The Network of Hematopoietic Cytokines

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Abstract. **Cell viability, multiplication, and differentiation to the various hematopoietic cell lineages are induced by a multigene cytokine family, and hematopoiesis is controlled by a network of interactions between these cytokines. This network includes positive regulators such as colony-stimulating factors and interleukins, and negative regulators such as transforming growth factor-β and tumor necrosis factor. The functioning of the network requires an appropriate balance between positive and negative regulators, and the selective regulation of programed cell death (apoptosis) by interaction of cytokines with their receptors. The cytokine network, which has arisen during evolution, allows considerable flexibility, depending on which part of the network is activated, and the ready amplification of response to a particular stimulus. This amplification occurs by autoregulation and transregulation of genes for the hematopoietic cytokines. There is also a transregulation by these cytokines of cytokine receptors. In addition to the flexibility of this network, both for response to present day infections and to infections that may develop in the future, a network may also be necessary to stabilize the whole system. The existence of a network and the cytokine-receptor regulation of apoptosis has to be taken into account in the clinical use of cytokines for therapy. Cytokines that regulate hematopoiesis induce the expression of genes for transcription factors. Cytokine signaling through transcription factors can thus ensure the autoregulation and transregulation of cytokine and receptor genes that occur in the network. Interactions between the cytokine network and transcription factors can also ensure production of specific cell types and stability of the differentiated state.**

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The Hematopoietic Cytokines

Normal hematopoietic cells are dependent on molecules produced by other cells (cytokines) to maintain their viability and to induce cell multiplication and differentiation to different lineages. This phenomenon was first demonstrated in a cell culture system in which normal cells from blood-forming tissues were cultured and cloned in liquid medium with feeder layers of other cell types such as embryo fibroblasts (1). This culture system with a feeder layer (1) was then applied to the cloning cells in semisolid medium containing agar (2, 3) or methyl cellulose (4). The colonies in these semisolid media contained macrophages and granulocytes. The inducers of colony formation were secreted by the feeder cells (2). This led to their discovery in conditioned media (4, 5), and these media were then used to purify the inducers. The continued presence of the inducers of colony formation was required to ensure development of the macrophage and granulocyte colonies (6). This bioassay was used to follow purification of the different factors that can induce colony formation and to determine the biological activity of cloned genes for these factors.

In cells belonging to the myeloid cell lineages, four different proteins that induce cell multiplication and can thus induce the formation of clones (colony inducing proteins) have been identified (7–10). These proteins have been given various names. After they were first discovered in cell culture supernatant fluids (4, 5), the first inducer identified was called *mashran gm* from the Hebrew word meaning "to send forth" with the initials for granulocytes and macrophages (11). This and other growth-inducing proteins were then renamed, being called such things as macrophage and

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granulocyte inducers (12) Type 1 (MGI-1) (13). They are now called colony-stimulating factors (CSFs) (14), though one protein is called more specifically interleukin-3 (IL-3) (15) (Table I). Of these four colony-stimulating factors, macrophage CSF (M-CSF) induces the development of clones with macrophages, granulocyte CSF (G-CSF) clones with granulocytes, granulocyte-macrophage CSF (GM-CSF) clones with granulocytes, macrophages, or both macrophages and granulocytes, and the fourth, IL-3, clones with macrophages, granulocytes, eosinophils, mast cells, erythroid cells, or megakaryocytes (Table I). These proteins induce cell viability and cell multiplication (reviewed in 9, 10, 16) and enhance the functional activity of mature cells (reviewed in 14). Cloning of genes from mice and humans for IL-3, GM-CSF, M-CSF, and G-CSF has shown that these proteins are coded for by different genes (17). It appeared unlikely that a CSF that induces cell multiplication is also a differentiation inducer whose action includes stopping cell multiplication in mature cells. Indeed, proteins that act as myeloid cell differentiation inducers and do not have colony-stimulating activity have been identified and called MGI Type 2 (MGI-2), D-factor, and differentiation-inducing factor (DIF) (reviewed in 10). MGI-2 was identified as IL-6 (18), D-factor was identified as a protein that has also been called leukemia inhibitory factor (LIF) and human interleukin for DA cells (HILDA) (19, 20), and DIF was found to be a form of tumor necrosis factor (TNF) (21, 22). IL-6 can induce viability and differentiation of normal myeloid precursors, but LIF and TNF, which induce differentiation in certain clones of myeloid leukemic cells, do not induce viability or differentiation of normal myeloid cells (reviewed in 10) (Table I).

Table I. Induction of Growth and Differentiation of Normal Myeloid Precursor Cells by Different Hematopoietic Regulatory Proteins

Nomenclature	Induction of colonies[a]	Induction of differentiation	
		Direct	Indirect[b]
MGI-1M = CSF-1 = M-CSF	+(M)	–	+
MGI-1G = G-CSF	+(G)	–	+
MGI-1GM = GM-CSF	+(G, M)	–	+
IL-3	+(G, M, others)	–	+
MGI-2 = IL-6	–	+(G, M, Meg)	–
IL-1	–	–	+(G, M, Meg)
D-factor = HILDA = LIF	–	CD	CD
DIF = TNF	–	CD	CD

[a] Colonies with macrophages (M); granulocytes (G); granulocytes and macrophages (G, M); and granulocytes, macrophages, eosinophils, mast cells, megakaryocytes, or erythroid cells (G, M, others); megakaryocytes (Meg) (10).

[b] The four CSFs, including IL-3 and IL-1, induce production of IL-6. CD = cell death.

References in (10).

In addition to IL-6 and LIF, three other cytokines, oncostatin M (23), interleukin-11 (IL-11) (24), and ciliary neurotrophic factor (CNTF) (25), show some structural and functional similarities and use the same cell surface signal-transducing protein gp130 as IL-6 and LIF (26). None of these cytokines have CSF activity on normal hematopoietic cells but oncostatin M can induce differentiation in M1 myeloid leukemic cells (23) and IL-11 synergizes with IL-3 in normal hematopoiesis (24). It will be interesting to determine whether oncostatin M, IL-11, or CNTF can exert a viability-promoting effect on normal hematopoietic cells as occurs with IL-6.

In addition to these cytokines, transforming growth factor-β1 (TGF-β1) can inhibit normal hematopoietic colony formation induced by different CSFs and can also inhibit IL-6 induced differentiation in leukemic cells (27–30). Like TGF-β1, TNF can also inhibit induction of colonies by normal hematopoietic cells induced by different CSFs. TNF and TGF-β1 can thus act as negative regulatory cytokines which can antagonize the action of the positive cytokines on normal hematopoietic cells. Both TGF-β1 and TNF can also induce programed cell death (apoptosis) in myeloid leukemic cells (31, 32) and this effect of TGF-β1 can be suppressed by IL-6, G-CSF, GM-CSF, or IL-3 (31). This again demonstrates the functional antagonism between the positive and negative cytokines that regulate the normal hematopoietic system.

Cytokine Network

The above results show that the different cytokines comprise a family of hematopoietic regulatory proteins, some of which show structural similarities, similarities in their surface receptors, sharing of signal-transducing surface molecules, and overlapping activities on viability, growth, and differentiation of hematopoietic cells, as well as in other nonhematopoietic cell systems (26, 33, 34). This indicates that the cytokines have evolved from ancestral genes presumably by gene duplications and modifications, thus creating a family of related proteins. This also provides the hematopoietic system with significant flexibility, since more than one type of cytokine can positively or negatively affect hematopoiesis. Furthermore, within the hematopoietic system these cytokines act in a network. This has clearly been demonstrated by the ability of the CSFs, IL-3, and IL-1 to induce the production of IL-6 in normal hematopoietic cells, thus creating a coupling system between growth and differ-

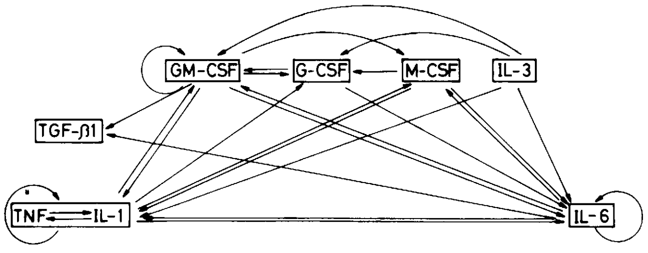

Figure 1. Network of interactions between hematopoietic regulatory proteins.

entiation (10, 35–37). In addition, in different types of myeloid leukemic cells, IL-6 and GM-CSF can positively autoregulate their own induction (38) and can also induce expression of positive cytokines including M-CSF, GM-CSF, IL-6, IL-1α and IL-1β as well as the negative cytokines TNF and TGF-β1 (39) (Fig. 1). LIF can also induce expression of IL-6 in myeloid leukemic cells (40). Although normal myelomonocytic cells can produce G-CSF, we have not found G-CSF induction in the M1 and 7-M12 myeloid leukemic cells (39) (Table II). This shows that myeloid leukemic cells can display abnormalities in parts of the cytokine network while maintaining the other parts. Another example for this differential disturbance of parts of the cytokine network is the inability of Hox-2.4 transfected M1 leukemic cells to express the GM-CSF gene when cultured with IL-6 whereas the expression of the IL-6 gene was unaffected (41).

IL-6- and GM-CSF-induced differentiation was also associated with expression of genes for some transcription factors including c-*jun*, *jun*-B, c-*fos* (42) which can participate in the activation of other genes during differentiation including the genes for other cytokines. Another transcription factor Egr-1/Zif 268 was expressed in GM-CSF inducible leukemic cells but not in IL-6 inducible leukemic cells (42). This shows that different cytokines can also induce differentially the expression of different transcription factors, and this may result in differences in expression of specific cell functions in the different cell types. The network therefore allows for amplification of the signals leading to increased hematopoiesis under stress conditions, such as infections, resulting in production of some cytokines such as IL-1, IL-6, G-CSF, M-CSF, GM-CSF, and TNF, and possibly also other cytokines, which can then amplify the system by switching on other cytokines.

The cytokine network allows not only amplification of signals but can also facilitate the indirect activity of cytokines by inducing the production of other cytokines. IL-1 can induce differentiation in myeloid leukemic cells indirectly by inducing the production of IL-6 (43). IL-1 can indirectly stimulate the growth of myeloma cells through induction of IL-6 (44). IL-2-induced differentiation of human B cells is also mediated by the IL-6 induced in these cells (45). GM-CSF and IL-3 can induce the *in vivo* differentiation of myeloid leukemic cells that do not respond to these cytokines *in vitro*, presumably by the IL-6 induced *in vivo* by these cytokines (46). Inhibition of *in vivo* production of different cytokines, including IL-6, by glucocorticoid hormones such as hydrocortisone inhibits this indirectly induced *in vivo* differentiation of myeloid leukemic cells by GM-CSF (47).

Another feature of the network involving an indirect action of cytokines is the induction of cytokines giving switch off signals to the system to ensure that the positive signals are not amplified beyond a certain limit. This is ensured by the production of TNF and TGF-β1 by GM-CSF or IL-6 (39), as well as by induction of other inhibitory molecules including β-interferon (48) and prostaglandin E1 (49). The role of TGF-β in negatively controlling normal hematopoiesis (27–30) is further demonstrated by the ability of antisense oligonucleotides to TGF-β1 to release early hematopoietic progenitors from quiescence (50). Another cytokine that can also participate in this network as a negative cytokine is interleukin-10 (IL-10), which is produced by activated macrophages and can suppress production of inflammatory cytokines including IL-1, IL-6, and TNF by LPS (51). This phenomenon is not peculiar to the hematopoietic system, and it has been shown that IL-6 can indirectly suppress the growth of human lung cancer cells by the induced TGF-β1 (52); IL-1 and TNF suppress the growth of certain types of tumor cells via induction of IL-6 (53), and the antiviral activity of TNF in fibroblasts is mediated by the production of β-interferon (54). Such indirect effects of cytokines *in vivo* can also account for the radioprotective effects of IL-1 and TNF in mice which is mediated by IL-6 (55) and the IL-3-induced acute phase response which is also mediated by IL-6

Table II. Expression of Cytokines in Normal and Differentiating Leukemic Myeloid Cells

	Expression							
Cells	IL-6	IL-1α	IL-1β	GM-CSF	M-CSF	TNF	TGF-β1	G-CSF
Normal myelomonocytic	+	+	+	+	+	+	+	+
Differentiating myeloid leukemic cells (M1 and 7M12)	+	+	+	+	+	+	+	−

Table III. Expression of Cytokine Receptors in Myeloid Leukemic Cells Before and After Induction of Differentiation

Leukemic cells	Inducer of differentiation	Cytokine receptor expression				
		IL-6	G-CSF	GM-CSF	IL-3	M-CSF
M1 (Clone 12)	None	+	+	−	−	−
	IL-6	+	+	−	+	+
7-M12	None	−	+	+	+	−
	GM-CSF	−	+	+	+	−

(56). The adverse effects of *in vivo* administration of IL-2 may also be due to the induced release of TNF, IL-1β, IL-6 and γ-interferon into the circulation (57, 58). The above effects on the cytokine network and, in turn, their indirect effects have to be taken into account when cytokines are injected, so as to avoid undesired effects of the cytokines *in vivo*.

Cytokine Receptors and the Cytokine Network

The interaction between different hematopoietic cytokines and their respective receptors in the myeloid system generates the signals which can activate or suppress different genes leading to induction of cell viability, multiplication, and differentiation (by the positive cytokines), or to their suppression (by the negative cytokines). As with the cytokines, the receptors also belong to a family of related proteins and some of them share the signal-transducing gp130 protein and certain of the proteins acting as the ligand binding chains (26, 59, 60). The amplification or suppression of the signals generated by the positive or negative cytokines is associated not only with the induction of other cytokines but also with regulating expression of cytokine receptors. During induction of differentiation with IL-6, myeloid leukemic cells are induced to express surface receptors for M-CSF and IL-3 which were not expressed before differentiation (61) (Table III). This enables the IL-6-treated cells, which show a factor-dependent state, to maintain viability by adding IL-3 or M-CSF for which they have developed surface receptors (61). Similarly, TGF-β1 that can inhibit cytokine expression can also decrease the expression of receptors for cytokines, thus ensuring the feedback inhibition of hematopoiesis at the level of both cytokines and receptors (62, 63). However, the network also allows for the separate regulation of cytokine genes and cytokine receptor genes. This is demonstrated in the IL-6-treated M1 leukemic cells that develop IL-3 receptors during differentiation but do not express IL-3, and although even before differentiation the cells have G-CSF receptors, they do not express G-CSF (39) (Table II and III). Similarly, other leukemic cells (7-M12), which are induced to differentiate with GM-CSF, are induced to express IL-6 and M-CSF (39) but do not express IL-6 (64) or M-CSF (c-*fms*) receptors (39) (Table II and III).

Evolution and the Cytokine Network

What one finds in nature today are the consequences of biological evolution. What is present is not only what the body uses today, but also what may be useful for further evolution. The production of different types of hematopoietic cells with a limited life span, both under normal conditions and in different emergency situations (i.e., infections, wound healing, and various diseases), requires a system with considerable plasticity. The development during evolution of a multigene family of different interacting cytokines that function in a network is therefore more useful for the functions required today, and for adaptation to functions that may be required in the future, than the existence of only independent cytokines with high specificity would be. The lack of function and flexibility of the latter would be lethal. The evolution of a family of cytokines, some of which have overlapping functions, is thus a useful safeguard so that if one cytokine does not function effectively under certain conditions another can take over. The multigene family of proteins which now exists to regulate the development of hematopoietic cells in health and disease is an effective system that contains such safeguards. In addition to the results discussed in previous sections, another example of safeguards is that the four CSFs, and other cytokines such as IL-1 and IL-6 which do not induce colonies, all function as viability factors by inhibiting programed cell death (65). The use of alternative pathways to regulate different functions and to prevent programed cell death provides a useful safeguard to regulate the number of cells in hematopoiesis. In addition to the advantages of a network in providing flexibility, safeguards, and evolutionary advantages, a network may also be necessary to stabilize the whole system.

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