribute to different functions. Overlapping actions by different cytokines can be explained by similar cellular distributions of specific receptors for different cytokines as well as by the sharing of signaling pathways, which particularly occurs when different receptors share similar motifs that mediate the coupling to the same pathways. In addition, however, cytokine pleiotropy and redundancy can be at least partially explained, respectively, by the ability of certain cytokines to signal via
more than one type of receptor complex and by the sharing of individual receptor component by more than one cytokine.

We will herein summarize a range of different systems wherein cytokine receptor components are shared, discussing the implications thereof. For type I cytokines, these include the sharing of the common β chain, βc, by interleukin-3 (IL-3), IL-5, and granulocyte-macrophage colony stimulating factor (GM-CSF); the sharing of gp130 by IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), novel neurotrophin-1/B cell-stimulating factor-3 (NNT-1/BSF-3), and cardiotrophin-1 (CT-1); the sharing of LIFRβ by LIF, OSM, CNTF, and CT-1; the sharing of IL-12Rβ1 by IL-12 and IL-23; the sharing of γ by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; the sharing of IL-2Rβ by IL-2 and IL-15; the sharing of IL-4Rα and IL-13Rα1 by IL-4 and IL-13; and the sharing of IL-7Rα by IL-7 and thymic stromal lymphopoietin (TSLP) (Table 1). The cytokines that can signal via more than one complex include IL-2, IL-4, human OSM and murine IL-3. For type II cytokines, we discuss the share of IL-10Rβ by IL-10 and IL-22, the sharing of IL20Rα and IL-20Rβ by IL-19, IL-20, and IL-24, and the sharing of IL-22Rα by IL-20, IL-22, and IL-24.

Basis for binding of type I cytokines to their receptors

The basic understanding of type I cytokine-receptor interactions comes from the original studies on growth hormone, a type I cytokine (4; reviewed in ref. 1). Growth hormone was shown to bind to a growth hormone receptor homodimer; remarkably, two different part of the ligand interacted with relatively similar regions of the receptor.
(4). The basic model is that growth hormone binds first to one monomer via a high affinity “Site 1” and then the second receptor monomer interacts with this complex, contacting growth hormone via “Site 2”. In the case of the growth hormone system, the complex is further stabilized via a receptor-receptor interaction site denoted as “Site 3” (4). Although this represent a homodimeric receptor system, it is easy to envision how receptor heterodimers would form if the second growth hormone receptor monomer were a distinctive receptor component. Such a second component is represented for example by the common cytokine receptor β chain (βc), gp130, and the common cytokine receptor γ chain (γc), which are discussed below.

IL-3, IL-5, and GM-CSF share a common cytokine receptor β chain, βc, and murine IL-3 has an additional distinctive βIL-3 chain that selectively mediates IL-3 but not IL-5 of GM-CSF signaling.

IL-3, IL-5, and GM-CSF are hematopoietic cytokines, with IL-3 having actions as a “multi-CSF” on multiple lineages, IL-5 being essential for eosinophil expansion, and GM-CSF acting mainly on granulocytes and macrophages/monocytes. Each of these cytokines has a distinctive α chain (IL-3Rα, IL-5Rα, and GM-CSFRα) but they all share a common β chain, βc, in both humans and mice (5-7, reviewed in 8). Interestingly, in mice but not in humans, there is an IL-3-specific β chain as well, denoted βIL-3 (8, 9). Despite the presumed importance of IL-3, IL-5, and GM-CSF for hematopoiesis, disruption of β, in a murine knockout model does not cause a severe defect within the hematopoietic system, although signaling in response to IL-5 and GM-CSF are
disrupted and these mice exhibit alveolar proteinosis and defective eosinophil responses (10, 11). As expected, signaling in response to IL-3 remains normal due to the present of $\beta_{IL-3}$, with IL-3 signaling being eliminated only in the context of $\beta_c/IL-3$ double knockout mice (12).

IL-6, IL-11, LIF, Oncostatin M, CNTF, NNT-1/BSF-3, and cardiotrophin-1 share gp130

IL-6, IL-11, LIF, OSM, CNTF, NNT-1/BSF-3, and CT-1 are seven cytokines, some of which were discovered in very different assay systems. Collectively, these cytokines exert multiple actions ranging from the immune system to the cardiovascular system to the central nervous system, but all of them share the gp130 signal transducing molecule as a component of their receptors (13-16). IL-6 was originally identified as a B-cell differentiation factor, but it also can exert effects related to T-cell growth, and on many other cell types as well, including the induction of acute phase proteins. IL-11 is a stromal factor that can induce acute phase proteins and has a number of hematopoietic related effects as well, cooperating with IL-3 and stem cell factor. LIF can suppress the differentiation of pluripotent stem cells, inhibit monocyte differentiation of M1 cells, and inhibit adipogenesis, as well as exerting effects in the central nervous system. LIF is identical to cholinergic neural differentiation factor. OSM was originally identified based on its ability to inhibit to growth of a melanoma cell line but it is also a growth potentiator, for example for Kaposi’s sarcoma. CNTF is primarily known for its ability to promote neuronal survival. NNT-1/BSF-3 also support survival of chicken embryo motor and sympathetic neurons whereas in mice it potentiates effects of IL-1 and IL-6
and has B-cell stimulating capability. Finally, although CT-1 was discovered based on its actions on cardiac muscle cells, it has a wide range of multi-functional roles, including actions with the hematopoietic and neural systems as well. Thus, a number of these factors have overlapping actions, but they are also distinctive. As noted above, these cytokines all share the gp130 signal transducing molecule (13-16). gp130 was originally cloned as a component, along with IL-6Rα, of the IL-6 receptor (17). The IL-11 receptor contains IL-11Rα and gp130; the LIF receptor contains LIFRβ and gp130; oncostatin M can act via receptors containing either OSMRβ and gp130 or LIFRβ and gp130; the CNTF receptor contains CNTFRα, LIFRβ, and gp130; the NNT-1/BSF-3 receptor contains LIFRβ and gp130; and the CT-1 receptor contains LIFRβ and gp130. Thus, IL-6 and IL-11 do not use LIFRβ, whereas LIF, OSM, CNTF, NNT-1/BSF-3, and CT-1 do. As noted, human OSM can signal through two types of receptors, one of which uses LIFRβ and one of which does not. As part of an investigation of IL-6 signaling, the gene encoding gp130 was disrupted in mice. Unexpectedly, in addition to certain defects in hematopoiesis, targeting of gp130 resulted in a fetal-lethal phenotype due to defect in myocardial development (18). This phenotype presumably does not relate to a defect in IL-6 signaling but instead may relate to other cytokines such as CT-1. LIFRβ gene disruption results in a neural defect (19, 20).

**IL-12 and IL-23 share IL-2Rβ1.**

IL-12 is structurally an interesting cytokine that consists of an IL-6-like cytokine, p35, that associates with p40, a protein that resembles a soluble cytokine receptor. The
p35-p40 heterodimer signals through a receptor that consists of IL-12Rβ1 and IL-12Rβ2 and is important for Th1-cell differentiation (21, 22). More recently, another IL-12 p40 partner, denoted p19, was identified (23). The p19/p40 dimer forms IL-23, which signals via IL-12Rβ1 but not IL-12Rβ2. Like IL-12, IL-23 activates Stat4 (23).

The receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 share the common cytokine receptor γ chain (γc) that is mutated in humans with X-linked severe combined immunodeficiency (X-SCID).

The common cytokine receptor γ chain (γ) was originally cloned as a third component of the IL-2 receptor and thus denoted as the IL-2Rγ chain, corresponding to α-β nomenclature of the first chains that were discovered (24). Noguchi et al. then discovered that mutations in IL-2Rγ resulted in X-linked severe combined immunodeficiency (XSCID; also denoted as SCID-X1) (25), a disease characterized by profoundly diminished numbers of T cells and NK cells but with normal albeit non-functional B cells (T/B’NK SCID). A defect in a component of the IL-2 receptor in this disease was unexpected given that humans and mice lacking expression of the IL-2 gene exhibited normal T-cell and NK-cell development (26-28). Thus, it was predicted that IL-2Rγ must exert additional actions beyond the IL-2 system (25), and indeed it was found that IL-2Rγ was a component of other cytokine receptors as well, resulting in the changing of its name to γc. In addition to IL-2, the receptors for IL-4, IL-7, IL-9, IL-15, and IL-21 also contain γc (reviewed in 29, Figure 1A), and this family of cytokines is sometimes denoted as the IL-2 family of cytokines. The phenotypes of Il7−/− (30) and Il7r−
mice as well as that of humans with mutations in the human IL7R gene have revealed that the lack of T-cells in XSCID results from defective IL-7 signaling (32). A range of in vitro experiments as well as the phenotype of mice lacking expression of either IL-15 or IL-15Rα together indicate that defective NK-cell development results from defective IL-15 signaling (33-35). All six of the γc-dependent cytokines have the ability to act, at least in vitro, as T-cell growth factors (29). IL-2 is the major T-cell growth factor that allows T-cell expansion following antigen encounter, but it also plays additional major roles, including for example in antigen-induced cell death and in the boosting of natural killer cytolytic activity (1). IL-4 is essential for T helper 2 (Th2) cell differentiation and for immunoglobulin class switch (36). IL-7 is essential for T-cell development in both humans and mice and for B-cell development in mice but not humans. IL-9 is important for mast cell growth and mucous production (37). IL-15 is essential for NK-cell development and memory CD8 T-cell expansion (34, 35, 38). The role of IL-21, a more recently identified cytokine, is not yet sufficiently understood in vivo. The IL-21 binding protein, IL-21R, is most similar to IL-2Rβ (39, 40). In vitro, IL-21 has a co-stimulatory effect on anti-CD3 T cell proliferation, can augment anti-CD40-induced B-cell proliferation, and inhibit B-cell proliferation induced by anti-IgM plus IL-4 (40). It was also reported to augment the maturation of CD56+ cytolytic NK cells from human bone marrow CD34+ cells in vitro in response to Flt-3 ligand + IL-15 (40), but a more recent report suggests that it may instead oppose the actions of IL-15 (41). IL-21R seems to be expressed primarily in lymphoid tissue such as thymus and spleen.
IL-21R levels are induced by TCR stimulation in human peripheral blood mononuclear cells (39).

There are three types of receptors for IL-2: the low affinity receptor (containing IL-2Rα), intermediate affinity receptor (containing IL-2Rβ and γc), and high affinity receptor (containing IL-2Rα, IL-2Rβ, and γc) (reviewed in 1, 29). The intermediate and high affinity receptors are the functional forms. The “type I” IL-4 receptor on T-cells contains IL-4Rα + γc, but there is a second functional IL-4 receptor (“type II IL-4 receptor”; see next section). The IL-7 receptor contains IL-7Rα + γc. The IL-15 receptor contains IL-15Rα, IL-2Rβ, and γc; thus, both the IL-2 and IL-15 receptors contain both IL-2Rβ and γc and differ only in distinctive α chains. Finally, the IL-21 receptor contains IL-21Rα + γc (reviewed in 29).

IL-4 and IL-13 and the sharing of the type II IL-4 receptor

IL-4 is closely related to another T-cell derived cytokine, IL-13. As noted above, the type I IL-4 receptor contains IL-4Rα + γc. IL-4Rα was cloned originally as a receptor for IL-4 (42). Overlapping actions of IL-4 and IL-13 and a range of other data, including the activation of the same STAT protein (Stat6) and the ability of IL-4 and IL-13 to cross-compete for binding had suggested that IL-4 and IL-13 would share a receptor component (43-47, reviewed in 48). Interestingly, the type II IL-4 receptor, present on fibroblasts and certain other cell types, consists of IL-4Rα + IL-13Rα1, and this complex also is the functional IL-13 receptor (49, 50, Figure 1B). Interestingly, whereas IL-4 primarily binds IL-4Rα, IL-13 primarily binds IL-13Rα1. There is a second IL-13
binding protein called IL-13Rα2, which binds IL-13 with even higher affinity than IL-13Rα1 but which appears to be a non-functional inhibitory “decoy” receptor (51, 52). Both IL-4 and IL-13 appear to be important for Th2 differentiation as Il13−/− mice also show a Th2 differentiation defect (53). As expected, disruption of the Il4ra gene in mice results in defective Th2 differentiation (54). In addition to its contribution to Th2 differentiation, IL-13 is essential for worm expulsion and for antigen-induced asthma (55-57).

**IL-7 and TSLP and the sharing of IL-7Rα**

Thymic stromal lymphopoietin (TSLP) was identified as a factor that was present in the medium of a thymic stromal cell line, Z210R.1 and was capable of supporting the growth of a pre-B cell line, NAG8/7 (58). Interestingly, the receptor for TSLP contains its own distinctive receptor chain, TSLPR, as well as IL-7Rα (59, 60). Thus, TSLP and IL-7 share IL-7Rα as a common receptor component (Figure 1C). This helps to explain why the phenotype of Il7r−/− mice is somewhat more severe than that seen in Il7−/− mice, because the former inactivates signaling in response to both IL-7 and TSLP and the latter only signaling in response to IL-7. Interestingly, IL-13Rα1, which can substitute for γc in the context of IL4 signaling, and TSLPR, which “replaces” γc as one transitions from IL-7 to TSLP signaling both are similar to γc. This is particularly true of TSLPR, which is the protein in public databases with highest amino acid similarity to γc (59).

TSLPR was cloned by four groups (59-62). Two groups reported the gene as one that encodes an orphan receptor (61, 62). In a third case, it was identified initially as an
orphan receptor as an EST that had substantial homology to the erythropoietin receptor cytoplasmic domain, but then it was directly demonstrated that this orphan receptor was in fact the elusive TSLPR (59). Another group reported the cloning of TSLP as well as its receptor (60, 63). TSLP only weakly binds to TSLPR, but exhibits higher affinity to the combination of TSLPR and IL-7Rα. The $K_d$ of TSLP binding to its receptor varies in different cell lines: the $K_d$ for NAG8/7, 70Z/3, and 7B9 were 2.2 nM, 7.1 nM, 0.1 nM respectively (59, 63); the basis for the differences are unknown but perhaps relate to different levels of expression of the different receptor components in each cell line.

TSLP supports and expands IgM+ B cells \textit{in vitro}, as reported previously (58), and also \textit{in vivo}. It also appears to have a minimal supporting activity for growth of thymocytes (63). Human TSLP and TSLPR were cloned and human TSLP was found to augment the maturation of dendritic cells and to induce chemokine production in monocytes (64-66).

\textbf{The complex sharing of receptor components by IL-10, IL-19, IL-20, IL-22, and IL-24.}

Together with the IFNs (IFNα, IFNβ, IFNγ, IFNω, IFNτ), IL-10, IL-19, IL-20, IL-22 (formerly denoted IL-TIF for IL-10-related T cell derived inducible factor), and IL-24 (formerly denoted as mda-7 for melanoma differentiation-associated gene 7) are designated as type II cytokines (reviewed in refs. 4, 67-69). IL-10 was the first of these molecules discovered as a potent immuno-modulator that could inhibit the production of pro-inflammatory cytokines (67). The receptor for IL-10 consists of IL-10Rα plus IL-10Rβ. More recently, an array of other molecules have been discovered, including IL-
19, IL-20, IL-22, IL-24. These exert a range of actions, partially overlapping, as is logical based on the extensive sharing of receptor chains (67-69) as summarized in Table 2.

Conclusions

Type I and type II cytokines exhibit both cytokine pleiotropy and redundancy. There are now multiple cases wherein the receptors for these cytokines share receptor chains. This can be viewed as cytokine receptor pleiotropy, wherein a single chain such as β, γ, gp130, LIFRβ, IL-2Rβ, IL-4Rα, IL-7Rα, IL-13Rα1, IL-10Rβ, IL20Rβ, IL-20Rα, IL-20Rβ, or IL-22Rα exist as part of more than a single receptor. In addition, there are examples of what can be viewed as possible cytokine receptor redundancy, wherein more than one functional receptor form can exist for a single cytokine. Examples include the intermediate and high affinity forms of the IL-2 receptor, type I and type II IL-4 receptors, murine IL-3 receptors that use either βc or βIL-3, and two forms of OSM, IL-20, and IL-24 receptors. However, whether these represent redundant receptor forms (as appears likely for IL-3) or instead represent two forms of functional receptors that exert distinctive actions (as perhaps is likely for IL-2 wherein the intermediate affinity form is critical on NK cells whereas the high affinity form is essential for the expansion of activated T-cells), still requires further investigation. Given how similar many type I cytokines are to each other and the close relatedness of multiple type I cytokine receptor chains, it is possible that co-evolution of the cytokines and their receptor chains is a process that has allowed the emergence of new distinctive cytokine functions. The same idea is also applicable to interferons and the IL-10, IL-19, IL-20, IL-22, and IL-24
set of type II cytokines. As additional data emerges on the three-dimensional structure of various cytokine-receptor complexes, a greater understanding of these systems will emerge. This should clarify the specific structural basis for the ability of cytokines to interact with more than one receptor and the ability of a receptor chain to interact with multiple cytokines.

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**Figure 1.** Schematic of receptors for IL-2 family cytokines. **(A)** IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 all share \( \gamma \). **(B)** The type II IL-4 receptor and IL-13 receptor both contain IL-4R\( \alpha \) and IL-13R\( \alpha 1 \). **(C)** The IL-7 and TSLP receptors share IL-7R\( \alpha \).
Table 1. Sharing of receptor subunits by multiple type I cytokines

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Herein, IL-22 binding protein is denoted as IL-22Rα
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