Cytokine

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Cytokines are low-molecular weight regulatory proteins or glycoproteins secreted by white blood cells and various other cells in the body in response to a number of stimuli. These proteins assist in regulating the development of immune effector cells, and some cytokines possess direct effector functions of their own.

- The susceptibility of the target cell to a particular cytokine is determined by the presence of specific membrane receptors.
- In general, the cytokines and their receptors exhibit very high affinity for each other, with dissociation constants ranging from 10^{-10} to 10^{-12} M; since their affinities are so high, cytokines can mediate biological effects at picomolar concentrations.
- A particular cytokine may bind to receptors on the membrane of the same cell that secreted it, exerting *autocrine* action; it may bind to receptors on a target cell in close proximity to the producer cell, exerting *paracrine* action; in a few cases, it may bind to target cells in distant parts of the body, exerting *endocrine* action.
- Cytokines bind to specific receptors on the membrane of target cells, triggering signal-transduction pathways that ultimately alter gene expression in the target cells.
- For example, cytokines produced by activated T_H cells can influence the activity of B cells, T_C cells, natural killer cells, macrophages, granulocytes, and hematopoietic stem cells, thereby activating an entire network of interacting cells.

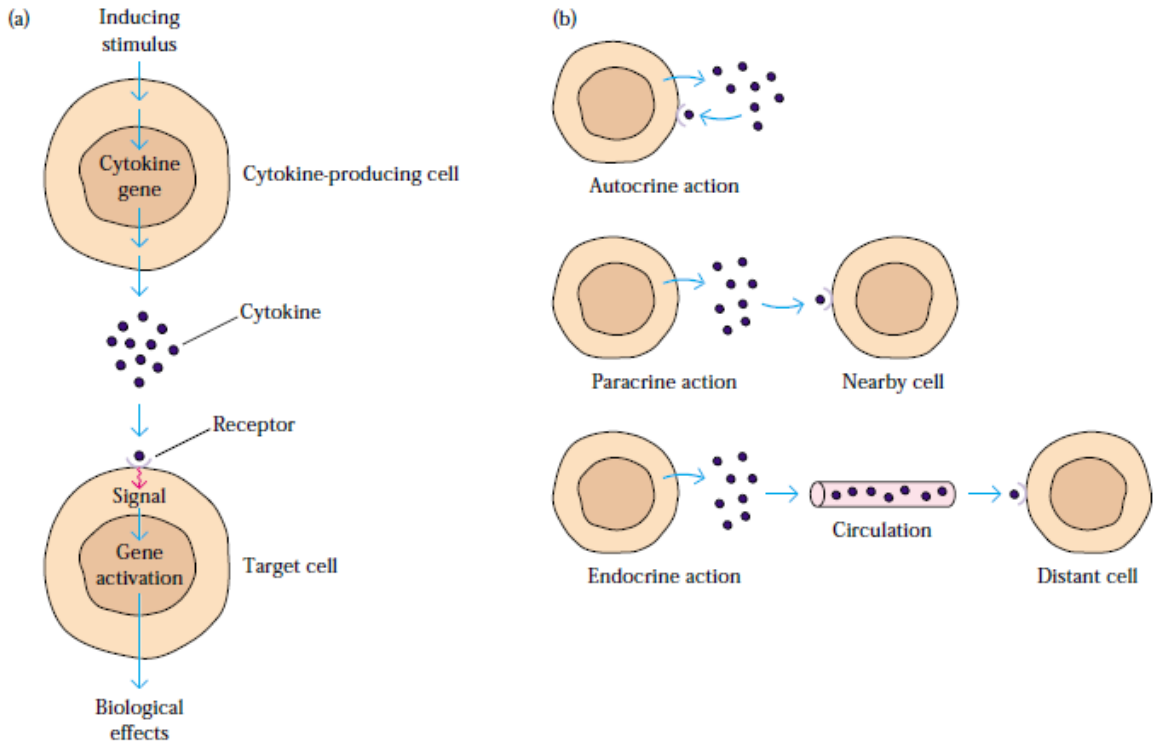


Figure: (a) Overview of the induction and function of cytokines. (b) Most cytokines exhibit autocrine and/or paracrine action; fewer exhibit endocrine action.

Few terminologies related to cytokine action:

A. **Pleotropism:** A given cytokine that has different biological effects on different target cells has a pleiotropic action.
B. **Redundancy:** Two or more cytokines that mediate similar functions are said to be redundant; redundancy makes it difficult to ascribe a particular activity to a single cytokine.
C. **Synergism:** Cytokine synergism occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of the individual cytokines.
D. **Antagonism**: In some cases, cytokines exhibit antagonism; that is, the effects of one cytokine inhibit or offset the effects of another cytokine.
E. **Cascade induction**: It occurs when the action of one cytokine on a target cell induces that cell to produce one or more other cytokines, which in turn may induce other target cells to produce other cytokines.

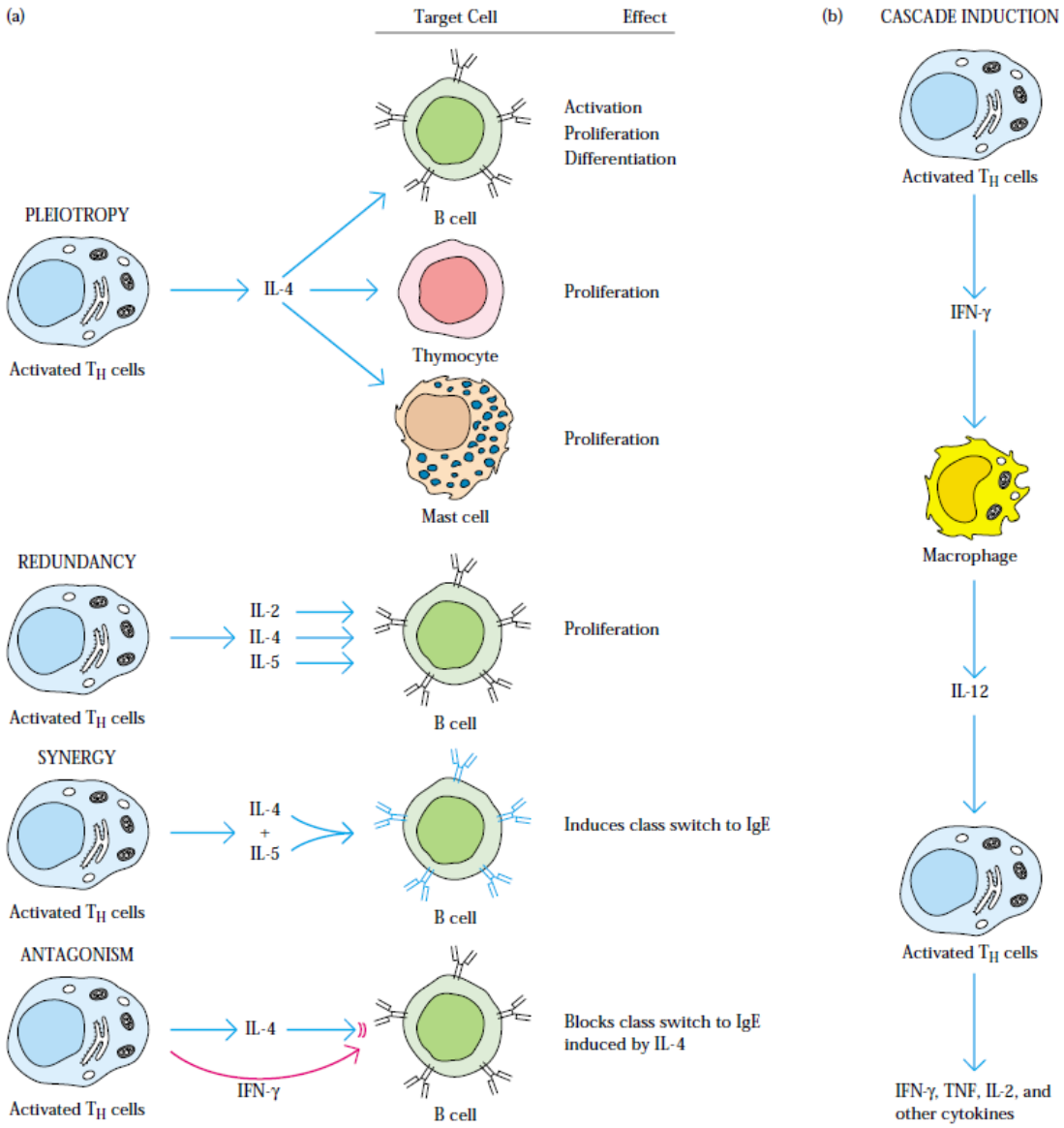


Figure: Attributes of cytokine action- (a) pleiotropy, redundancy, synergy (synergism), antagonism, and (b) cascade induction

Interleukines/chemokines:

- Many cytokines are referred to as *interleukins*, a name indicating that they are secreted by some leukocytes and act upon other leukocytes. Interleukins 1–25 have been identified.
- Some cytokines are known by common names, including the interferons and tumor necrosis factors.
- Another subgroup of cytokines, the *chemokines*, a group of low-molecular weight cytokines that affect chemotaxis and other aspects of leukocyte behavior. These molecules play an important role in the inflammatory response.

Structural attributes of cytokines:

- Cytokines generally have a molecular mass of less than 30 kDa.
- Structural studies have shown that the cytokines share a similar polypeptide fold, with four α-helical regions (A–D) in which the first and second helices and the third and fourth helices run roughly parallel to one another and are connected by loops.
- In the figure below, (a, Left) topographical representation of the primary structure of IL-2 showing α -helical regions (α and A–D) and connecting chains of the molecule; (a, Right) proposed three-dimensional model of IL-2.
- In figure (b), ribbon model of IL-4 deduced from x-ray crystallographic analysis of the molecule.
- In (a) and (b) the α helices are shown in red and the β sheets in blue.
- The structures of other cytokines belonging to the hematopoietin family are thought to be generally similar.

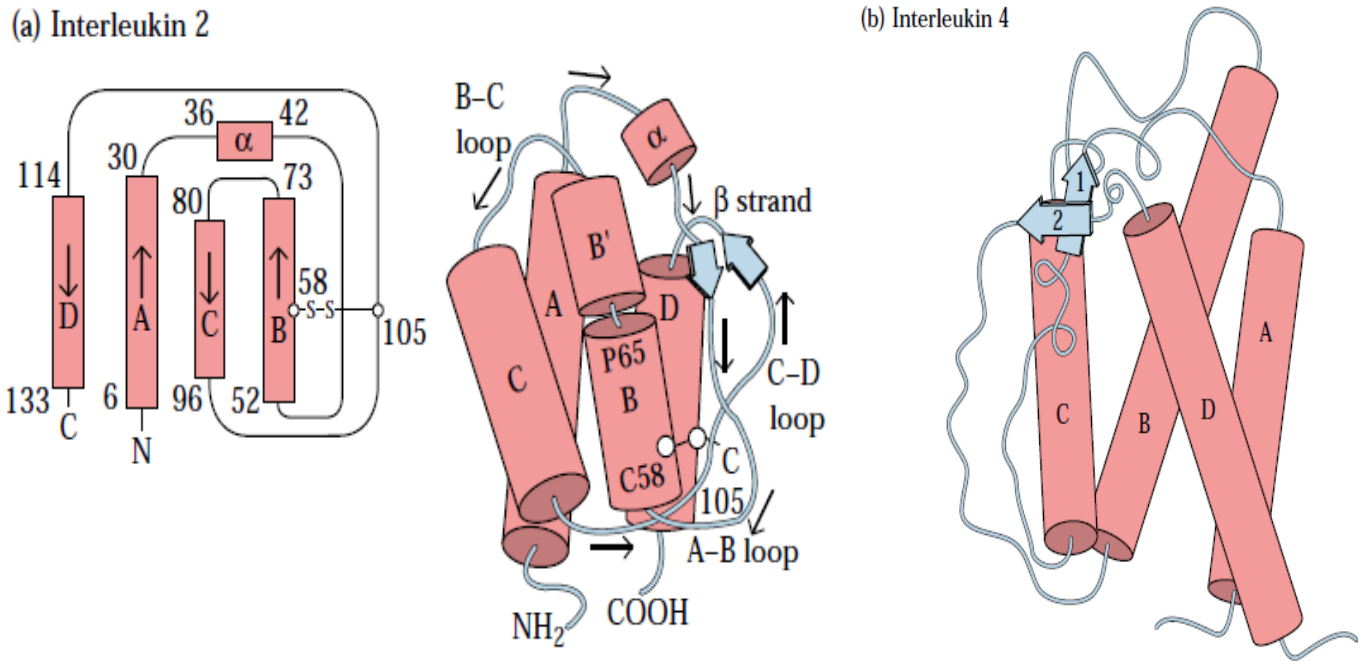


Figure: Several representations of structures in the hematopoietin family

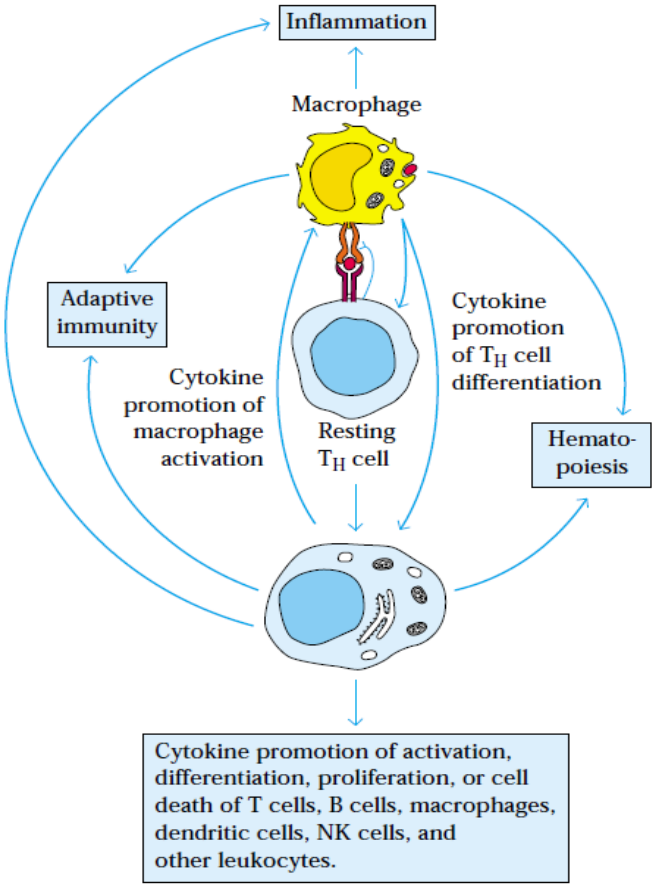


Figure: Interaction of Ag with MΦ and the subsequent activation of resting T_H cells leads to release of numerous cytokines (blue arrows), generating a complex network of interacting cells in the immune response.

Functional attributes:

- Although a variety of cells can secrete cytokines, the two principal producers are the T_H cell and the macrophage.
- Among the numerous physiologic responses that require cytokine involvement are development of cellular and humoral immune responses, induction of the inflammatory response, regulation of hematopoiesis, control of cellular proliferation and differentiation, and the healing of wounds.
- In *in vivo* condition, a target cell is exposed to surroundings containing a mixture of cytokines, whose combined synergistic or antagonistic effects can have very different consequences.
- In addition, cytokines often induce the synthesis of other cytokines, resulting in cascades of activity.

Remark:

Although the immune response to a specific antigen may include the production of cytokines, it is important to remember that cytokines act in an antigen-nonspecific manner i.e. they affect whatever cells they encounter that bear appropriate receptors and are in a physiological state that allows them to respond.

Cytokine*	Secreted by**	Targets and effects
SOME CYTOKINES OF INNATE IMMUNITY		
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); l iver (induction of acute phase proteins)
Tumor Necrosis Factor-α (TNF-α)	Macrophages	Vasculature (inflammation); liver (induction of acute phase proteins); loss of muscle, body fat (cachexia); induction of death in many cell types; neutrophil activation
Interleukin 12 (IL-12)	Macrophages, dendritic cells	NK cells; influences adaptive immunity (promotes T_H1 subset)
Interleukin 6 (IL-6)	Macrophages, endothelial cells	Liver (induces acute phase proteins); influences adaptive immunity (proliferation and antibody secretion of B cell lineage)
Interferon α (IFN-α) (This is a family of molecules)	Macrophages	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
Interferon β (IFN-β)	Fibroblasts	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK cells
SOME CYTOKINES OF ADAPTIVE IMMUNITY		
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote AICD. NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T_H2 cells; mast cells	Promotes T_H2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T_H2 cells	Eosinophil activation and generation
Interleukin 25 (IL-25)	Unknown	Induces secretion of T_H2 cytokine profile
Transforming growth factor β (TGF-β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgE; inhibits macrophages
Interferon γ (IFN-γ)	T_H1 cells; $CD8^+$ cells; NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation

What keeps the nonspecific cytokines from activating cells in a nonspecific fashion during the immune response?

- One way in which specificity is maintained is by careful regulation of the expression of cytokine receptors on cells.
- Often cytokine receptors are expressed on a cell; only after that cell interacts with antigen. In this way cytokine activation is limited to antigen-activated lymphocytes.
- Another means of maintaining specificity may be due to a need for direct interaction between the cytokine-producing cell and the target cell to trigger cytokine secretion, thus ensuring that effective concentrations of the cytokine are released only in the vicinity of the intended target.
- In the case of the T_H cell, a major producer of cytokines, close cellular interaction occurs when the T-cell receptor recognizes an antigen-MHC complex on an appropriate antigen-presenting cell, such as a macrophage, dendritic cell or B lymphocyte.
- Cytokines secreted at the junction of these interacting cells reach high enough local concentrations to affect the target APC but not more distant cells.
- In addition, the half-life of cytokines in the bloodstream or other extracellular fluids into which they are secreted is usually very short, ensuring that they act for only a limited period of time and thus over a short distance.

Cytokine receptors:

Receptors for the various cytokines are quite diverse structurally, but almost all belong to one of five families of receptor proteins

- Immunoglobulin superfamily receptors
- Class I cytokine receptor family (hematopoietin receptor family
- Class II cytokine receptor family (interferon receptor family)
- TNF receptor family
- Chemokine receptor family

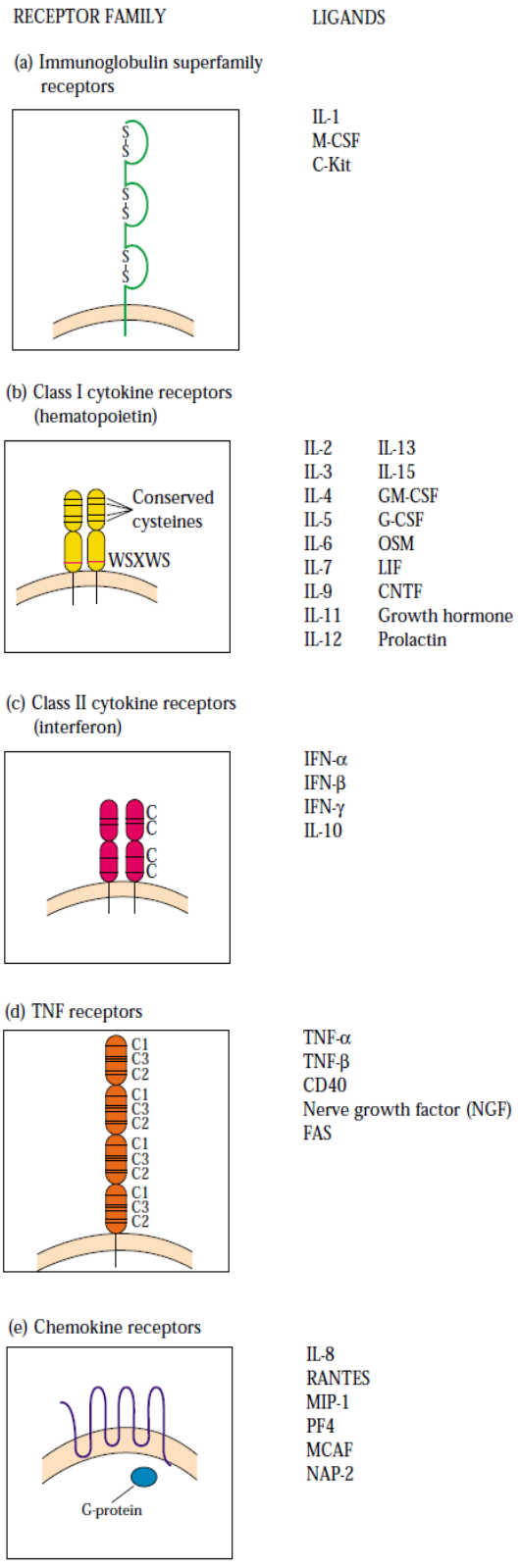


Figure: The structural features that define the five types of receptor proteins to which most cytokines bind. The receptors for most of the interleukins belong to the class I cytokine receptor family. C = conserved cysteine.

- Many of the cytokine-binding receptors that function in the immune and hematopoietic systems belong to the class I cytokine receptor family.
- The members of this receptor family have conserved amino acid sequence motifs in the extracellular domain consisting of four positionally conserved cysteine residues (CCCC) and a conserved sequence of Tryp-Ser-(any amino acid)-Tryp-Ser (WSXWS, where X is the nonconserved amino acid).
- The receptors for all the cytokines classified as hematopoietins belong to the class I cytokine receptor family, which also is called the *hematopoietin receptor family*.
- The class II cytokine receptors possess the conserved CCCC motifs, but lack the WSXWS motif present in class I cytokine receptors.
- Initially only the three interferons, α, β and γ were thought to be ligands for these receptors. However, recent work has shown that the IL-10 receptor is also a member of this group.
- Hematopoietin (class I cytokine) and the class II cytokine receptor families have multiple subunits: one subunit that binds specific cytokine molecules and another that mediates signal transduction.

Remark:

However, these two functions are not always confined to one subunit or the other. Engagement of all of the class I and class II cytokine receptors has been shown to induce tyrosine phosphorylation of the receptor through the activity of protein tyrosine kinases closely associated with the cytosolic domain of the receptors.

Subfamilies of Class I Cytokine Receptors

- ***The GM-CSF receptor subfamily***, which includes the receptors for IL-3, IL-5, and GM-CSF.
- Each of these cytokines binds to a unique low affinity, cytokine-specific receptor formed of an α-subunit only.
- All three low-affinity subunits can associate noncovalently with a common signal-transducing _ subunit.
- The resulting dimeric receptor not only exhibits increased affinity for the cytokine but also can transduce a signal across the membrane after binding the cytokine.
- Interestingly, IL-3, IL-5, and GM-CSF exhibit considerable redundancy.
- IL-3 and GM-CSF both act upon hematopoietic stem cells and progenitor cells, activate monocytes, and induce megakaryocyte differentiation.
- These three cytokines induce eosinophil proliferation and basophil degranulation with release of histamine.

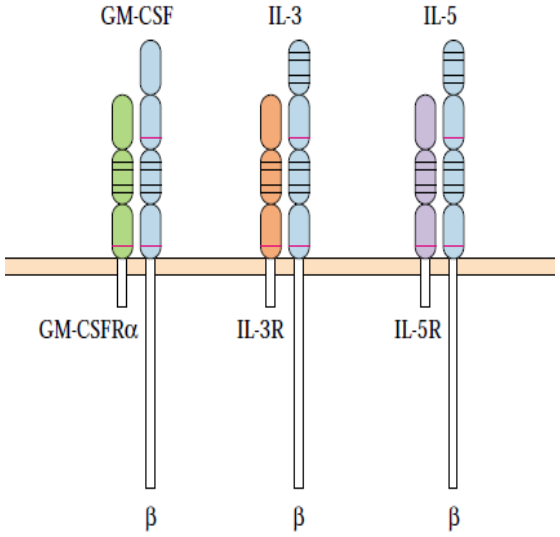


Figure: GM-CSF receptor subfamily (common β subunit)

Remark: IL-3 and GM-CSF exhibit antagonism; IL-3 binding has been shown to be inhibited by GM-CSF, and conversely, binding of GM-CSF has been shown to be inhibited by IL-3. Since the signal-transducing β subunit is shared between the receptors for these two cytokines, their antagonism is due to competition for a limited number of β-subunits by the cytokine-specific α-subunits of the receptors.

- ***IL-6 receptor*** subfamily includes the receptors for IL-6, IL-11, leukemiainhibitory factor (LIF), oncostatin M (OSM), and ciliary neurotrophic factor (CNTF).
- In this case, a common signal-transducing subunit called gp130 associates with one or two different cytokine-specific subunits.
- LIF and OSM, which must share certain structural features, both bind to the same α-subunit.
- The cytokines that bind to receptors in this subfamily display overlapping biological activities: IL-6, OSM, and LIF induce synthesis of acute-phase proteins by liver hepatocytes and differentiation of myeloid leukemia cells into macrophages; IL-6, LIF, and CNTF affect neuronal development, and IL-6, IL-11, and OSM stimulate megakaryocyte maturation and platelet production.
- The presence of gp130 in all receptors of the IL-6 subfamily explains their common signaling pathways as well as the binding competition for limited gp130 molecules that is observed among these cytokines.

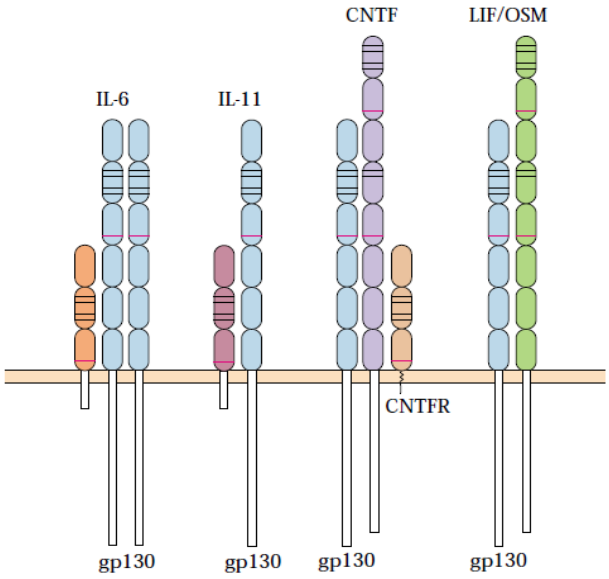


Figure: IL-6 Receptor subfamily (common gp130 subunit)

- ***The IL-2 receptor subfamily*** is the third type which includes receptors for IL-2, IL-4, IL-7, IL-9, and IL-15.
- The IL-2 and the IL-15 receptors are heterotrimers, consisting of a cytokine-specific α-chain and two chains β and γ are responsible for signal transduction.
- The IL-2 receptor γ chain functions as the signal-transducing subunit in the other receptors in this subfamily, which are all dimers.

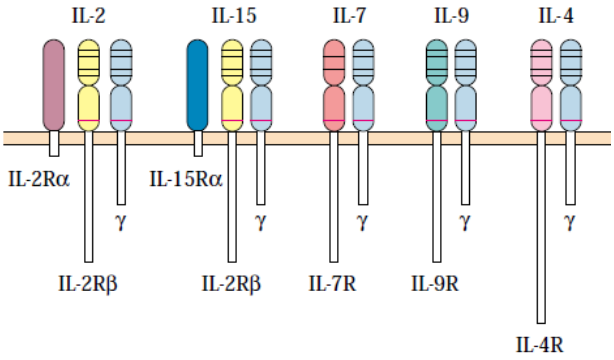


Figure: IL-2 receptor subfamily (common γ subunit)

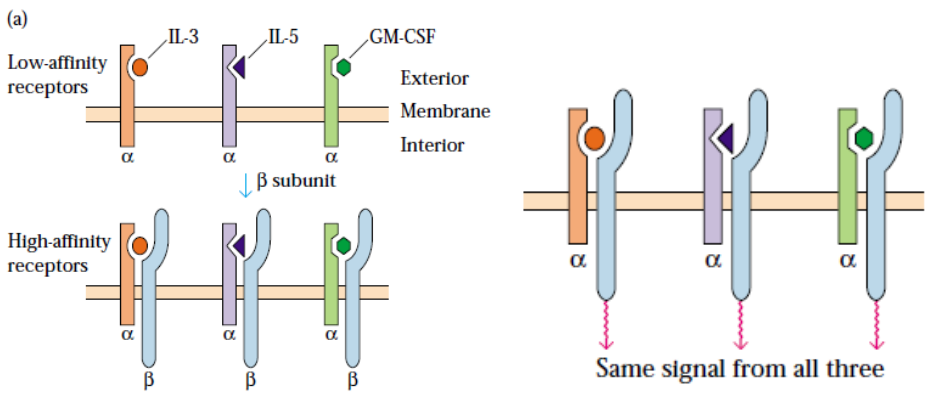


Figure: Interactions between cytokine-specific subunits and a common signal-transducing subunit of cytokine receptors. (a) The low-affinity and high-affinity receptors for IL-3, IL-5, and GM-CSF. The cytokine-specific subunits exhibit low-affinity binding and cannot transduce an activation signal. Noncovalent association of each subunit with a common β subunit yields a high-affinity dimeric receptor that can transduce a signal across the membrane. (b) Association of cytokine β -specific subunits with a common signaling unit, the β subunit, allows the generation of cytokine-specific signals despite the generation of the same signal by the different cytokine receptors shown. (c) Competition of ligand-binding chains of different receptors for a common subunit can produce antagonistic effects between cytokines. Binding of IL-3 by α- subunits of the IL-3 receptor allows them to out-compete α-chains of the GM-CSF receptor for β subunits.

Cytokine Receptors IL-2R

Due the key role of IL-2 and its receptor in the clonal proliferation of T cells, the IL-2 receptor has been studied intensively. The complete trimeric receptor comprises 3 distinct subunits— the α, β and γ chains.

- The IL-2 receptor occurs in three forms that exhibit different affinities for IL-2: the low-affinity monomeric IL-2R α, the intermediate-affinity dimeric IL-2Rβγ, and the high affinity trimeric IL-2Rαβγ .
- As the α-chain is expressed only by activated T cells, it is often referred to as the TAC (T-cell activation) antigen.
- Signal transduction by the IL-2 receptor requires both the β and γ chains, but only the trimeric receptor containing the α chain as well binds IL-2 with high affinity.

Remark: Although the γ-chain appears to be constitutively expressed on most lymphoid cells, expression of the α and β chains is more restricted and is markedly enhanced after antigen has activated resting lymphocytes. This phenomenon ensures that only antigen activated $CD4^+$ and $CD8^+$ T cells will express the high affinity.

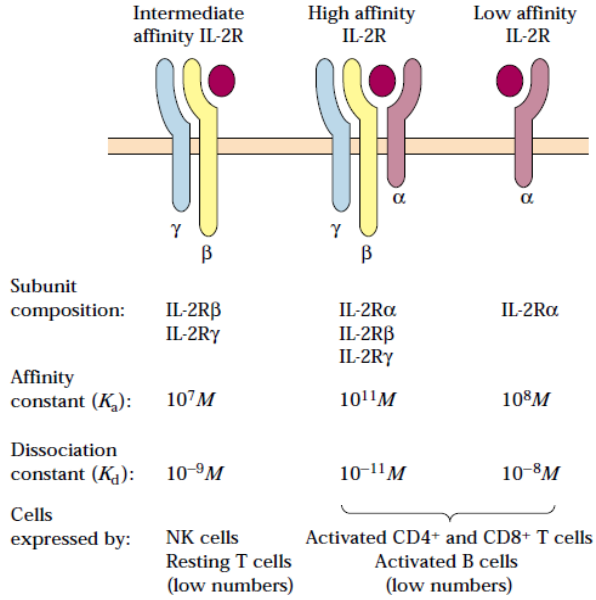


Figure: The three forms of the IL-2 receptor

Generalized Signaling Pathways

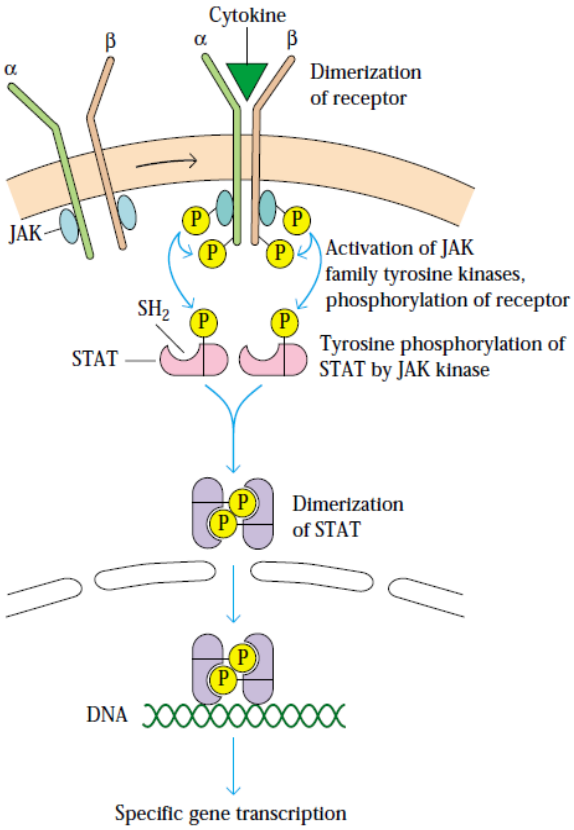


Figure: General model of signal transduction mediated by class I and class II cytokine receptors

- Cytokine binding induces the association of the two separate cytokine receptor subunits and activation of the receptor-associated JAKs.
- The IFN- γ, which binds to a class II cytokine receptor, has the ability to associate the ligand-binding chains of its receptor.
- Activated JAKs create docking sites for the STAT transcription factors by phosphorylation of specific tyrosine residues on cytokine receptor subunits.
- Once receptor associated JAKs are activated, they phosphorylate specific tyrosines in the receptor subunits of the complex.
- Transcription factor STATs (signal transducers and activators of transcription) bind to these phosphorylated tyrosine residues.
- After undergoing JAK-mediated phosphorylation, STAT transcription factors translocate from receptor docking sites at the membrane to the nucleus, where they initiate the transcription of specific genes.
- While docked to receptor subunits, STATs undergo JAK-catalyzed phosphorylation of a key tyrosine.
- Next, the dissociation of the STATs from the receptor subunits and their dimerization occur.
- The STAT dimers then translocate into the nucleus and induce the expression of genes containing appropriate regulatory sequences in their promoter regions.

Cytokine and development of T_H1 and T_H2 subsets

- Antigen-activated naive $CD4^+$ T cell produces IL-2 and proliferates.
- If it proliferates in an IL-12 dominated environment, it generates a population of T_H1 cells that secretes a characteristic profile of cytokines including interferon γ.
- A positive feedback loop is established when IFN-γ secreted by the expanding T_H1 population stimulates dendritic cells or macrophages to produce more IL-12.
- If the environment is dominated by IL-4, a T_H2 population emerges and secretes a profile of cytokines that promotes eosinophil activation and the synthesis of certain antibody classes.
- Key cytokines produced by each subset positively regulate the subset that produces it and negatively regulate the other subset.

Cytokine/function	T_H1	T_H2
CYTOKINE SECRETION		
IL-2	+	–
IFN-γ	++	–
TNF-β	++	–
GM-CSF	++	+
IL-3	++	++
IL-4	–	++
IL-5	–	++
IL-10	–	++
IL-13	–	++
FUNCTIONS		
Help for total antibody production	+	++
Help for IgE production	–	++
Help for IgG2a production	++	+
Eosinophil and mast-cell production	–	++
Macrophage activation	++	–
Delayed-type hypersensitivity	++	–
T_C-cell activation	++	–

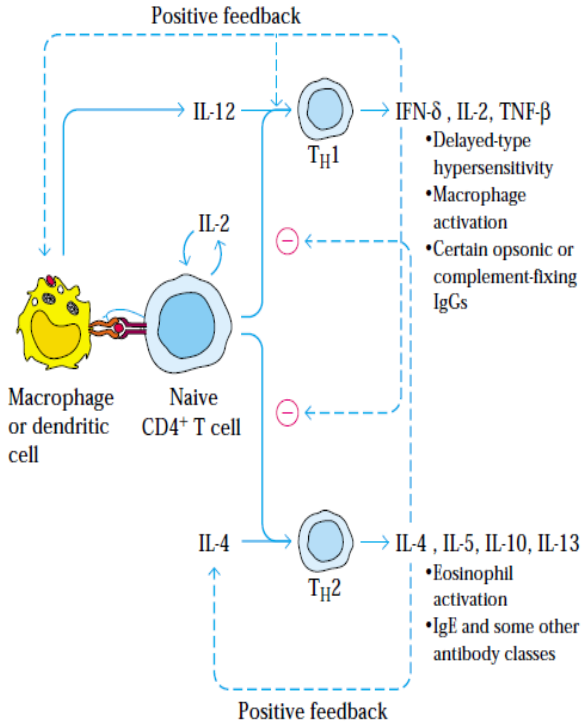


Figure: Cytokine-mediated generation and cross regulation of T_H subsets

Cytokine mimic

- Some viruses also produce cytokine-binding proteins or cytokine mimics.
- The evolution of such anti-cytokine strategies by microbial pathogens is the evidence suggesting cytokines in organizing and promoting effective anti-microbial immune responses.
- The poxviruses encode a soluble TNF-binding protein and a soluble IL-1–binding protein. Since both TNF and IL-1 exhibit a broad spectrum of activities in the inflammatory response, these soluble cytokine-binding proteins may prohibit or diminish the inflammatory effects of the cytokines, thereby conferring upon the virus a selective advantage.

Virus	Product
Leporipoxvirus (a myxoma virus)	Soluble IFN-γ receptor
Several poxviruses	Soluble IFN-γ receptor
Vaccinia, smallpox virus	Soluble IL-1 β receptor
Epstein-Barr	IL-10 homolog
Human herpesvirus-8	IL-6 homolog; also homologs of the chemokines MIP-I and MIP-II
Cytomegalovirus	Three different chemokine receptor homologs, one of which binds three different soluble chemokines (RANTES, MCP-1, and MIP-1α)

Cytokine cross regulation

- The critical cytokines produced by T_H1 and T_H2 subsets have two characteristic effects on subset development.
  - First, they promote the growth of the subset that produces them;
  - Second, they inhibit the development and activity of the opposite subset, an effect known as *cross-regulation*.

Example: IFN-γ (secreted by the T_H1 subset) preferentially inhibits proliferation of the T_H2 subset, and IL-4 and IL-10 (secreted by the T_H2 subset) down-regulate secretion of IL-12, one of the critical cytokines for T_H1 differentiation, by both macrophages and dendritic cells.

- Similarly, these cytokines have opposing effects on target cells other than T_H subsets.
- IFN- γ secreted by the T_H1 subset promotes IgG2a production by B cells but inhibits IgG1 and IgE production.
- On the other hand, IL-4 secreted by the T_H2 subset promotes production of IgG1 and IgE and suppresses production of IgG2a.

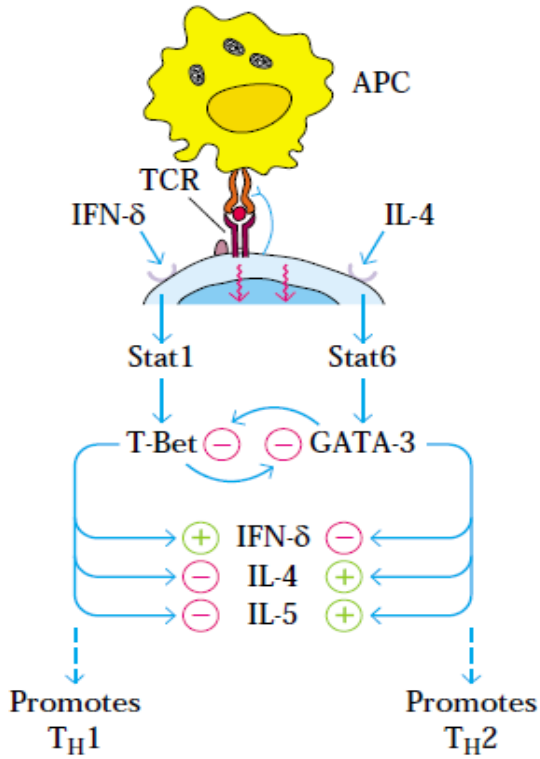


Figure: Cytokine cross regulation at intracellular level.

Evidence:

- Signals through the TCR and cytokine receptors determine whether the cell will produce the T_H1-promoting transcription factor, T-Bet, or the T_H2-promoting transcription factor, GATA-3.
- Evidence suggests, exposure of cells bearing receptors for IFN- γ to IFN- γ induces the formation of T-Bet, which up-regulates the synthesis of IFN- γ and represses the expression of GATA-3.
- Exposure of IL-4 R–bearing cells to IL-4 induces the formation of GATA-3, which up-regulates the synthesis of IL-4 and IL-5 but represses the expression of T-Bet.

Remark:

- ✓ The phenomenon of cross-regulation explains the observation that there is often an inverse relationship between antibody production and cell-mediated immunity; that is, when antibody production is high, cell mediated immunity is low, and vice versa.
- ✓ Again, IL-4 and IFN- γ make members of the T-cell subset that releases them less responsive to the cytokine that directs differentiation of the other T-cell subset.
- ✓ Thus, IL-4 enhances T_H2 cell development by making T_H cells less susceptible to the cytokine signals that cause these cells to enter a differentiation pathway that would lead to T_H1 development.
- ✓ On the other hand, IFN- γ up-regulates the expression of a key regulatory molecule that favors the differentiation and activity of T_H1 cells.

Therapeutic use of cytokine/cytokine receptors

- ❖ Various approaches are being explored include cytokine receptor blockade and the use of cytokine analogs and cytokine-toxin conjugates for therapeutic use.
- ❖ For instance, proliferation of activated T_H cells and activation of T_C cells can be blocked by anti-TAC, a monoclonal antibody that binds to the α-subunit of the high-affinity IL-2 receptor. Administration of anti-TAC has prolonged the survival of heart transplants in rats.

- Similar results have been obtained with IL-2 analogs that retain their ability to bind the IL-2 receptor but have lost their biological activity.
- Such analogs have been produced by site-directed mutagenesis of cloned IL-2 genes. Finally, cytokines conjugated to various toxins (e.g., the β chain of diphtheria toxin) have been shown to diminish rejection of kidney and heart transplants in animals. Such conjugates containing IL-2 selectively bind to and kill activated T_H cells.

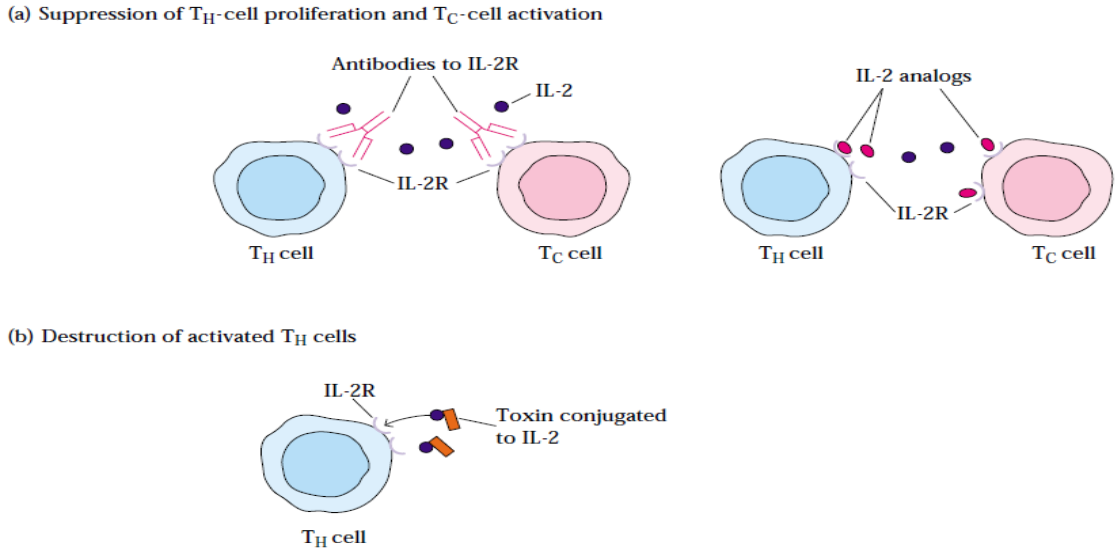
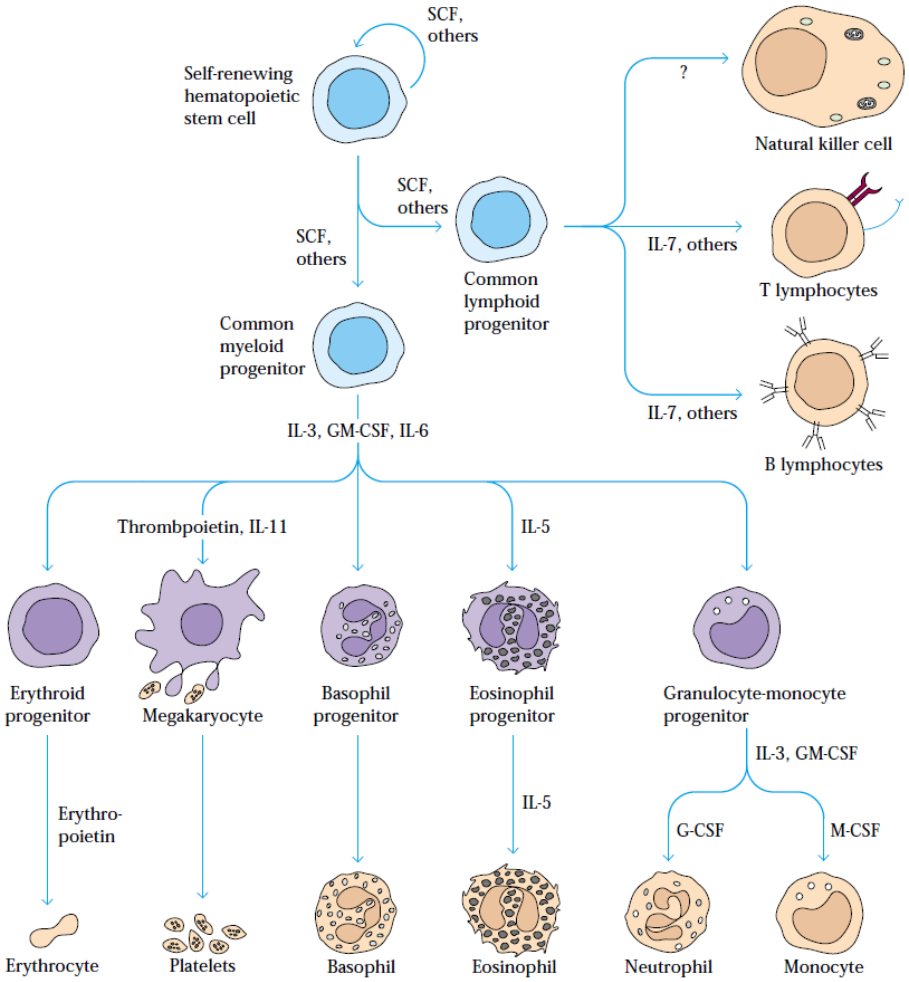


Figure: Therapeutic use of cytokines: (a) The anti-IL-2R monoclonal antibody binds to the cytokine receptor (IL-2R) on the cell surface, thereby preventing interaction of the cytokine with its receptor. (b) Conjugation of a toxin with a cytokine results in destruction of cells expressing the cytokine receptor.

Cytokine-Based Therapies In Clinical Use

Agent	Nature of agent	Clinical application
Enbrel	Chimeric TNF-receptor/IgG constant region	Rheumatoid arthritis
Remicade	Monoclonal antibody against TNF-α receptor	Rheumatoid arthritis
Interferon α-2a	Antiviral cytokine	Hepatitis B Hairy cell leukemia Kaposi's sarcoma
Interferon α-2b	Antiviral cytokine	Hepatitis C Melanoma
Interferon β	Antiviral cytokine	Multiple sclerosis
Actimmune	Interferon γ	Chronic granulomatous disease (CGD) Osteopetrosis
Neupogen	G-CSF (hematopoietic cytokine)	Stimulates production of neutrophils Reduction of infection in cancer patients treated with chemotherapy
Leukine	GM-CSF (hematopoietic cytokine)	Stimulates production of myeloid cells after bone-marrow transplantation
Neumega	Interleukin 11 (IL-11), a hematopoietic cytokine	Stimulates production of platelets
Epogen	Erythopoietin (hematopoietic cytokine)	Stimulates red-blood-cell production

Cytokines in hematopoiesis



Haematopoietic growth factor	Sites of production	Main functions
Erythropoietin	Kidney, liver	Erythrocyte production
G-CSF	Endothelial cells, fibroblasts, macrophages	Neutrophil production
Thrombopoietin	Liver, kidney	Platelet production
M-CSF	Fibroblasts, endothelial cells, macrophages	Macrophage and osteoclast production
SCF/c-*kit* ligand	Bone marrow stromal cells, constitutively	Stem cell, progenitor cells survival/division; mast cell differentiation
Flt-3 ligand	Fibroblasts, endothelial cells	Early progenitor cell expansion; pre-B cells
GM-CSF	T cells (T_H1 and T_H2), macrophages, mast cells	Macrophage, granulocyte production; dendritic cell maturation and activation
IL-3	T cells (T_H1 and T_H2), macrophages	Stem cells and myeloid progenitor cell growth; mast cells
IL-5	Activated helper T cells –T_H2 response only	Eosinophil production murine B-cell growth
IL-6	Activated T cells monocytes, fibroblasts, endothelial cells	Progenitor cell stimulation; platelet production; immunoglobulin production in B cells
IL-11	As above	As LIF
IL-7		T-cell survival

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; SCF, stem cell factor. Adapted from D. Thomas and A. Lopez, 2001.

Table 8.1 Cytokines: their origin and function. Note that there is not an interleukin-14 (IL-14). This designation was given to an activity that, upon further investigation, could not be unambiguously assigned to a single cytokine. Interleukin-8 is a member of the chemokine family. These cytokines are listed separately in table 8.2.

CYTOKINE	SOURCE	EFFECTOR FUNCTION
INTERLEUKINS		
IL-1α, IL-1β	Mono, Mϕ, DC, NK, B, Endo, Eosino	Costimulates T activation by enhancing production of cytokines including IL-2 and its receptor; enhances B proliferation and maturation; NK cytotoxicity; induces IL-1,-6,-8, TNF, GM-CSF and PGE_2 by Mϕ; proinflammatory by inducing chemokines and ICAM-1 and VCAM-1 on endothelium; induces fever, APP, bone resorption by osteoclasts
IL-2	Th1, Eosino	Induces proliferation of activated T- and B-cells; enhances NK cytotoxicity and killing of tumor cells and bacteria by monocytes and Mϕ
IL-3	T, NK, MC, Eosino	Growth and differentiation of hematopoietic precursors; MC growth
IL-4	Th2, Tc2, NK, NK-T, γδ T, MC, Eosino	Induces Th2 cells; stimulates proliferation of activated B, T, MC; upregulates MHC class II on B and Mϕ, and CD23 on B; downregulates IL-12 production and thereby inhibits Th1 differentiation; increases Mϕ phagocytosis; induces switch to IgG1 and IgE
IL-5	Th2, MC, Eosino	Induces proliferation of eosino and activated B; induces switch to IgA
IL-6	Th2, Mono, Mϕ, DC, BM stroma, Eosino	Differentiation of myeloid stem cells and of B into plasma cells; induces APP; enhances T proliferation
IL-7	BM and thymic stroma	Induces differentiation of lymphoid stem cells into progenitor T and B; activates mature T
IL-8	Mono, Mϕ, Endo, Eosino	Mediates chemotaxis and activation of neutrophils
IL-9	Th	Induces proliferation of thymocytes; enhances MC growth; synergizes with IL-4 in switch to IgG1 and IgE
IL-10	Th (Th2 in mouse), Tc, B, Mono, Mϕ, Eosino	Inhibits IFNγ secretion by mouse, and IL-2 by human, Th1 cells; downregulates MHC class II and cytokine (including IL-12) production by mono, Mϕ and DC, thereby inhibiting Th1 differentiation; inhibits T proliferation; enhances B differentiation
IL-11	BM stroma	Promotes differentiation of pro-B and megakaryocytes; induces APP
IL-12	Mono, Mϕ, DC, B	Critical cytokine for Th1 differentiation; induces proliferation and IFNγ production by Th1, $CD8^+$ and γδ T and NK; enhances NK and $CD8^+$ T cytotoxicity
IL-13	Th2, MC, Eosino	Inhibits activation and cytokine secretion by Mϕ; co-activates B proliferation; upregulates MHC class II and CD23 on B and mono; induces switch to IgG1 and IgE; induces VCAM-1 on endo
IL-15	T, NK, Mono, Mϕ, DC, B	Induces proliferation of T, NK and activated B and cytokine production and cytotoxicity in NK and $CD8^+$ T; chemotactic for T; stimulates growth of intestinal epithelium
IL-16	Th, Tc, Eosino	Chemoattractant for CD4 T, mono and eosino; induces MHC class II
IL-17	T	Proinflammatory; stimulates production of cytokines including TNF,IL-1β,-6,-8, G-CSF
IL-18	Mϕ, DC	Induces IFNγ production by T; enhances NK cytotoxicity
IL-19	Mono	Modulation of Th1 activity
IL-20	Keratinocytes?	Regulation of inflammatory responses to skin?
IL-21	Th	Regulation of hematopoiesis; NK differentiation; B activation; T costimulation
IL-22	T	Inhibits IL-4 production by Th2
IL-23	DC	Induces proliferation and IFNγ production by Th1; induces proliferation of memory cells
COLONY STIMULATING FACTORS		
GM-CSF	Th, Mϕ, Fibro, MC, Endo, Eosino	Stimulates growth of progenitors of mono, neutro, eosino and baso; activates Mϕ
G-CSF	Fibro, Endo	Stimulates growth of neutro progenitors
M-CSF	Fibro, Endo, Epith	Stimulates growth of mono progenitors
SLF	BM stroma	Stimulates stem cell division (c-*kit* ligand)
TUMOR NECROSIS FACTORS		
TNF (TNFα)	Th, Mono, Mϕ, DC, MC, NK, B, Eosino	Tumor cytotoxicity; cachexia (weight loss); induces cytokine secretion; induces E-selectin on endo; activates Mϕ; antiviral
Lymphotoxin (TNFβ)	Th1, Tc	Tumor cytotoxicity; enhances phagocytosis by neutro and Mϕ; involved in lymphoid organ development; antiviral
INTERFERONS		
IFNα	Leukocytes	Inhibits viral replication; enhances MHC class I
IFNβ	Fibroblasts	Inhibits viral replication; enhances MHC class I
IFNγ	Th1, Tc1, NK	Inhibits viral replication; Enhances MHC class I and II; activates Mϕ; induces switch to IgG2a; antagonizes several IL-4 actions; inhibits proliferation of Th2
OTHERS		
TGFβ	Th3, B, Mϕ, MC, Eosino	Proinflammatory by, e.g., chemoattraction of mono and Mϕ but also anti-inflammatory by, e.g. inhibiting lymphocyte proliferation; induces switch to IgA; promotes tissue repair
LIF	Thymic epith, BM stroma	Induces APP
Eta-1	T	Stimulates IL-12 production and inhibits IL-10 production by Mϕ
Oncostatin M	T, Mϕ	Induces APP

APP, acute phase proteins; B, B-cell; baso, basophil; BM, bone marrow; Endo, endothelium; eosino, eosinophil; Epith, epithelium; Fibro, fibroblast; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; LIF, leukemia inhibitory factor; Mϕ, macrophage; MC, mast cell; Mono, monocyte; neutro, neutrophil; NK, natural killer; SLF, steel locus factor; T, T-cell; TGFβ, transforming growth factor-β.

Reference:

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