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REVIEW

Cytokine receptors and hematopoietic differentiation

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Colony-stimulating factors and other cytokines signal via their cognate receptors to regulate hematopoiesis. In many developmental systems, inductive signalling determines cell fate and, by analogy with this, it has been postulated that cytokines, signalling via their cognate receptors, may play an instructive role in lineage specification in hematopoiesis. An alternative to this instructive hypothesis is the stochastic or permissive hypothesis. The latter proposes that commitment to a particular hematopoietic lineage is an event that occurs independently of extrinsic signals. It predicts that the role of cytokines is to provide nonspecific survival and proliferation signals. In this review, we look at the role of cytokine receptor signalling in hematopoiesis and consider the evidence for both hypotheses. Data from experiments that genetically manipulate receptor gene expression *in vitro* or *in vivo* are reviewed. Experiments in which cytokine receptors were installed in multipotential cells showed that, in some cases, stimulation with the cognate ligand could lead to alterations in lineage output. The creation of genetically manipulated mouse strains demonstrated that cytokine receptors are required for expansion and survival of single lineages but did not reveal a role in lineage commitment. We conclude that hematopoietic differentiation involves mainly stochastic events, but that cytokine receptors also have some instructive role.
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Introduction

Hematopoiesis, the process of generation of blood cells, begins in the early embryo and continues throughout life. As most mature blood cells are short-lived, new blood cells continually arise from hematopoietic stem cells and become committed to the erythroid, megakaryocytic, granulocytic, monocytic and lymphocytic lineages. In addition to maintaining steady-state hematopoiesis, the system also responds to physiological stresses, such as bleeding or infection. The intricate, finely tuned regulatory pathways that control both basal and emergency hematopoiesis are mediated largely by cytokines and their cognate receptors. Cytokines are a large family of specific extracellular ligands that can stimulate biological responses in diverse cell types by binding to, and activating, a family of structurally and functionally conserved cytokine receptors.

Cytokines of the hematopoietic system include interleukins (ILs), colony-stimulating factors (CSFs), interferons, erythropoietin (EPO) and thrombopoietin (TPO). They bind to a family of cytokine receptors that share a number of features. The receptors can be composed of dimers of a single receptor (granulocyte (G)-CSF receptor (R), EPO receptor (EPOR), TPO receptor (c-MPL)) or can be heterodimeric with a common signalling subunit and a unique ligand-binding chain (reviewed by Nicola, 1994; Wells and de Vos, 1996). The heterodimeric receptors can be grouped into those receptors that share the common β-chain (granulocyte–macrophage (GM)-CSFRα, IL-3Rα, IL-5Rα), those that share the gp130 receptor (IL-6Rα, leukemia inhibitory factor receptor β, ciliary neurotrophic factor receptor α, IL-11Rα, oncostatin M receptor α, cardiotrophin-like cytokine factor 1) and those that share the common γ-chain (IL-2Rα, IL-2Rβ, IL-4Rα, IL-7Rα, IL-9Rα, IL-13Rα, IL-15Rα and IL-21Rα; Figure 1). The homodimeric and heterodimeric groups together constitute the type 1 cytokine receptors, which share basic structural features and are characterized by the presence of four conserved cysteine residues, a tryptophan-serine-x-serine-tryptophan motif and fibronectin type III domains in the extracellular part of the receptor and by conserved Box1/Box2 regions in the membrane proximal intracytoplasmic domain. The type II receptors, which include those for interferons and IL-10, retain Box 1/2 but lack the tryptophan-serine-x-serine-tryptophan motif. The cytokines bind to their receptors with high picomolar affinity. This event triggers receptor homodimerization (for example G-CSFR; Horan *et al*., 1996; Tamada *et al*., 2006) or heterodimerization/oligomerization of receptor subunits (for example GM-CSFR; Hayashida *et al*., 1990) or induces a conformational change in preformed receptor dimers (EPOR; Livnah *et al*., 1999; Constantinescu *et al*., 2001) resulting in the activation of the Janus kinases (JAKs). These tyrosine kinases are constitutively associated with cytokine receptors with binding mediated by interactions between the FERM domain of JAK and the Box1 membrane proximal intracytoplasmic region of the receptor. On ligand binding, JAKs phosphorylate themselves and their associated receptors. The close

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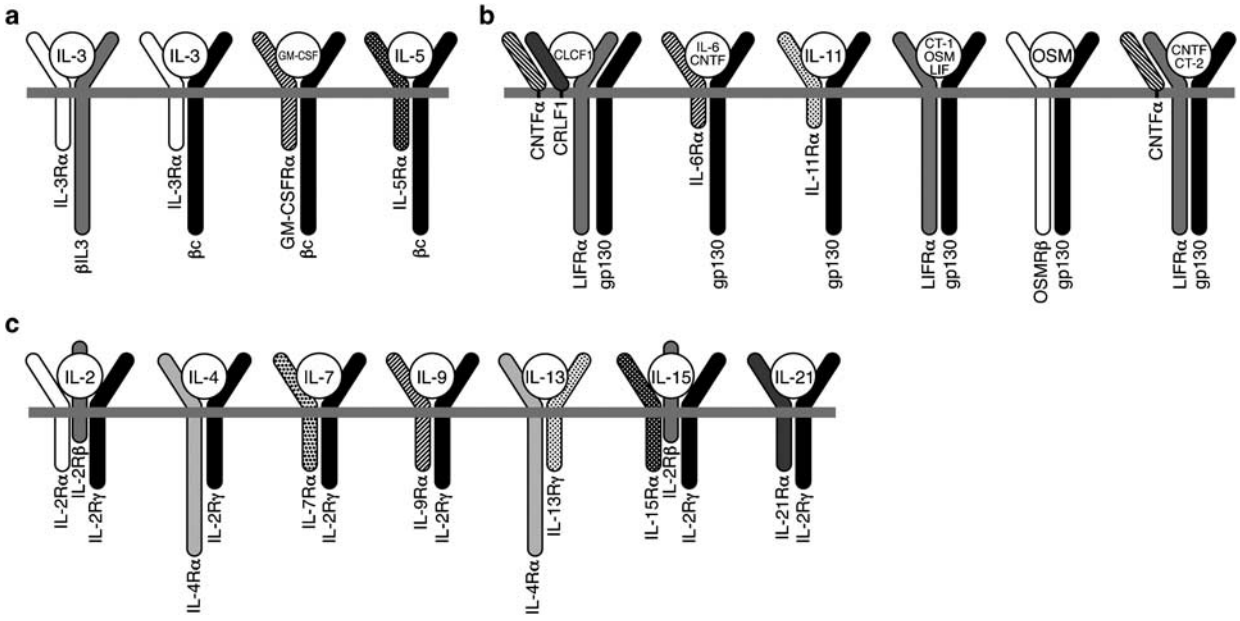

Figure 1 Some class1 cytokine receptors share common subunits. Class 1 cytokine receptors comprise three families of heterodimeric receptors each of which shares a common receptor: (**a**) the common β-chain; (**b**) the gp130 receptor or (**c**) the common γ-chain. The G-CSF, EPOR and c-MPL receptors, which consist of homodimers, are also part of the class 1 cytokine receptor family (not shown). EPOR, erythropoietin receptor; G-CSF, granulocyte colony-stimulating factors.

association of JAKs with cytokine receptors creates the functional equivalent of a receptor tyrosine kinase, such as FLT3 or c-KIT, that has intrinsic tyrosine kinase activity in its cytoplasmic portion (Behrmann *et al*., 2004). Mutagenesis studies have shown that there are distinct regions of individual phosphorylated receptors that transmit signals for cell survival, proliferation, differentiation and/or activation via interaction with adaptor molecules of multiple signalling cascades (reviewed by Watowich *et al*., 1996; Heim, 1999). One of the most crucial interactions is the generation of docking sites for the SH2 domains of the signal transducer and activator of transcription proteins. Once bound to the receptor/JAK complex, signal transducer and activator of transcription molecules are themselves phosphorylated and dimerize. The dimers translocate to the nucleus, where they bind to DNA sequence in the promoters of pathway target genes to activate transcription. Stringent mechanisms of signal attenuation are also essential for ensuring controlled cellular responses via a number of different proteins. Among them are phosphotyrosine phosphatases such as Src-homology 2 containing phosphatase (SHP) proteins, inhibitors of activated (PIAS) and suppressors of cytokine signalling proteins (Wormald and Hilton, 2004). The suppressors of cytokine signalling proteins are rapidly induced in response to cytokine signalling and act to inhibit cytokine signalling both by inhibiting JAK activation and also by targeting components of the signalling pathway for degradation. Expression of receptors is regulated at several molecular and cellular levels, including gene transcription, protein translation, internalization and degradation. In turn, the receptors themselves act as a clearance sink for circulating cytokines. While there are more than 50 cytokines that in some way regulate hematopoietic cells, there are only four mammalian JAKs and seven signal transducer and activator of transcriptions; therefore, it is clear that cell and tissue specificity of cytokine action must be regulated at multiple levels. In this review, we focus on the role of cytokine receptors in the regulation of hematopoiesis.

The identification of the first hematopoietic cytokines was made possible primarily by cell culture assays developed from the mid-1960s to early 1980s (Metcalf, 1984). These studies revealed biological factor activities that stimulated immature hematopoietic progenitor cells (colony forming units or colony forming cells) to survive, proliferate and differentiate in semisolid agar cultures into morphologically distinct colonies and led to the purification of the first CSFs and subsequently to cloning of their receptors (reviewed by Nicola, 1989). Over the last 15 years, there has been a wealth of data demonstrating that cytokines act to stimulate proliferation and differentiation of both immature and maturing hematopoietic cells. *In vitro* culture systems demonstrated that some growth factors support the development of specific lineages, while others affect multiple lineages. EPO, for example, primarily regulates levels of erythrocyte progenitors, while IL-3 stimulates the growth of most lineages. This has led to the notion that both hematopoietic cell development and cytokines can be arranged in a hierarchical system with broadly acting cytokines, such as GM-CSF, stem cell factor and Fms-like tyrosine kinase 3 (FLT3), IL-2, IL-3 and IL-7 acting on the multipotential cells and lineage-specific cytokines acting on specific lineages (Metcalf, 1998; Figure 2). However, over time, and with increasingly

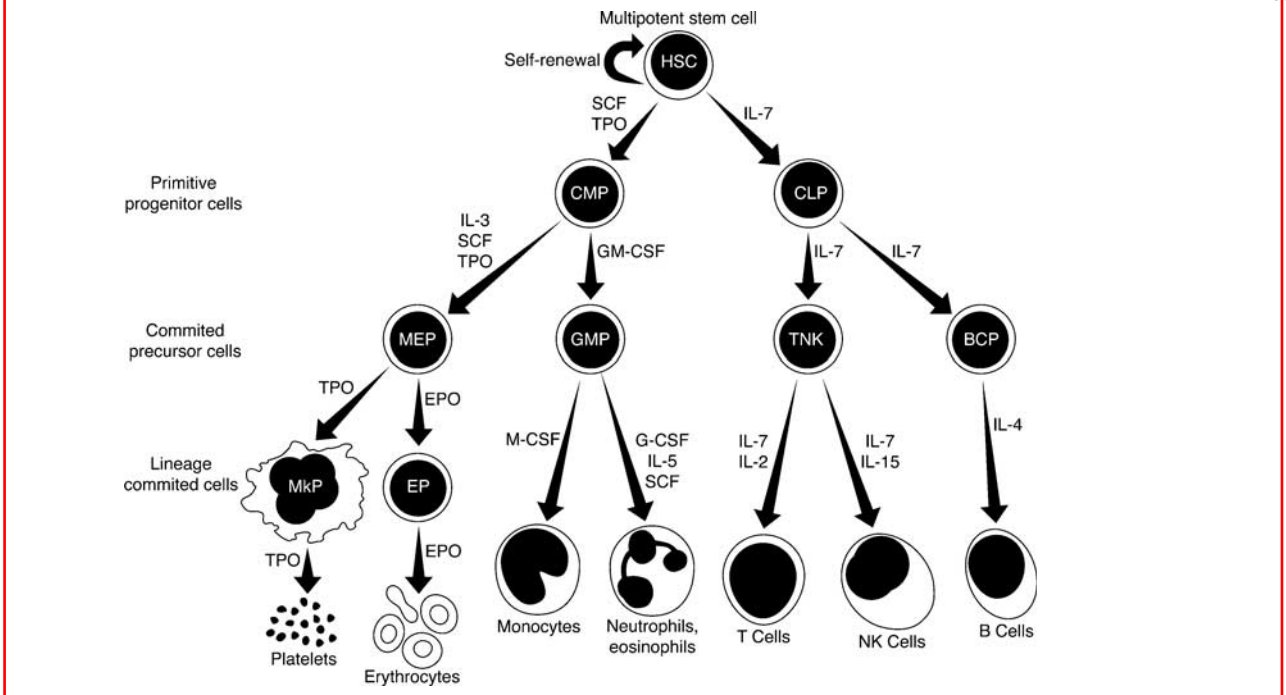

Figure 2 Hematopoiesis and the role of cytokines *in vivo*. Cytokines act on both multipotential progenitors and their committed offspring. Major points, pinpointed by gene-targeting studies, at which cytokines act to provide survival and proliferation signals and, in some cases, differentiative signals are indicated. BCP, B-cell progenitor; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; EP, erythroid progenitor; HSC, hematopoietic stem cell; GMP, granulocyte–macrophage progenitor; MEP, megakaryocyte erythroid progenitor; MkP, megakaryocyte progenitor; TNK, T-cell natural killer cell progenitor.

refined analysis of genetically modified animal models, it has become apparent that even the more 'lineage restricted' cytokines, like EPO, can have pleiotropic effects both within the hematopoietic system and in other tissues (Jegalian *et al*., 2002; Kertesz *et al*., 2004; Tsai *et al*., 2006). Because of their very low numbers, there have been few attempts to accurately quantify receptor numbers on different hematopoietic cell types (McKinstry *et al*., 1997). Nevertheless, it is likely that pleiotropic cytokine effects are the result of differential expression of cytokine receptors in different cell types, as well as availability of cytokines, synergistic interactions between cytokines and the differential attenuation of cytokine signals in a cell-type-specific manner by negative regulators. Knowledge of how specific cytokine signals lead to hematopoietic cell survival and proliferation has led to therapeutic intervention in disorders of blood cell production: the use of EPO and G-CSF to increase erythrocyte and neutrophil production, respectively, is a pharmaceutical landmark (Kaushansky, 2006). Cytokines act in concert with signalling pathways, epigenetic factors and critical transcription factors in lineage determination, and these regulatory mechanisms form the subject of other reviews in this series.

Cytokines: instructive or permissive?

Hematopoiesis is usually depicted as a hierarchy, with hematopoietic stem cells giving rise to precursors that are committed to one or more pathways. It is generally accepted that a variety of cytokines sustain hematopoiesis (Figure 2). Two general models for the role of cytokines in hematopoietic differentiation have been proposed: the instructive model and the stochastic model (reviewed by D'Andrea, 1994). In the instructive model, cytokines transmit specific signals to multipotential hematopoietic cells, directing their lineage commitment and differentiation. In the stochastic, or permissive, model, lineage commitment and terminal determination are intrinsically determined with cytokines providing permissive growth and survival signals. Their actions are permissive for the pathway of differentiation, as they promote cell viability and proliferation. In the stochastic model, hematopoiesis is seen as being primarily driven by a program of transcription factors that activate unique programs of gene expression and exert inhibitory effects on alternative lineage gene programs by directly antagonizing the action of opposing transcription factors (Orkin, 2000; Cantor and Orkin, 2001). The committed cell expresses cytokine receptors that provide survival, proliferation and differentiation signals. The instructive model recognizes the role of transcription factors but proposes that cytokine signalling also plays a fundamental role in lineage determination.

The stochastic hypothesis was first put forward by Till *et al*. (1964) based on examination of the fate of colony forming units-spleen colonies in transplanted mice, and many of the early experiments predated the discovery of the current plethora of hematopoietic cytokines. The most striking *in vitro* evidence that cytokines can directly

influence lineage choice came from studies of bipotential GM-colony forming cells (GM-CFCs). It was demonstrated that the GM-CFC could develop into macrophages when cultured with macrophage (M)-CSF and into granulocytes when cultured with stem cell factor or G-CSF, and that cloned daughter cells gave rise to different lineages depending on the cytokine environment (Metcalf and Burgess, 1982).

In support of the stochastic model, it was shown that ectopic expression of cytokine receptors in primary murine hematopoietic progenitors allowed ligand-dependant differentiation. Transduction of primary erythroid cells with a retrovirus encoding the M-CSFR enabled generation of erythroid colonies in response to M-CSF, and experiments with multipotential progenitors showed the same trend (McArthur *et al*., 1994; Pharr *et al*., 1994). The prolactin receptor, growth hormone receptor and c-MPL were all shown to be able to replace the requirement for EPOR in primary erythroid cell differentiation *in vitro* (Socolovsky *et al*., 1997; Goldsmith *et al*., 1998). Strong experimental support for the stochastic model came from the demonstration that ectopic expression of the prosurvival factor bcl-2 in certain hematopoietic cell lines resulted in hematopoietic differentiation in the absence of cytokines (Fairbairn *et al*., 1993). Furthermore, enforced expression of bcl-2 was shown to rescue T-cell defects in IL-7-deficient mice and monocyte defects in M-CSF-deficient mice (Akashi *et al*., 1997; Lagasse and Weissman, 1997; Maraskovsky *et al*., 1997).

Transgenic approaches were also used to test the role of cytokine receptors in lineage commitment. Mice that ubiquitously expressed a constitutively active form of EPOR had normal baseline hematopoiesis, and when EPO was administered, the multipotential progenitor pool expanded but the erythropoietic response was similar to that of wild-type animals (Kirby *et al*., 1996). In other experiments, a human GM-CSF receptor transgene expressed in EPOR-null fetal liver cells was shown to be able to restore erythropoiesis when cells were stimulated by GM-CSF (Hisakawa *et al*., 2001). In an elegant experiment, the cytoplasmic domain of the G-CSFR was targeted to the c-MPL locus to create mice bearing a chimeric receptor (Stoffel *et al*., 1999). This chimeric receptor was able to functionally substitute for the c-MPL receptor, despite lacking the cytoplasmic component of the c-MPL receptor. The mice did not have a c-MPL-null phenotype, and, moreover, there was no increase in granulocytic progenitors. This demonstration that G-CSFR could functionally replace c-MPL to support normal megakaryopoiesis and platelet formation strongly supported the permissive model. A mouse strain with a targeted mutation of the G-CSF receptor such that the cytoplasmic (signalling) domain of the G-CSFR was replaced with that of the EPOR was also studied (Semerad *et al*., 1999). The resulting chimeric receptor bound G-CSF but transmitted EPOR signals. Treatment of the mice with G-CSF did not alter the number of myeloid or erythroid progenitors in bone marrow, supporting the stochastic/permissive model. Interestingly, aspects of neutrophil function, such as chemotaxis and G-CSF-stimulated mobilization of neutrophils and hematopoietic progenitors to peripheral blood, remained impaired (Semerad *et al*., 1999; Semerad *et al*., 2002). Overall, these experiments suggest that the signals generated by specific receptors are not required for lineage commitment, but rather that the receptors provide nonspecific survival and proliferation signals, and, in some instances, maturation signals.

In favor of the instructive model, ectopic expression of lineage-restricted cytokines or their receptors in established hematopoietic cell lines was shown, in some cases, to result in lineage-specific gene induction (Just *et al*., 1991). In one example, a chimeric human IL-3/GM-CSFRα chain composed of the extracellular domain of human IL-3 and the cytoplasmic domain of GM-CSFR was introduced into murine IL-3-dependent FDCP-mix cells. When the cells were treated with human IL-3, the cells underwent granulocytic/monocytic differentiation, suggesting that the cytoplasmic GM-CSFRα chain delivered an instructive signal leading to lineage commitment (Evans *et al*., 1999). However, this cytokine-stimulated induction of cell fate was not observed when EPOR was overexpressed. Moreover, domains essential for generating a differentiation signal but dispensable for mitogenesis have been identified for several cytokine receptors (Fukunaga *et al*., 1993; Porteu *et al*., 1996). The most striking observations that support the instructive model are those from two groups showing that ectopic expression of cytokine receptors in multipotential cells can lead to alterations in developmental outcome (Kondo *et al*., 2000; Iwasaki-Arai *et al*., 2003). Kondo *et al*. (2000) studied common lymphoid progenitor cells, a cell type that normally gives rise to T-, B lymphocytes and natural killer cells, which had been engineered to ectopically express IL-2βR. When these cells were cultured on bone marrow stroma in the presence of IL-2, the cells rapidly generated granulocytes and macrophages, instead of only lymphoid cells. Based on the finding that low but detectable levels of GM-CSFR were expressed in hematopoietic stem cells but not in common lymphoid progenitors, it was hypothesized that downregulation of the GM-CSFR was among the initial events during the process of commitment to the common lymphoid progenitor. Therefore, the cells were transfected with GM-CSFR and treated with GM-CSF and again the cells were reprogrammed into myeloid cells. However, when the experiment was repeated with receptors for EPO or IL-7, no myeloid differentiation was obtained. This experiment strongly suggested that myeloid differentiation signals could emanate from the GM-CSF receptor. Similar results were obtained by a second group using IL-7Rα-null mice that were transgenic for the human GM-CSF receptor. The replacement of the IL-7Rα with the human GM-CSFRα caused lymphoid progenitors stimulated with human GM-CSF to differentiate into granulocytes, monocytes and dendritic cells (Iwasaki-Arai *et al*., 2003). Strikingly, however, the administration of the GM-CSF could not replace the function of the IL-7 receptor and restore T- and B-cell lymphopoiesis. Taken together, the results underscore the plasticity of the transition from multipotential stem cells to lymphoid

and myeloid progenitors and suggest that some cytokines can, within a certain window of opportunity, 'instruct' hematopoietic differentiation.

Knockouts of cytokine receptors

Gene targeting studies have provided important insights into the functionally distinct roles of cytokine receptors. Many receptor subunits have been altered by targeted gene disruption to create mice genetically deficient in that receptor (Table 1). In general, the phenotypes are consistent with conclusions drawn from *in vitro* cell culture studies, although there have been some surprises. EPO- and EPOR-null fetuses died at mid-gestation due to severe anemia; however, bone marrow cultures showed that erythroid progenitor cells were present (Wu *et al*., 1995; Kieran *et al*., 1996; Lin *et al*., 1996). Moreover, primitive (yolk sac) erythropoiesis was present in EPO- and EPOR-null embryos, suggesting that another growth factor, possibly TPO, could support erythropoiesis in the yolk sac (Kieran *et al*., 1996). Surprisingly, mice with null mutations of GM-CSF or the βc chain (the signalling component of the GM-CSF receptor complex) had normal numbers of myeloid progenitors (Stanley *et al*., 1994; Nishinakamura *et al*., 1995; Robb *et al*., 1995). Analysis of mice in which either TPO or c-MPL was deleted revealed that, in addition to its activity as a

Table 1 Phenotypes of mouse strains with genetically engineered deletions of class 1 cytokine receptors

Receptor	*Ligand*	*Phenotype*	*Reference*
GH-R family			
EPO-R	Erythropoietin	Embryonic lethal, cardiac (ventricular) hypoplasia, failure of definitive erythropoiesis, partial defect yolk sac erythropoiesis, normal development BFU-E, CFU-E	Kieran *et al*. (1996), Lin *et al*. (1996) and Wu *et al*. (1999)
c-MPL (TPO-R)	Thrombopoietin	Viable, reduced hematopoietic stem cells, reduced Meg-CFC and megakaryocytes, thrombocytopenia	Alexander *et al*. (1996), Gurney *et al*. (1994)
G-CSF-R	G-CSF	Viable, chronic neutropenia, deficiency in GM-CFC and G-CFC, impaired neutrophil mobility	Liu *et al*. (1996)
β_c family			
β_c	IL-3, IL-5, GM-CSF	Viable, eosinopenia, alveolar proteinosis	Nishinakamura *et al*. (1995) and Robb *et al*. (1995)
β_{IL-3}	IL-3	Viable, normal	Nicola *et al*. (1996)
IL-3Rα	IL-3	Viable, normal	Ichihara *et al*. (1995)
IL-5Rα	IL-5	Viable, reduced B-1 cells, eosinopenia	Yoshida *et al*. (1996b)
GM-CSFRα	GM-CSF	NA	
gp130 family			
gp130	LIF, OSM, CNTF, IL-11, IL-6, CTF1, CTF2, CLCF1	Mid to late fetal lethality, multiple defects, including cardiac (ventricular) hypoplasia, abnormal placentation, reduced fetal liver hematopoiesis and reduced primordial germ cell number conditional deletion: female infertility and neurological, cardiac, hematopoietic, immunological, hepatic and lung defects,	Yoshida *et al*. (1996a) and Betz *et al*. (1998)
IL-6Ra	IL-6	NA	
IL-11Ra	IL-11	Viable, female infertility	Nandurkar *et al*. (1997) and Robb *et al*. (1998)
LIFRα	LIF, CNTF, CLCF1	Neonatal lethality, placental, skeletal, neural and metabolic defects, motor neuron deficit	Li *et al*. (1995) and Ware *et al*. (1995)
OSM-R	OSM	Viable, reduced erythrocytes and platelets	Tanaka *et al*. (2003)
CNTF-R	CNTF	Neonatal lethality, severe motor neuron deficit	DeChiara *et al*. (1995)
γc family			
γc	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	Severe combined immunodeficiency	DiSanto *et al*. (1995)
IL-2Rα		Polyclonal T- and B-cell proliferation, autoimmune disease	Willerford *et al*. (1995)
IL-2Rβ	IL-2, IL-15	Viable, dies around 12 weeks, spontaneous T-cell activation, dysregulated B-cell differentiation and immunoglobulin secretion, myeloproliferative disorder	Suzuki *et al*. (1997)
IL-4Rα	IL-4, IL-13	Viable, defective Th2 cell development and response	Barner *et al*. (1998)
IL-7Rα	IL-7, TSLP	Viable, T- and B-cell cytopenia, no γδ T cells	Peschon *et al*. (1994) and Maki *et al*. (1996)
IL-9R	IL-9	NA	
IL-13Rα	IL-13	NA	
IL-15R	IL-15	Viable, lymphopenia, reduced lymphocyte homing, defective memory T-cell and NK-cell development	Lodolce *et al*. (1998)
IL-21R	IL-21	Viable, altered serum immunoglobulin levels, Th2 responses	Ozaki *et al*. (2002) and Frohlich *et al*. (2007)

Abbreviations: CNTF, ciliary neurotrophic factor receptor; CLCF, cardiotrophin-like cytokine factor; EPOR, erythropoietin receptor; GM-CSFR, granulocyte macrophage colony-stimulating factor receptor; IL, interleukin; LIFR, leukemia inhibitory factor receptor; NA, not available; NK, natural killer; OSM, oncostatin M; TPO, thrombopoietin.

regulator of the megakaryocytic lineage, TPO also has non-redundant activity on stem cells. The mice had around 10% of the normal number of platelets, reduced numbers of megakaryocytes and reduced numbers of hematopoietic stem cells as well as markedly reduced stem cell expansion after bone marrow transplantation (Gurney *et al*., 1994; Alexander *et al*., 1996; Carver-Moore *et al*., 1996; Solar *et al*., 1998; Fox *et al*., 2002). Disruption of the IL-7Rα led to early death due to severe lymphocyte hypoplasia, with deficiencies of B cells, T cells and natural killer cells, but the development of the earliest unipotent T- and B-cell precursors was found to be normal (Peschon *et al*., 1994; Maki *et al*., 1996). Gene targeting studies also revealed novel functions for cytokines, such as a role for GM-CSF and its receptor signalling in pulmonary physiology through regulation of alveolar macrophages and for IL-11Rα signalling in induction of the uterine response to embryo implantation (Nishinakamura *et al*., 1995; Robb *et al*., 1995; Robb *et al*., 1998). Mice with deletion of two or more cytokine receptors and/or cytokines have also been generated. The outcome of these genetic crosses has yielded few surprises, with the phenotypes generally being additive (Liu *et al*., 1997; Seymour *et al*., 1997; Gainsford *et al*., 1999; Scott *et al*., 2000; Kaushansky *et al*., 2002). The phenotypes of mice bearing genetic deletion of cytokine receptors contrast with those in which transcription factors are deleted, such as stem cell leukemia (SCL) and GATA binding protein (GATA-1). Unlike the cytokine receptor-null mice, deletion of key transcription factors often results in a complete block of one or more hematopoietic cell lineages (Shivdasani and Orkin, 1996).

Targeted mutant mouse models provide an incomplete account of the importance of cytokine signalling in hematopoiesis, because functional redundancies among family members may mask the relevance of individual components. This was demonstrated for the G-CSFR-null mouse. Mice with a null mutation of the G-CSFR, like G-CSF-null mice, had ineffective granulopoiesis with chronic neutropenia, a decrease in mature myeloid elements in their bone marrow and diminished neutrophil release from bone marrow (Lieschke *et al*., 1994; Liu *et al*., 1996; Semerad *et al*., 2002). Surprisingly, however, the bone marrow of G-CSFR-deficient mice has only a modest reduction in the committed myeloid progenitors. It was reasoned that compensatory mechanisms, such as increases in the levels of other cytokines, induced by the severe neutropenia in G-CSFR-null mice might be masking the role of G-CSFR in myeloid development. Therefore, the function of G-CSFR-null bone marrow was tested in a competitive repopulation assay. This demonstrated that G-CSFR signals to regulate production not only of mature cells but also of early multipotential myeloid progenitors (Richards *et al*., 2003).

Overall, the results of the gene-targeting studies in mice generally do not support an instructive role for cytokine signalling in hematopoiesis. For example, the EPO- and EPO-R-deficient mouse phenotype, in which erythroid progenitors were present in fetal liver, indicated that this cytokine is not playing an instructive role in erythroid lineage commitment. Other knockout experiments with lineage-restricted cytokines and their receptors also demonstrate that lineage commitment decisions can be made in the absence of these signals. A caveat to this conclusion is that in such experiments compensatory pathways cannot be ruled out. Compound mutational analysis has gone some way to resolving the issue of compensatory mechanisms, and these studies are ongoing, but to date the compound phenotypes have not resulted in the absence of specific lineages.

Conclusions

Cytokine receptors provide signals that enable the survival and proliferation of multipotential and mature hematopoietic cells. The class 1 family of cytokine receptors share a number of properties, including receptor components, receptor structure and positive and negative downstream signalling pathways. Studies with knockout mice have pointed to previously unrecognized physiological roles for some receptors and have revealed unique spectra of activity for individual receptors. A wealth of evidence, reviewed elsewhere in this series, supports the role of transcription factors as the critical positive and negative drivers of hematopoietic differentiation. In addition to their controlling role in survival and proliferation and maturation of hematopoietic lineages, there is accumulating evidence that some, but not all, cytokine receptors can transduce a genuine lineage-determining signal at some points in hematopoiesis, especially at the point of divergence of the myeloid and lymphoid lineages. Further studies are needed to fully explore the scope of instructive signalling by cytokines and to understand the mechanisms.

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