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A Primer on Cytokines: Sources, Receptors, Effects, and Inducers

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INTRODUCTION

Most mammals are continuously challenged by microorganisms, as a result of which defense mechanisms must be maintained throughout their life span. The first line of defense is provided by the skin or the mucosa of the gastrointestinal tract, which forms an impermeable barrier for the vast majority of microorganisms. However, when this barrier becomes damaged, an easy path of entry is provided. Furthermore, some microorganisms are capable of penetrating these barriers and can thereby gain access to the underlying tissues. There they are encountered by immunological defense mechanisms and may elicit an inflammatory reaction. These defense mechanisms can be nonspecifically directed against a broad range of microorganisms (e.g., neutrophils that phagocytose and kill bacteria) but may also be specifically directed against a single organism (e.g., antibody-mediated inactivation of the organism). The generation and maintenance of these immunological responses is controlled by a network of small, nonstructural, intercellular regulatory proteins that mediate a multiplicity of immunologic as well as nonimmunologic biological functions (4, 121, 177). These so-called cytokines and chemokines (referred to here as cytokines) are induced by specific stimuli, such as several types of bacterial products, and are responsible for the generation, stimulation, and differentiation of multiple cell types as well as for the control of production of other cytokines that may enhance or inhibit the synthesis of protein products and/or biological effects of other cell types and proteins. This results in a complex, fine-tuned regulatory network that may ultimately succeed in the eradication of the invading microorganism(s). The ability or inability to generate certain cytokines or cytokine patterns in response to infection often determines the clinical course of infection (126, 196) and may greatly affect the outcome. In certain circumstances, mistuning or massive overproduction of cytokines may even lead to shock, multiorgan failure, or death (74).

The availability of recombinant cytokines, cytokine-neutralizing antibodies, antagonists, cytokine-inhibitory drugs, and cytokine knockout laboratory animals (61, 91, 110, 166, 206) enables researchers to study and modulate immune responses. The knowledge thus obtained may eventually lead to the development of new strategies for therapy of infectious diseases (123, 126), which would be particularly valuable in light of the increasing ineffectiveness of antibiotic treatment due to development of resistance of microorganisms to antibiotics.

Due to the ever-increasing number of cytokines that are being discovered and new insights into cytokine functions, it is almost impossible to remember all cytokines and their effects. It would therefore be helpful to have a quick reference guide in which the major cytokines as well as their sources, receptors, biological actions, and inducers are listed. As a result of the vast amount of research on cytokines currently being con-

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ducted and the continuous flow of publications concerning cytokines, it is not possible to provide a completely updated overview. Therefore, the aim of this review is to provide a list of the most common cytokines involved in inflammatory and immune responses which may be expanded on a regular basis.

The list of references predominantly contains review articles on specific cytokines or groups of cytokines that may be useful as a source of more background information and as a starting point for a search for more specific articles on a specific cytokine(s).

Although cytokines have sometimes been divided into groups according to their source (lymphokines or monokines), it has become difficult to maintain this categorization since most of the cytokines can be produced by a variety of cell types depending on the stimulating agent and interaction with other cells. Therefore, the cytokines are described in the following order: interleukins (IL), tumor necrosis factors (TNF) and lymphotoxins (LT), interferons (IFN), colony-stimulating factors (CSF), chemokines, and miscellaneous cytokines. The tables present contemporary and historical names and abbreviations, information on receptors and receptor-related proteins, cytokine sources and gene locations, biochemical properties of the protein, information on cytokine-specific bioassays, molecular properties such as amino acid homologies and species specificities, and information on various biological effects and inducers.

IL

It has now been more than 12 years since the first two members of the IL family, IL-1α and IL-1β, were cloned. Furthermore, several other molecules that have been known and studied for some time have been named as IL, such as IL-2, formerly known as T-cell growth factor. Since the introduction of the term IL, at least 17 cytokines have been described and given that designation, the last one being IL-17 (204).

IL-1

Since the cloning of IL-1 it has become clear that IL-1 can evoke a wide variety of biological effects (Tables 1 and 2) at very low concentrations, sometimes even in the femtomolar range (54, 55). It is a remarkably potent molecule that is able to induce its effects by triggering as few as one or two receptors per cell. The first effects ascribed to IL-1 were the induction of fever, augmentation of lymphocyte responses, and stimulation of the acute-phase response, hence the older names such as endogenous pyrogen and lymphocyte-activating factor. Two different molecules with agonistic effects are known, IL-1α and IL-1β. While IL-1α is predominantly membrane bound, IL-1β is secreted. A clear distinction should be made between local and systemic effects of IL-1 (52). The induction of an inflammatory reaction in response to infection is to a large extent attributed to the effects of IL-1. Apart from the induction of other proinflammatory cytokines and chemotactic cytokines at the site of infection, IL-1 also up-regulates cell adhesion molecules, which ultimately leads to the production of an effective defense mechanism. Indeed, in several models of bacterial, fungal, and parasitic infection, IL-1 is associated with protection (188, 189). Furthermore, the radiation-protective effect of IL-1 (possibly because of its stimulatory effect on hematopoiesis) may hold promise for treatment during cancer therapy. In contrast, however, overproduction of IL-1 may sometimes be associated with disease (51, 114).

A molecule named IL-1 receptor antagonist (IL-1ra) is also part of the IL-1 family. This cytokine, which strongly resembles IL-1, completely lacks an agonistic effect in vitro and in vivo (53, 55, 144). Therefore, IL-1ra may act by dampening IL-1 responses. Furthermore, the IL-1 receptor type II (IL-1-RII) presumably may act as a decoy receptor, thereby attenuating the potential effects of IL-1 (173, 174). In addition, it has become clear from models of infection that treatment with IL-1ra may have protective effects (189); e.g., treatment of *Plasmodium berghei*-infected mice with IL-1ra protects against the development of cerebral malaria (39). Therefore, treatment with soluble IL-1-Rs (sIL-1-Rs) or IL-1ra may be beneficial in some disease states, such as chronic inflammation. It has become evident that the time and location of IL-1 production together with production of IL-1ra and IL-1-R expression is crucial in determining the final biological effect.

IL-2

The T-cell-derived cytokine IL-2 targets a variety of cells to induce their growth, differentiation, and functional activation (Table 3). Previous names for IL-2, such as lymphocyte mitogenic factor and T-cell growth factor, indicate that one of the major functions of this cytokine is in the activation, growth, and differentiation of T cells. Indeed, within minutes after interaction of the T-cell receptor (TCR) with the major histocompatibility complex (MHC) class II antigen complex on antigen-presenting cells, T cells transcribe three categories of genes that are expressed early during T-cell activation: cellular proto-oncogenes, cytokine genes, and cytokine receptor genes. Transcription of the gene for IL-2 as well as of that for IL-2-R begins within 1 h of TCR-mediated stimulation of human lymphocytes. In this way secreted IL-2, produced by an activated T cell in an autocrine fashion, stimulates growth and proliferation of antigen-specific T lymphocytes as well as B cells. The major T-cell subclass that produces IL-2 is the $CD4^+$ T cell, although $CD8^+$ cells may also produce small quantities of IL-2. Apart from the autocrine effect, IL-2 also induces the production of other T-cell-derived cytokines such as IFN-γ and TNF-β, which results in activation of monocytes, neutrophils, and natural killer cells (NK cells). It is evident that in that way IL-2 contributes to the generation and propagation of antigen-specific immune responses. A strong induction of IL-2 (and IFN-γ and TNF-β) is also found after stimulation of the TCR β chain by superantigens; this induction leads to extensive proliferation of T-cell subsets.

The functional human IL-2-R is composed of subunit complexes of α, β, and γ chains or β and γ chains. Together with the β chain, the γ chain participates in increasing the IL-2 binding affinity and is responsible for signal transduction. Remarkably, signaling through the γ chain is shared by receptors for at least IL-4, IL-7, IL-9, and IL-15 (56, 84). The importance of signaling through the γ chain can be demonstrated by the fact that mutations of the γ-chain gene are the cause of the human X-linked severe combined immunodeficiency syndrome (178).

IL-2 has been used for several therapeutic applications, such as infusions of IL-2-activated lymphokine-activated killer (LAK) cells and tumor-infiltrating lymphocytes for antitumor therapy, the augmentation of IL-2 levels in immunodeficiency disorders, and the increase of NK cell activity following bone marrow transplants (88). Studies to determine beneficial effects of IL-2 during human immunodeficiency virus (HIV) infection are currently being conducted. Increases in the numbers of circulating B and T cells have been observed at relatively high doses of IL-2, although toxicity due to activation of NK cells and the resulting production of proinflammatory cy-

TABLE 1. IL-1[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-1α/β	Interleukin-1	Two independent proteins: IL-1RI and IL-1RII.	Monocytes / macrophages, activated alveolar macrophages, T-, B- and NK cells, neutrophils, dendritic cells, Langerhans' cells, keratinocytes, endothelial cells, epithelial cells, neuronal cells, astrocytes, glial cells, mesangial cells, fibroblasts, synovial cells, smooth muscle cells, rat intestinal epithelial cell line IEC-6 (only IL-1α and only intracellular). IL-1α precursor is biologically active, IL-1β precursor is biologically inactive. precIL-1α is cleaved by protease → IL-1α. precIL-1β is cleaved by pyrogenic exotoxin B (proteinase precursor). ICE (IL-1β converting enzyme, mammalian cysteine endoproteinase) cleaves preIL-1β at 2 sites: preIL-1 β → IL-1β (does not cleave IL-1α). ICE activity is inhibited by p-benzoquinone [134, 184]. IL-1 transcription is short-lived and is suppressed by corticoids. Translation is increased by calcium ionophores and leukotrienes and is inhibited by PGE_2-induced cAMP.	human (h) IL-1: 17.5 kDa, chromosome 2q. murine (m) IL-1: 17.5 kDa. 31 kDa precursor (prec). mIL-1α: pI 5.0. mIL-1β: pI 7.0. human recombinant (hrec) IL-1β: iso-electric point (pI) 5.6. rrecIL-1β: pI 8.74. IL-1α intracellular or exposed on membrane. IL-1β secreted (also as precIL-1β). rrecIL-1β blocked by hIL-1ra. rrecIL-1β binds with rIL-1RI and not with COS-1 or COS-7 (monkey) IL-1RI. hrecIL-1β does not bind to rIL-1R but has bioactive effect on rat cells carrying IL-1RI. Therefore, dissociation between receptor binding and bioactivity (or high dissociation rate of human ligand from rat receptor).	hIL-1α: 159 aa. hIL-1β: 153 aa. mIL-1α and mIL-1β: 26% aa homology. Much higher homology in predicted 3D structure. Species specificity: rrecIL-1β and hrecIL-1β have the same max. dose in the mouse thymocyte proliferation assay but the peak response of rrecIL-1β is twice that of hrecIL-1β. Rat IL-1R binds poorly to mIL-1β and hIL-1β. Half-life of mRNA enhanced by porins from *Salmonella typhimurium.*	**Activates:** T-, B- and NK cells (synergistically with IL-2 and IFNα), polymorphonuclear cells (priming), eosinophils (degranulation), endothelial cells and smooth muscle cells (ICAM-1, VCAM-1 and E-selectin expression), nerve cells, adipocytes, chondrocytes, osteoclasts, fibroblasts, thymocytes and pancreatic β-cells (at low concentrations), hepatocytes. **Cytotoxic for:** Melanocytes, pancreatic β-cells (at high concentration), islets of Langerhans *in vitro* (in pico- to nanomolar concentrations). ***In vivo* effects:** Fever (endogenous pyrogen), anorexia, slow-wave sleep, neuro-peptide production, acute phase protein induction, insulin-, ACTH- and cortisol induction, leukocytosis, radioprotection, protection against several infections (bacterial as well as parasitic), adjuvant effect independent of IL-2, stimulation of central release of CRH in primates. **Down-regulates:** IL-1R expression on T-cells (suppression of steady-state mRNA), Fas-antigen expression on synovial cells (thereby inhibits Fas-Ag-mediated apoptosis and perpetuates synovial hyperplasia in rheumatoid arthritis), collagen in human smooth muscle cells. **Up-regulates:** TNF-R expression on human bone marrow stromal cell strain, IL-2R expression. **Increases:** ACTH, endorphins, vasopressin and somatostatin release, oxidative burst of neutrophils (bovine), proliferation of B-cells and antibody formation (synergistically with various B-cell growth and differentiation factors), nerve growth factor in rat brain tissue after CNS trauma, shedding of sol TNF-R75 from monocytes (not sol TNF-R55). **Induces:** Pro-inflammatory cytokines and hematopoietic growth factors, coagulation (formation of thrombin~anti-thrombin III [TAT] complexes), fibrinolysis (plasmin-α_2~anti-plasmin [PAP] complexes), release of tissue-type plasminogen activator (t-PA) and its inhibitor plasminogen activator inhibitor (PAI), release	LPS (IL-1β in whole blood independent of TNFα) and other microbial products (toxins). Viruses. Various cytokines. Phagocytosis. Pyrogenic exotoxin A. Streptolysin O. sol CD23 (IL-1β by monocytes). BCG (only in primed macrophages). *Mycoplasma* membrane lipoproteins (monocyte) through a mechanism distinct from LPS (involves post-translational events and critically depends on tyrosine phosphorylation). CRH up-regulates IL-1β and IL-1ra mRNA and protein in the absence of LPS or at low LPS concentrations. These cytokines are inhibited by CRH at high LPS concentrations. Tissue injury. *Candida* species.
LAF	Lymphocyte activating factor	IL-1RI / CDw121a (80 kDa). 213 amino acids (aa), glycosylated, cytoplasmic domain necessary for signal transduction. Found on B-cells, monocytes, neutrophils. Preference for IL-1α. Down-regulated by IL-1, up-regulated by corticosteroids, T-cell activation, epidermal growth factor, IL-2 and IL-4. Mediates IL-1β-induced fever in rats. IL-1RII / CDw121b (68 kDa). 29 aa cytoplasmic domain, no signal transduction. Possibly acts as decoy receptor. Found on endothelial cells, hepatocytes, fibroblasts, keratinocytes, T-cells. Preference for IL-1β. Devoid of signaling. Both types of receptors are encoded by separate genes, 28% aa homology in extra-cellular regions of RI & RII. Genes map to the IL-1 gene cluster on chromosome 2 (2q12-22) together with the genes for IL-1α *(IL1A)*, IL-1β *(IL1B)* and IL-1ra *(IL1RN)*. The functional IL-1 receptor is a complex of at least 2 sub-units. Soluble (sol) IL-1RI and sol IL-1RII are detected in human					
BAF	B-cell activating factor						
HP-1	Helper peak-1						
TRF III / TRF_M	T-cell replacing factor III						
BDF	B-cell differentiation factor						
MCF	Mononuclear cell factor						
MP	Mitogenic protein						
LP	Leukocytic pyrogen						
EP	Endogenous pyrogen						
LEM	Leukocyte endogenous mediator						
HP-1	Hematopoietin-1						
OAF	Osteoclast activating factor						
	Catabolin						
MGIF	Melanoma growth inhibitor factor						
TIF-2	Tumor inhibitor factor-2						
	Lymphocyte proliferation promoting factor of neutrophils						

		serum. Rat sol IL-1RI binds to rat recombinant (rrec) IL-1β but not to hIL-1β or murine (m) IL-1β. Extracellular domain of rIL-1 RI: pI 4.7 (hIL-1RI pI 6.7). IL-1β binds to IL-1RI and IL-1 RII through different sites. Agonist (IL-1β) and antagonist (IL-1ra) binding to IL-1RI occurs through distinct sites. IL-1R AcP (IL-1 receptor accessory protein): forms complex with IL-1RI + IL-1 α/β but not with IL-1ra. Increases affinity of IL-1β and IL-1RI. 570 aa ~ 66 kDa, Ig super-family. Murine & human. Limited homology to RI & RII. Expressed in many murine tissues. Regulated by IL-1. IIP1: protein that interacts with a functionally important region of the IL-1R, co-immuno-precipitates with IL-1R and appears critical for IL-1 signal transduction. IL-1Rrp (IL-1 receptor related protein): does not bind known IL-1 ligands. IL-1Rrp cytoplasmic domain coupled to IL-1R membrane domain leads to IL-1 binding and signal transduction. IRAK: IL-1RI-associated kinase that associates with IL-1~IL-1RI complex and is subsequently phosphorylated leading to activation of NFκB. [Refs. 21, 45, 151, 173, 174]		cAMP signaling pathway(s) is important in the regulation of IL-1β at the trans-criptional level. Bioassay: Proliferation of mouse thymocytes or D10G4.1 cells. Synthetic nona-peptide of IL-1β (aa 163-171) still has T-cell activating effect but no pyrogenic effect.		of soluble plasmin-α_2 ($sPLA_2$), infection-induced malnutrition, monocyte chemoattractant protein-1 (synergistically with platelet derived growth factor), lymphokine gene expression, cyclooxygenase and lipoxygenase gene expression, acute phase response, early cartilage damage in immune complex arthritis in mice, protein phosphorylation. **Suppresses:** Somatotropic axis (together with corticotropin-releasing factor). IL-1α and IL-1β inhibit IL-4 production by human peripheral blood mononuclear cells. IL-1β suppresses apoptosis in $CD34^+$ bone marrow cells through IL-1RI. **Stimulates:** Late shedding of TNF-R75 from human monocytes (not TNF-R55), mucin exocytosis through IL-1RI located basolaterally on HT-29Cl.16E human colon epithelial cell line. **Enhances:** Antigen-specific activity of T_H cells, IL-2 production, immune responses to T-cell-independent antigens, secondary antibody response of mice to BSA (50-fold), FcγR-mediated phagocytosis by human PMN, collagenase expression in human smooth muscle cells. **Miscellaneous:** IL-1 is able to replace the requirement for Ia^+ cells in the proliferation of antigen-primed T-cells. IL-1 mediates increased plasma levels of eicosanoids and IL-6 in patients with sepsis syndrome. Treatment with solIL-1R protects non-obese diabetic mice from experimental auto-immune diabetes. Two PstI polymorphisms of IL-1RI are known: RFLP-A and RFLP-B. RFLP-A is significantly associated with insulin-dependent diabetes mellitus in contrast to RFLP-B. Intra-colonic release of IL-1β is increased in chronic ulcerative colitis and cell-associated IL-1β is enhanced in inflamed mucosa. IL-1β is implicated for the *in vitro* disruption of the blood-brain-barrier (mediated by cyclooxygenase activation).	*Aspergillus* species. Autologous platelets or factors produced by them enhance production of IL-1α. Selegiline (monoamine oxidase B inhibitor) increases IL-1β production by peripheral blood mononuclear cells.
[Refs. 46, 51, 52, 54, 55, 114, 121, 177, 197]							

[a] Abbreviations: aa, amino acids; prec, precursor; 3D, three dimensional; VCAM-1, vascular cell adhesion molecule 1; ACTH, adenocorticotropic hormone; CRH, corticoid-releasing hormone; BCG, bacillus Calmette-Guérin; AG, antigen; PGE_2, prostaglandin E_2; CNS, central nervous system; BSA, bovine serum albumin; PMN, polymorphonuclear leukocyte; RFLP, restriction fragment length polymorphism.

TABLE 2. IL-1ra[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major functions	Inducers
IL-1ra IL-1i **sol IL-1ra** **icIL-1ra** **icIL-1raII** [Refs. 46, 53, 55, 90, 114, 144]	IL-1 receptor antagonist IL-1 inhibitor Soluble IL-1ra Intracellular IL-1ra	IL-1RI / CDw121a. IL-1RII / CDw121b. IL-1raBF (IL-1 receptor antagonist binding factor): present in serum and immunologically related to IL-1RI. Binds exclusively to IL-1ra. Consists of a 35-40 kDa protein backbone that is glycosylated, its carbohydrate moieties are necessary for binding to IL-1ra.	Monocytes / macrophages, neutrophils, astrocytes, keratinocytes, endothelial cells, epithelial cells, neuronal cells, fibroblasts, T-cells (small amounts). icIL-1raII: Activated fibroblasts, keratinocytes, myelomonocytic cells (at low level). Cortisol inhibits LPS-induced IL-1ra production via glucocorticoid- and mineralocorticoid-receptor.	hIL-1ra: 17.5 kDa (23-25 kDa), chromosome 2q. icIL-1raII: 25 kDa, new molecular form generated by expression of a new 63 basepair (bp) exon located 2 kb downstream of the first ic-exon.	icIL-1ra: 152 aa. Two molecular forms generated from the same gene: sol IL-1ra and icIL-1ra. They differ because of the absence of a leader sequence in icIL-1ra and are differentially regulated.	**Inhibits:** All known effects of IL-1α and IL-1β by competing for binding to the IL-1R. ***In vivo* inhibition of:** Death from endotoxin and bacterial infections, endotoxin fever and systemic IL-6 induction in rats, LPS-induced pulmonary inflammation in rats, cerebral malaria in mice, arthritis in rodents, diabetes mellitus in rats, graft-versus-host disease in mice, inflammatory bowel disease in rats and rabbits. Neutralization of IL-1ra (antibody) leads to exacerbation of inflammation in animal models of formalin-immune complex arthritis, *Schistosoma mansoni* egg-induced granuloma formation, and *Propionibacterium acnes*-induced hepatitis. **Miscellaneous:** icIL-1ra, icIL-1raII and sol IL-1ra have similar capacities to inhibit IL-1 activity in terms of induction of E-selectin and HIV replication. icIL-1ra alters IL-1-inducible gene expression without blocking exogenous signaling by IL-1β (attenuates IL-1 responses downstream of the initial IL-1~IL-1R interaction by decreasing IL-1 mRNA stability). The role of IL-1ra *in vivo* is modulation of inflammatory events mediated by IL-1, whereas icIL-1ra is suggested to act by destabilizing IL-1-induced mRNA's. **Rat:** studies with mutant proteins yIL-1βΔ4 (binds preferentially to rIL-1RII) and yIL-1βN7/Q (binds equally well to IL-1RI and IL-1RII) showed that IL-1RI exerts gastroprotective effects against indomethacin-induced ulcers while stimulation of IL-1RII leads to an anti-secretory (gastric acid) response.	LPS. IL-4. TGFβ. TNFα (enhanced by IL-10). IgG. Ultraviolet light (UVB) induces IL-1ra in mouse epidermal cells [90].

[a] Abbreviation: aa, amino acid.

TABLE 3. IL-2[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-2 LMF BF TCGF [Refs. 4, 35, 122, 177]	Interleukin-2 Lymphocyte mitogenic factor Blastogenic factor T-cell growth factor	IL-2Rα / CD25 (dissociation constant (K_d) 5-10 nM). IL-2Rβ / CD122 (K_d ~70 nM). IL-2Rγ. α-chain: Tac-ag, 55 kDa. β-chain: 75 kDa. γ-chain: 64 kDa, shared with IL-4R, IL-7R and IL-9R. The 3 chains form a functional high-affinity receptor (K_d 5-80 pM) and are members of hematopoietic cytokine receptor superfamily. Human: αβγ trimer (K_d 10^{-11} M) or βγ dimer (K_d 10^{-9} M) → signal transduction. Mouse: only αβγ trimerization leads to signal transduction. Cytoplasmic domain of IL-2 Rα is dispensable for mitogenic signaling. Human and mouse IL-2R sytems differ in that the α-chain is absolutely required for a functional (binding and signaling) mouse IL-2R. Therefore, regulation of $CD8^+$ T-cell growth during immune reaction in the mouse depends upon α-chain expression. Soluble bioactive form of IL-2 R (δMST) = 178 N-terminal aa-residues of mature IL-2R. Staphylococcal enterotoxin A or B (super-antigen): - after 4 h: IL-2Rα unaffected, IL-2Rβ down-regulated and IL-2Rγ slightly up-regulated. - after 16 h: IL-2Rα upregulated, IL-2Rβ remains low and IL-2Rγ up-regulated. [Refs. 6, 48, 56, 84, 94, 118, 136, 178]	T-cells (T_H0, T_H1), CD4 >> CD8. (B-cells, NK cells). PGE_2 inhibits acquisition of ability to produce IL-2 by naive $CD4^+$ T-cells. Enhanced in serum during the onset of insulin dependent diabetes mellitus.	hIL-2: 15-20 kDa, chromosome 4q. mIL-2: 15-30 kDa. Homology h - m: 63% aa. Bioassay: Proliferation of IL-2-dependent CTLL-2 indicator cells. hIL-2 is also active on rat and mouse cells.	153 aa incl. 20 aa leader sequence. IL-2 gene expression can be blocked by cyclosporine. Suppression of IL-2 gene transcription by T2 (*Tripterygium wildfordii* Hook F extract).	**Promotes:** T- and B-cell growth and differentiation, immunoglobulin secretion by B-cells, NK cell growth and (cytolytic) activity, production of the cytokines IFNγ, TNFβ and BCGF, development of LAK cells. **Induces:** IL-2 alone induces proliferation of T_H2 cells (IL-4 and IL-5 producers) and generates IgG_1 and IgE secreting cells. IL-2 + IFNγ induces T_H1 cells which activates macrophages, induces delayed type hypersensitivity responses and IgG_{2a} (but not IgE). Eosinophilia, capillary leak (*in vivo*). **Enhances:** IL-7R expression on γδ intra-epithelial lymphocytes. **Miscellaneous:** Il-2 plays a major role in the control of memory T_H-cell induction. IL-2 is elevated in intestinal mucosa lymphokine-secreting cells of patients with active Crohn's disease. IL-2 is involved in the *in vivo* maintenance of self-tolerance in mice [91].	Antigen / mitogen. Superantigens: - pyrogenic exotoxin A. - staphylococcal toxic shock toxin-1. - staphylococcal enterotoxins. - M-proteins.

[a] Abbreviations: Tac-ag, T-cell accessory antigen; PGE_2, prostaglandin E_2; aa, amino acid; incl., including.

tokines is one of the side effects. However, B and T cells express high-affinity IL-2Rs while NK cells express low-affinity IL-2Rs; therefore, low doses of IL-2 may be beneficial in increasing the numbers of B and T cells without induction of proinflammatory cytokine production by NK cells.

IL-3

Murine IL-3 (Table 4) was first described in 1974 as a factor released from T cells after stimulation with the mitogen phytohemagglutinin (PHA) and was named CFU-stimulating activity. Later this factor was renamed IL-3 because treatment of splenic lymphocytes with this factor gave rise to mature T cells. Several years after the discovery of murine IL-3, the human equivalent was identified from a cDNA clone from concanavalin A (ConA)-activated human T-helper cells.

IL-3 exerts its ability to support multilineage-colony formation early in the development of multipotent progenitors and exhibits synergy with stem cell factor in inducing human $CD34^+$ cells to form basophils and mast cells. IL-3 apparently supports only a few cell divisions, giving rise to neutrophils or erythroid bursts only upon addition of granulocyte-macrophage CSF (GM-CSF) or erythropoietin, respectively. These observations are in agreement with data indicating that multilineage colonies become less sensitive to IL-3 as they mature. IL-3 has indeed been used successfully in combinations with later-acting factors such as GM-CSF to stimulate hematopoiesis in primates. In addition, sequential administration of IL-3 and IL-6 in primates stimulates thrombopoiesis.

Based upon in vitro studies, IL-3 may be an effective treatment for reversing the hematopoietic toxicity associated with zidovudine. Furthermore, therapies directed at down-regulating IL-3 or its receptor may be an effective treatment in patients with non-Hodgkin's lymphoma because of the ability of IL-3 to promote the proliferation of follicular B cells from lymphomas (34). In clinical trials IL-3 has been used in combination with other CSF as a possible treatment for aplastic anemia (80).

IL-4

Formerly designated B-cell growth factor (BCGF) (Table 5), IL-4 was first described in 1982 as a factor present in the supernatants of cultures of phorbol myristate acetate-stimulated thymoma cells (EL-4) capable of supporting the growth of anti-immunoglobulin (Ig)-stimulated B cells by driving them into the S phase (92).

IL-4 is also designated as a type 2 cytokine because it is mainly produced by T_H2 cells. Indeed, when it was shown that $CD4^+$ cells do not constitute a homogeneous class of cells, IL-4 together with IL-5, IL-10, and IL-13 proved to be produced primarily by the $CD4^+$ subset (T_H2) whereas the other subset (T_H1) mainly produced IL-2, IFN-γ, and TNF-β. T_H1 cells are assumed to be well suited for induction of enhanced microbicidal activity by macrophages (enhanced cellular immunity), whereas T_H2 cells make products that are well adapted to help B cells develop into antibody-producing cells. Apart from its involvement in the generation of the humoral immune response, a striking effect of IL-4 is its ability to suppress many monocyte proinflammatory responses such as IL-1 and TNF-α production, and it may thus act as an anti-inflammatory cytokine involved in the fine-tuning of an immunological response (32, 35, 116, 154). Therefore, IL-4 may hold promise as a therapeutic agent in chronic inflammatory processes. However, during lepromatous leprosy the enormous accumulation of intracellular organisms is associated with IL-4 production. On the other hand, tuberculoid leprosy, in which there are very few organisms and little tissue damage mediated by immunologically induced inflammation, is characterized by T_H1 cell responses. Furthermore, IL-4 is involved in the pathogenesis of *Leishmania* infection (126). Few infections in which IL-4 production correlates with protection are known; e.g., in nematode infections in mice, IL-4 is involved in clearance of the primary infection and in immunity to rechallenge.

As a multifunctional cytokine that can augment certain T- and B-cell responses, IL-4 may have potential therapeutic value in several instances, such as reconstitution of humoral and cellular immune function following bone marrow transplantation, induction of terminal differentiation of acute lymphoblastoid leukemias, and amelioration of immunodeficiency associated with hyper-IgM syndrome (88).

IL-5

Eosinophil differentiation factor (Table 6), later designated IL-5, was first isolated and characterized in 1985 from conditioned culture supernatants of parasite-specific, antigen-stimulated T-cell clones isolated from *Mesocestoides corti*-infected mice. However, in the early 1970s the first observations that foretold the discovery of IL-5 had been made: eosinophilia was shown to be a T-cell-dependent condition, and supernatants of activated murine spleen cell cultures were shown to be capable of inducing eosinophil colony formation.

Mainly produced by activated T cells, IL-5 exhibits activity on eosinophils (chemotaxis and activation), basophils (activation), B cells (differentiation), and thymocytes (up-regulation of IL-2R). Some observations made with IL-5 in mice have not yet been confirmed in humans, i.e., induction of B-cell differentiation, synergism with IL-2 in production of cytotoxic T lymphocytes (CTL) from thymocytes, and BCGF II activity (167).

Based on the activities of IL-5 in humans one can only speculate about possible therapeutic uses for this cytokine. During schistosomiasis, IL-5 may be beneficial through its activating effect on eosinophils (28). Conceivably, IL-5 antagonists may be of benefit in hypereosinophilic syndromes (180) or in reducing the production of asthma-related lesions of respiratory epithelium (73).

IL-6

One of the oldest names for IL-6, IFN-β_2, came from observations that fibroblastoid cells could be induced to produce a protein with weak antiviral activity. Since then IL-6 has received a large number of designations based upon its great variety of effects (Table 7) (190). One of the best-known biological effects of IL-6 is undoubtedly the induction and control of acute-phase protein synthesis and release by hepatocytes in response to noxious stimuli such as trauma, infection, and burns (8). An additional important effect is the stimulation of growth and differentiation of and antibody production by B cells. Therefore, IL-6 is considered to play an important role in host defense mechanisms. Abnormal production of IL-6, however, has been suggested to be involved in the pathogenesis of a variety of diseases, such as rheumatoid arthritis, Castelman's disease, mesangial proliferative glomerulonephritis, and several autoimmune diseases (103, 179). Furthermore, there are several indications that IL-6 is a possible autocrine growth factor for human myeloma cells. Although IL-6 is produced early in inflammation (shortly after IL-1 and TNF-α) and displays several proinflammatory properties (e.g., maturation and activation of neutrophils, maturation of macrophages, differentiation and maintenance of CTL and NK cells, and increased expression of IL-1 and TNF-α), it cannot be regarded as a

TABLE 4. IL-3[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducing condition
IL-3 CSF-2α CFU-SA HCGF BPA PSF [Refs. 34, 80, 121, 124]	Interleukin-3 Colony stimulating factor 2α CFU stimulating activity (factor) Hematopoietic cell growth factor Burst promoting activity Persisting cell stimulating factor Multi-CSF Histamine producing cell stimulating factor Multilineage hemopoietic growth factor Thy-1 inducing factor Mast cell growth factor Eosinophil-CSF Megakaryocyte-CSF Erythroid-CSF Neutrophil-granulocyte CSF Hemopoietin-2 Synergistic activity factor WEH1-3 growth factor Pan-specific hemopoietin	IL-3R / CD123, heterodimer. h: α-chain (ca. 70 kDa, low affinity) and β-chain (130-140 kDa). Association of both chains forms high affinity receptor ($K_d \sim 5x10^{-11}$ M). Both chains are members of hematopoietic cytokine receptor superfamily. α-chain homologous with IL-5 Rα and GM-CSF-Rα. β-chain (KH97 = human β-chain, AIC2B = mouse β-chain) shared by IL-5Rα and GM-CSF-Rα and can react with all three distinct α-chains. IL-3R expressed on subset T_H2 cells, induced by TCR stimulation. TCR stimulation + IL-3 → IL-4 production + proliferation. MoAb 7G3: hIL-3ra, recognizes N-terminal part of hIL-3 Rα. [Ref. 111]	T-cells (T_H2), thymic epithelial cells, activated NK cells, keratinocytes, neuronal cells, mast cells, mesothelial cells, lamina propria monocytes (production reduced by prostaglandin E_2 (PGE_2)).	hIL-3: 15-25 kDa, chromosome 5q. mIL-3: 30-40 kDa. Larger forms due to glycosylation. Species specific.	hIL-3: 152 aa. mIL-3: 166 aa precursor. Two forms of mIL-3 are generated from the same precursor: 134 aa and 140 aa residues. Homology m - h: 45% DNA level / 29% aa level.	**Activates:** Hematopoetic progenitor cells (differentiation of early stages), mast cells (differentiation into mucosal mast cells), megakaryocyte progenitors, PMNs. **Promotes:** Proliferation of multipotential progenitor cells. **Increases:** IgM and IgG response in mice against human IgG (T-cell dependent Ag) but not against pneumococcal polysaccharide (T-cell independent Ag). **Induces:** Expression of MHC class II molecules (HLA-DR) on neutrophils, differentiation and growth of thymocytes, recovery of B- and T-cell functions in sublethally irradiated mice, chronic expression of P-selectin on endothelial cells. **Miscellaneous:** Synergizes with M-CSF in producing macrophages and with G-CSF in producing neutrophils. Synergizes with M-CSF and IL-1 in maximally stimulating growth of primitive hematopoietic stem cells. Promotes growth of mast cells in the mouse (enhanced by IL-4, IL-9 and IL-10). Interacts with IL-2 to stimulate growth of T-cells and to induce IgG secretion from activated B-cells.	T-cell activation. Cross-linking of IgE-FcR.

[a] Abbreviations: aa, amino acid; PMN, polymorphonuclear leukocyte; Ag, antigen; MoAb, monoclonal antibody.

TABLE 5. IL-4[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-4 BCGF-1 BSF-1 TCGF-2 MCGF-2	Interleukin-4 B-cell growth factor-1 B-cell stimulatory factor-1 T-cell growth factor-2 Mast cell growth factor-2	IL-4R / CDw124. hIL-4Rα chain: 140 kDa, glycoprotein, member of hematopoietic cytokine receptor superfamily (K_d 1-2 x10^{-10} M). Associated chain identical with IL-2R γ-chain [165]. Soluble form of extracellular domain inhibits biological effects. mIL-4Rα chain: 3 different forms (a 140 kDa membrane-bound receptor, a form lacking the cytoplasmin region and a soluble form). sIL-4R regulates IL-4 activity. Species specificity is due to species specific interaction with IL-4Rα chain. Present on many hematopoietic as well as non-hematopoietic cells, e.g., human fibroblasts, epithelial cells, hepatic, pancreatic, and bladder tumor cell lines, as well as murine fibroblasts, muscle cells, neuroblasts, epithelial cells, and a variety of stromal cell lines. Human colon carcinoma cells (HT-29 & WiDr): IL-4Rs do not associate with common γ-chain. High affinity IL-4Rs (140 & 70 kDa; K_d = 200 pM). Thus: IL-4R complex is composed of different sub-units in different tissues.	Naive T-cells (very low levels), $CD4^+$ Th_2-cells, MHC class I selected $CD4^-CD8^-TCR\alpha\beta^+$ T-cells (during primary immune response), $NK1.1^+$ cells (strong and fast production) basophils, mucosal mast cells (partly IL-3-dependent), monocytes / macrophages, neutrophils, B-cells, bone-marrow stromal cells. Enhanced in serum during Graves' disease.	hIL-4: 12-20 kDa. mIL-4: 12-20 kDa. Glycosylated. pI: 10.4 (h) / 6.5 (m). Gene location: chr. 5q23 - 31 (h) / 11 (m). Species specific biological action. Bioassays: hIL-4 proliferation of PHA-activated human PBL. mIL-4 proliferation of mouse HT-2 cells. Inhibition of growth of human lung carcinoma cell line CCL-185 (2 pg/ml) [153]. IL-4δ2: alternative splice variant of hIL-4. Binds to IL-4R and inhibits IL-4 stimulated T-cell proliferation. Glycosylated, 13-15 kDa core protein. mRNA expressed in peripheral blood mononuclear cells (lower than IL-4) and thymocytes (higher than IL-4). Alternatively spliced mRNA transcripts not only in activated T-cells	Precursor IL-4: 153 aa (h) / 140 aa (m). Secreted IL-4: 129 aa (h) / 120 aa (m). *N*-glycosylation sites: 2 (h) / 3 (m). Relatively high aa homology with IL-13. hIL-4 and mIL-4 share 50% aa homology.	**Promotes:** T- and B-cell growth (naive T → T_H2) and differentiation, proliferation and differentiation of B-cells, expansion and recruitment of early myeloid progenitors, IL-1ra production, VCAM-1 expression on endothelial cells (NFκB-independent), IgE production by B-cells. Enhances macrophage antigen processing and presentation. **Induces:** IL-1ra by macrophages, together with TNFα, IFNα, IL-10, IL-3, and GM-CSF. IFNγ production by NK cells, lipase production by T-cells, LAK cell activity, IL-6 and TNF production by B-cells. G-CSF, M-CSF, and IL-6 production by fibroblasts. IL-6, IL-8, and MCP production by endothelial cells. Isotype shift in B cells (towards IgE, IgG_1 and IgG_4 production) and soluble IgM production by B-cells. Activation of 15-lipooxygenase (which catalyzes 15-HETE production). CR3 (complement receptor 3) expression on and CR3-mediated ingestion by monocytes. **Inhibits:** Antigen presenting cell function, $T_H1$development. IL-1α, IL-1β, IL-6, TNF, IL-8, PGE_2, GM-CSF, G-CSF, IFNα/β and superoxide production by macrophages, TNF and serine esterase by NK cells, IFNγ production by T-cells, GM-CSF and PGE_2 production by fibroblasts, IFNγ production by IL-2 activated NK cells, IL-1β, IL-6 and IL-8 production by rheumatoid synovial cells, TNFα- or IL-1β- or LPS-induced expression of IL-8 on human umbilical cord vascular endothelial cells, ICAM-1 and E-selectin expression on endothelial cells. Reduces FcgRI, RII, RIII expression on monocytes and FcγR-mediated ingestion and decreases CD14 expression on human monocytes (mRNA level). **Suppresses:** Ig production by human B-cells stimulated with *Staphylococcus aureus* and IL-2, antibody secretion by IgA-committed human B-cells, cyclooxygenase-2 (COX2)-dependent PGE_2 synthesis in osteoclasts (→ inhibition of bone resorption), expression of α_2, α_3, β_1, and β_4 integrin subunits on HT-29 colon carcinoma cells.	Antigen / mitogen. IL-2. *In vivo* anti-CD3. Cholera toxin acts as a mucosal adjuvant to enhance T_H2 type responses and thus IL-4 production.

				but also in human lymphoid tissues, B-cells, B-cell-derived cell lines and non-lymphoid cell lines.		Down-regulates M-CSF-R on human macrophages rapidly. **Enhances:** Expression of HLA class I and class II (HLA-DR) antigens on melanoma cells, expression of VCAM-1 on endothelial cells, MHC class II expression on resting B-cells, CD23 expression on B-cells and monocytes, TNFα- or IL-1β- or LPS-induced expression of IL-6 on human umbilical vein endothelial cells, Enhancement of proliferation of granulocyte-macrophage progenitors, erythrocyte progenitors and megakaryocytes in response to G-CSF, erythropoietin, and IL-1, respectively. IL-4R expression on splenocytes. **Antagonizes:** TGFβ-induced CD16 (FcγRIII) expression on human monocytes. **Miscellaneous:** Plays a major role in modulation of the cytokine cascade. Protects mice against sepsis induced by staphylococcal enterotoxin B (superantigen).	
[Refs. 17, 35, 92, 116, 121, 154]		[Refs. 84, 94, 142, 149, 165]					

[a] Abbreviations: K_d, dissociation constant; aa, amino acid; TCR, T-cell receptor; VCAM-1, vascular cell adhesion molecule 1; MCP, monocyte chemotactic protein; PGE_2, prostaglandin E_2; TGFβ, transforming growth factor β; PBL, peripheral blood leukocytes.

TABLE 6. IL-5[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-5 TRF BCGF-II BCDFμ EDF EO-CSF IgA-EF [Refs. 19, 110, 121, 167, 181]	Interleukin-5 T-cell replacing factor B-cell growth factor II B-cell differentiation factor μ Eosinophil differentiation factor Eosinophil colony stimulating factor IgA enhancing factor	IL-5R / CD125. hIL-5Rα: 60-70 kDa, glycoprotein. hIL-5Rβ (KH97): 130-140 kDa, shared with IL-3Rα and GM-CSF-Rα. mIL-5R: α and β chain. IL-5 Rα: epitopes on loop 3 helix D region confer species specificity. [Refs. 5, 23, 94]	T-cells (T_H2), mast cells, eosinophils.	hIL-5: 21.5 kDa, chromosome 5q. Forms interdigitating glycosylated disulfide-linked homodimers of 40-45 kDa. Glycosylation not required for biological activity (13 kDa recombinant protein). mIL-5: 22-25 kDa, biologically active as 45-50 kDa glycosylated dimer. Bioassay: Proliferation of TF-1 cells (m + h).	134 aa (h) / 133 aa (m). Human-mouse homology at nucleotide (77%) and aa (70%) level. Species cross-reactivity.	**Promotes:** B-cell differentiation and isotype switch towards IgA, eosinophil differentiation and function. **Chemotactic for:** Eosinophils. **Activates:** Peritoneal B-1 (Ly-1) cells for antibody production.	Antigen / mitogen. Cross-linking of IgE FcR.

[a] Abbreviation: aa, amino acid.

TABLE 7. IL-6[a]

Acronym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-6 IFN-β_2 BCDF BSF-2 HPGF IL-HP1 HSF MGI-2A PCT-GF CDF BCDF2 [Refs. 8, 19, 32, 89, 103, 104, 105, 110, 121, 177, 179, 190]	Interleukin-6 Interferon β_2 B-cell differentiation factor B-cell stimulatory factor 2 Hybridoma / plasmacytoma growth factor Interleukin hybridoma plasmacytoma-1 Hepatocyte stimulating factor Monocyte granulocyte inducer type 2A Plasmacytoma growth factor Cytotoxic T-cell differentiating factor B-cell growth differentiating factor 2 TRF-like Factor 26 kDa protein Monocyte derived human B-cell growth factor	IL-6Rα / CD126 / gp80: ligand binding. IL-6Rβ / gp130 / CD130: non-ligand binding signaling molecule. Member of hematopoietic cytokine receptor superfamily. hIL-6Rα-chain: 80 kDa / 468 aa (incl. 19 aa putative signaling peptide, 28 aa transmembrane domain and 82 aa cytoplasmic domain), binds IL-6 with low affinity, then association of this complex with IL-6Rβ. IL-6Rβ subsequently forms homodimers which leads to signal transduction. IL-6R complex can transduce signals independent of the presence of the cytoplasmic domain of the gp80 subunit. hIL-6Rβ: 597 aa extracellular domain, 22 aa transmembrane domain & 277 aa cytoplasmic domain. mIL-6Rα: 460 aa, 69% / 54% homology with hIL-6R at DNA/protein levels. mIL-6Rβ 76.8% homology with hIL-6Rβ at aa level. Soluble hIL-6Rα present and consists of the extracellular domain of IL-6R (339 aa / 48 kDa glycosylated / 41-44 kDa non-glycosylated). It enhances IL-6 activity by transporting IL-6 to the IL-6Rβ. [Refs. 85, 89, 94, 103, 106, 198]	Monocytes / macrophages, activated alveolar macrophages, T-cells (T_H2), germinal center ($CD39^-sIgD^-$) and mantle zone ($CD39^+sIgD^+$) B-cells, eosinophils, basophils, fibroblasts, osteoblasts, hepatocytes, endothelial cells, mast cells, neuronal cells, astrocytes and glial cells, cardiac myxoma cells, thymocytes, pancreatic islet β-cells, myelomas, osteosarcomas, renal / lung carcinomas, astrocytomas. In general, IL-6 is produced later than IL-1 and TNFα *in vitro* as well as *in vivo*.	hIL-6: 22-29 kDa, chromosome 7p21. Post-translational *N*- and *O*-linked glycosylations and phosphorylations. mIL-6: 19-26 kDa, chromosome 5, *O*-linked glycosylation sites only. *C*- and *N*-terminus contains binding sites that are critical for biological functions → monomeric bivalent cytokine. Two alternatively spliced forms of hIL-6 mRNA: 26-29 kDa and 17 kDa. The 17kDa form misses the gp130 signal transducing domain but retains IL-6R (p80) domain. Therefore, it may act as natural antagonist. Belongs to the LIF, CNTF, OSM, CT-1, and IL-11 cytokine family (based on aa-sequence similarity). Bioassay: Proliferation of T1165.85. 2.1 cells (m + h) or B9 cells (h).	human: 212 aa, incl. 28 aa leader sequence and 28 aa hydrophobic signaling sequence. 2 potential N-linked glycosylation sites. mouse / rat: 211 aa, incl. 24 aa leader sequence. hIL-6 homology with rat (68%) and mouse (65%) at DNA level; 58% and 42% at protein level. Mouse and rat sequences are 93% identical. hIL-6 can stimulate mouse cells but mIL-6 cannot stimulate human cells. Half-life of mRNA enhanced by porins from *Salmonella typhimurium*.	**as IL-1 (with few exceptions) and as IL-11 (LIF and OSM). Exhibits pleiotropy and redundancy in biological activities.** **Induces:** Entry of primitive hematopoietic progenitor cells into cell cycle, maturation of megakaryocytes, myelopoiesis, acute phase proteins (hepatocytes), ACTH formation in pituitary, B-cell differentiation, infection-induced malnutrition, vascular endothelial growth factor (VEGF) expression, anemia in rats due to intestinal blood loss. HSP90 expression in human peripheral blood mononuclear cells. **Stimulates:** Hepatocytes (acute phase protein production), hematopoiesis, T-cell differentiation, growth and effector function, production of platelets (thrombopoiesis), IFNγ production by T-cells, differentiation and maintenance of cytotoxic T-cells. Neutrophils (i.e., oxidative burst and destructive capacity) [18]. **Shortens:** G_0 phase in hematopoietic progenitor cells. **Promotes:** Growth and differentiation of B-cells (into IgM and IgG secreting B-cells) and T-cells, Ig secretion by activated B-cells. IL-6 (separate or together with IL-5) greatly augments IgA production (plays a critical role in IgA B-cell development, i.e. terminal differentiation of already IgA-committed B-cells) [11, 59, 112]. Growth of mesangial cells. **Inhibits:** Proliferation of untransformed small intestinal IEC18 cells (reversible). No inhibition of transformed SW260 or HT29 colonic cell lines. Inhibitory response is lost during carcinogenic transformation. Thus, IL-6 is involved in normal growth control of intestinal epithelium. Vascular contraction (through increased cAMP synthesis), production of IL-1 and TNFα (regulatory feedback loop), neutrophil apoptosis (dependent on neutrophil concentration). **Enhances:** Antibody response to sheep red blood cells in mice. **Augments:** Cellular resistance to *Listeria* infection by activating T-cells to produce IFNγ. **Miscellaneous:** IL-6 is an endogenous pyrogen; it mediates pyrogenic effects of LPS and IL-1β.	Cytokines: IL-1, TNFα (through p55), IL-4 and IFNγ. PHA and ConA. Viruses, EBV, HIV. *Candida* species. *Mycoplasma* membrane lipoproteins (monocytes) through a mechanism distinct from LPS (involves post-translational events and critically depends on tyrosine phosphorylation). LPS (also independent of TNFα in whole blood). Platelet derived growth factor (PDGF). Muramyl dipeptide. CD40 Ligand or anti-CD40 in SV80 (transformed fibroblast cell line), NFκB-dependent. Histamine. Ca-ionophore. Endothelin-1 + thrombin (synergistically induce IL-6 mRNA in HUVECs). Leustroducsin-B. Selegiline (monoamine oxidase B inhibitor) increases IL-6 production by peripheral blood mononuclear cells.

[a] Abbreviations: aa, amino acid; ACTH, adenocorticotropic hormone; EBV, Epstein-Barr virus; sol, soluble; HUVEC, human umbilical vein endothelial cells.

TABLE 8. IL-7[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-7 LP-1 [Refs. 3, 17, 31, 108, 146]	Interleukin-7 Lymphopoietin-1 Pre-B-cell growth factor	IL-7R / CDw127. h: 75-79 kDa and 159-162 kDa chain (other studies: 93 kDa & 107 kDa chain). Member of hematopoietic cytokine receptor superfamily. Binding studies with hIL-7 to acute lymphoblastic leukemia cell lines revealed 2 classes of IL-7R's: high affinity receptor (K_d 3-5x10^{-11} M) and low affinity receptor (K_d 2-75x10^{-9} M). The high affinity IL-7R (75-80 kDa) is mainly found on T-cells, whereas the low-affinity IL-7R (62-70 kDa) is predominantly expressed on B-cells and monocytes. hIL-7R gene maps to chromosome 5p13. Soluble IL-7R present (derived from the low affinity IL-7R). Associated chain identical with IL-2R γ-chain. [Ref. 84]	Bone marrow stromal cells, fetal liver cells, intestinal epithelial cells. Transcripts found in thymus and spleen.	hIL-7: 22-25 kDa, glycosylated, chromosome 8q. Specific activity: 4x10^6 U/μg. Active at a half-maximal concentration of 10^{-13} M. mIL-7: 25 kDa, glycosylated. Contains 6 cysteine residues which are important for biological activity. Bioassay: Proliferation of PHA-activated PBL (m + h).	152 aa (h) - 149 aa (m). hIL-7 and mIL-7 share 60% aa sequence homology.	**Promotes:** Pre-B- and pre-T-cell growth and maturation (crucial factor), mature (activated) T-cell (CD4 and CD8) growth only together with ConA, proliferation and differentiation of CTL and LAK cells, NK cell function (induces TNFα production and CD56 expression). **Stimulates:** Tumoricidal activity of monocytes and macrophages, mobilization of pluripotent stem cells and myeloid progenitors, proliferation of γδ intra-epithelial lymphocytes, secretion of IL-1α/β, IL-6 and TNFα by monocytes (only in the absence of IL-4), $NK1.1^+$ cells (exquisitely sensitive to IL-7). **Induces:** ICAM-1 (CD54) expression on pre-B-cells, mRNA for IL-8 and MIP-1β in monocytes (cytokine gene expression), CD4 and CD8 expression within 1 day and CD3 expression after 2 days (IL-7 is survival-factor for triple negative $CD3^-CD4^-CD8^-$ cells). **Enhances:** T-cell function, IL-7R expression on γδ intra-epithelial lymphocytes, IL-1-induced proliferation of murine thymocytes. **Miscellaneous:** IL-7 differentially modulates IFNγ and IL-4 expression in activated T-cells by transcriptional and post-transcriptional mechanisms [17]. IL-7 is suggested to function through IL-2 production on mature T-cells (not thymocytes). IL-7 is directly mitogenic for thymocytes and acts as a lymphopoietin. IL-7 stabilizes mRNA for IL-3 and GM-CSF in T-cells after ConA stimulation. IL-7 stimulates protective immunity in mice against intracellular *Toxoplasma gondii*: enhances IFNγ response, reverses parasite-mediated down-regulatory response on IL-2 and augments $CD8^+$ T-cell-mediated CTL response.	Constitutive, increased by LPS.

[a] Abbreviations: K_d, dissociation constant; aa, amino acid; CTL, cytotoxic T lymphocyte; PHA, phytohemagglutinin; LAK cells, lymphokine-activated killer cells; NK, natural killer cells.

TABLE 9. IL-8[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-8 NAP-1 MDNCF MDNAP NAF GCP [Refs. 19, 24, 32, 40, 79, 107, 113, 141, 177]	Interleukin-8 Neutrophil attractant activating protein-1 Monocyte-derived neutrophil chemotactic factor Monocyte-derived neutrophil activating peptide Neutrophil activating factor Granulocyte chemotactic protein T-lymphocyte chemotactic factor Leukocyte adhesion inhibitor	IL-8R / Cdw128. 58 kDa and 67 kDa. IL-8Rα (IL-8RA / CXC-CR1) and IL-8Rβ (IL-8RB / CXC-CR2). IL-8Rα: K_d = 0.8-4 nM, binds IL-8 exclusively. IL-8Rβ: K_d = 0.3-2 nM, also binds GROα and NAP-2. Thus, 2 distinct (recycling) receptors with seven membrane-spanning domains, coupled to G-protein receptor family, shared with other members of the inflammatory protein family. IL-8R is coupled to specific hetero-trimeric G-proteins, incl. G(i) and G(16). IL-8R is transcriptionally enhanced by G-CSF. IL-8R is transcriptionally and post-transcriptionally down-regulated by LPS. IL-8RA/B: 77% aa identity. At 37°C the IL-8~IL-8R complex is rapidly internalized (Ca^{2+}-dependent). Serum-activated LPS (10 ng /ml) induces expression of functionally active IL-8R expression by 120% within 30 min. through *de novo* protein synthesis; these receptors are downregulated within 90 min. at 37°C by metalloproteases or aminopeptidases. [Refs. 107, 201]	Monocytes / macrophages, activated alveolar macrophages, T-cells, fibroblasts, chondrocytes, synovial cells, keratinocytes, endothelial cells, epithelial cells, hepatocytes, neoplastic cells, neutrophils, mesangial cells, smooth muscle cells, amnion cells, astrocytes, eosinophils (C5a, FMLP), respiratory epithelial cells (in response to diverse *Pseudomonas aeruginosa* gene products).	hIL-8: 8-10 kDa, chromosome 4q12-21. pI 8.0-8.5. Forms homodimer with intersubunit disulfide bonds. 4 cysteine residues. Heat-stable and resists extreme pH. Multiple forms that differ in truncation at *N*-terminus (dependent on source). Member of the inflammatory and growth regulatory protein family / chemokine α or CXC family. Bioassay: Proliferation of human neutrophils (hIL-8).	69-77 aa (h) (99 aa pre-cursor).	**Chemotactic for:** Neutrophils (activates also), T-lymphocyte subsets, basophils (and activates histamine release), keratinocytes (and activates), melanoma cells. Enzymes: myeloperoxidase, α-mannosidase, β-glucuronidase. **Induces:** Degranulation (lysosomal enzymes) by neutrophils, respiratory burst in neutrophils, leukotriene B_4 (LTB_4) release from neutrophils, adherence of peripheral mononuclear cells to unstimulated endothelial cells through enhanced expression of CD11/CD18 (these cells do not bind well to TNF-stimulated endothelial cells), adherence of mononuclear cells to endothelial cells, cellular shape change, calcium mobilization, upregulation of complement receptors CR1 & CR3 in human neutrophils, infection-induced malnutrition. **Stimulates:** Transendothelial chemotaxis of $CD3^+$ T-cells. **Monodansyl cadaverine (MDC):** 70% inhibition of IL-8~IL-8R endocytosis, 70% inhibition of IL-8-mediated chemotaxis, 66% inhibition of IL-8-induced neutrophil oxidative burst.	LPS. Viruses. Cytokines (TNF, IL-1). Tissue invasion. Soluble CD23 (IL-8 by monocytes). *Candida albicans.* IgG.

[a] Abbreviations: K_d, dissociation constant; GROα, growth-related oncogene α; FMLP, formyl-Met-Leu-Phe; aa, amino acid; incl., including.

TABLE 10. IL-9[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-9	Interleukin-9	hIL-9R: 64 kDa, member of hematopoietic cytokine receptor superfamily. Associated chain identical with IL-2R γ-chain, K_d ~100 pM.	T (T_H2) cells (IL-2 mediated).	hIL-9: 32-39 kDa, glycosylated, chromosome 5q31-35.	126 aa (h).	**Promotes growth of:** T-cells, mast cells (when combined with IL-3), erythroid progenitors (synergizes with EPO), megakaryocytes.	Antigen / mitogen.
MEA	Mast cell growth-enhancing activity				High sequence homology between mIL-9 and hIL-9 (56% at aa and 69% at nucleotide levels).	**Enhances:** Mast cell activity, T-cell survival, IgG and IgE production synergistically with IL-4. Differentiation of hippocampal progenitors.	
TCGF III	T-cell growth factor III	hIL-9R: 522 aa (53% homology with mIL-9R), 231 aa cytoplasmic domain.		mIL-9: 20-30 kDa, glycosylated, chromosome 13.			
p40		mIL-9R: 468 aa, 2 hydrophobic regions (signal & transmembrane domain), 233 aa extracellular domain., 177 aa cytoplasmic domain.		mIL-9 - hIL-9: 55% homology at protein level.			
[Ref. 121, 159]		[Refs. 94, 159]		Bioassay: hIL-9: proliferation of M07e cells. mIL-9: proliferation of TS-1 cells.			

[a] Abbreviations: K_d, dissociation constant; aa, amino acid; EPO, erythropoietin.

typical proinflammatory cytokine. IL-6 possesses some anti-inflammatory properties as well: it inhibits the synthesis of IL-1 and TNF-α in response to several stimuli, it suppresses the production of macrophages induced by macrophage CSF (M-CSF), it protects against lung damage during pulmonary inflammation, and it induces inhibitors of matrix metalloproteases. Even during allergic inflammation, IL-6 suppresses the formation of IgE-producing plasma cells (88, 103). Studies with IL-6-deficient mice revealed an impaired immune and acute-phase response in deficient animals (109). Furthermore, in several animal models of infection IL-6 appears to be involved in protection, e.g., in infections with *Helicobacter felis* (20), *Listeria monocytogenes* (42), *Escherichia coli* (43), and *Candida albicans* (162). The lack of protection in these models is linked to inefficient neutrophilia, impaired T_H1 development, or both.

IL-7

In 1988, a factor called lymphopoietin-1 was first described. This factor was capable of supporting the growth of pre-B cells in the absence of other cytokines or stromal cells. Later it became clear that this cytokine, now designated IL-7, displays stimulatory effects on many types of lymphocytes (Table 8) (17, 31, 146). Indeed, studies with IL-7 transgenic mice pointed out that IL-7 is important for B- and T-cell development in vivo. More specifically, IL-7 stimulates development of pro-B cells into pre-B cells, common B/T-cell progenitors into prethymic pre-T cells and intrathymic pre-T-cells into mature thymocytes, $CD4^-$ $CD8^+$ thymocytes into CTL or LAK cells, and NK cells into NK-LAK cells (3). IL-7 has also been reported to have T-cell growth factor activity for early T-cell progenitors; in this effect, stem cell factor synergizes with IL-7. Inhibitory regulation of IL-7-induced pre-B-cell colony formation is displayed by IL-1α and transforming growth factor β (TGF-β) (3).

No data from clinical studies with IL-7 have been published yet, and one can expect a variety of side effects to occur, as has been shown for IL-2. However, IL-7 holds promise as a treatment for human cancers because of its effects on LAK cells and CTL. The stimulation of lymphoid regeneration in patients with lymphopenia as a result of B- and T-cell immunodeficiency disorders or chemotherapy may be another therapeutic application of IL-7 (108).

IL-8

In the late 1980s, several laboratories independently isolated a novel protein with neutrophil-activating capacity, and hence this protein was called neutrophil-activating protein-1 (NAP-1) (Table 9). Based on its chemotactic properties (141), this protein was categorized within a newly identified group of other chemotactic proteins, the chemokines (described below).

IL-8 is produced by macrophages (together with IL-1, IL-6, and TNF-α) soon after infection or tissue injury. Several investigators found that neutrophils not only respond to IL-8 but also are capable of synthesizing IL-8 and other chemokines under the appropriate conditions. Therefore, the classic view of neutrophils as being terminally differentiated cells with high phagocytic and low protein-synthesizing activities had to be adjusted. The biosynthetic activity of these cells must be considered an important source of cytokines during acute infection, since neutrophils may comprise up to 70% of the circulating pool of leukocytes. In addition, localized inflammatory responses are usually characterized by the influx of neutrophils into the affected tissue followed by the recruitment of mononuclear cells, indicating that neutrophils may play a role in mononuclear cell elicitation. Vascular endothelial cells are involved in the control of leukocyte trafficking during diapedesis,

TABLE 11. IL-10[a]

Acronym, or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-10 CSIF	Interleukin-10 Cytokine synthesis inhibitory factor	IL-10R: 90-110 kDa, related to IFN receptors. Characteristics of the receptor remain to be defined.	**T-cells:** Human T_H0, T_H1, T_H2. Murine T_H2 (delayed production). $CD8^+$ T-cells. **B-cells:** Ly-1 B-1-cells ($CD5^+$, the main source of IL-10). Germinal center and mantle zone B-cells. Activated monocytes (monocytes that fail to secrete IL-10 may express IL-10 on their surface [66]), Kupffer cells (expression in response to LPS), keratinocytes, mast cells, thymocytes, various tumor cell lines, certain melanomas, ovarian and colon carcinomas. Enhanced in serum during Graves' disease. IL-10 mRNA after LPS (h): $CD14^{++}$ monocytes within 4 h., $CD14^+/CD16^+$ monocytes no mRNA after 4 h (high TNF) but low expression after 16 hrs. IL-10 production is up-regulated by cAMP and PGE_2. Phosphodiesterase (PDE) IV is positively involved in the production of IL-10. IL-10 release elicited by LPS is not mediated by PAF or IL-6.	hIL-10: 18 kDa, forms homodimers, non-glycosylated, chromosome 1. mIL-10: 17 kDa non-glycosylated form and two glycosylated forms (19 and 21 kDa). Homologous to Epstein Barr virus gene (BCRF1). 73% homology between mIL-10 and hIL-10. hIL-10 acts on mouse and human cells; mIL-10 is species specific. Bioassay: MC/9 cells (m + h).	178 aa including 18 aa leader sequence (h).	IL-10 is a pleiotropic cytokine that modulates the functions of many immunocompetent cells including T-, B-, and NK cells, monocytes / macrophages, and neutrophils. **Coactivates:** T_c-cells and thymocytes (with IL-2 and/or IL-4). B-cells: MHC class II expression, viability, Ig secretion (IgG_1, IgG_3 and IgA) and thus stimulates B-cell proliferation and differentiation but not Ig-class switch and proliferation of LPS-stimulated B-cells. Mast cells (growth), stem cells, T-cell growth. IL-10 & anti-CD40: B-cells → plasma cells. Peritoneal B-1 (Ly-1) cells (for antibody production, as IL-5). **Inhibits (through inhibition of IL-1β and/or IL-12):** [44] IFNγ production by T_H1 cells, antigen presenting cell function. IL-1, IL-6 and TNFα production of macrophages in response to LPS and IFNγ at the transcriptional level (also in Kupffer cells). Monocytes / macrophages and NK cells (MHC II, IL-1, IL-6, TNFα, nitric oxide, reactive oxygen but not nitrogen intermediates, parasite killing). Macrophage-dependent development of T_H1 cells and cytokine production by T_H1 cells. CD1 expression. Prevents antigen-specific T-cell proliferation. TNFα- or IL-1β- or LPS-induced expression of IL-6 and IL-8 on human umbilical vein endothelial cells. **Induces:** IL-11R in human myeloma cell lines (HMCL produce IL-10 and express IL-10R → IL-11R). IL-1ra production by human neutrophils synergistically with TNFα and IL-4. **Stimulates:** Murine antibody responses (except IgE) correlating with a T_H1 towards T_H2 shift. Differentiation and proliferation of BFU-E and CFU-E colony growth synergistically with erythropoietin. **Enhances:** TNF-R2 mRNA and soluble TNF-R2 release by activated macrophages, IL-2Rα expression on T-cells. Augments growth and differentiation of human monocytes	Antigen / mitogen. LPS (7-8 h, max. after 24 h). LPS-induction of IL-10 mediated by TNFα. Suppressed by IL-4. Respiratory syncytial virus induces IL-10 production by human alveolar macrophages.

						cultured in M-CSF, i.e., higher expression of FcγRI, II, III and enhanced Fcγ-mediated phagocytosis, increased O_2 and H_2O_2 (zymosan), and IL-6 (LPS) production. Bcl-2 expression and survival in primary human $CD34^+$ hematopoietic progenitor cells [197]. **Miscellaneous:** Surface IL-10 regulates macrophage's bactericidal activity (negatively). Production of IL-10 by monocytes is down-regulated by IL-4, IL-13 and IFNγ. Furthermore, IL-10 down-regulates IL-10 mRNA expression in activated human monocytes. Thus, IL-10 has important autoregulatory negative feedback activity. ***In vivo* effects:** Controls the type of immune response that develops upon parasitic infections (T_H1 [cellular] / T_H2 [humoral]). IL-10 is not needed for development of T_H2 cells but limits the development of T_H1 cells during a parasite-induced T_H2 response. IL-10 is not essential for the generation of $CD4^+$ and $CD8^+$ T-cell subsets nor for B- or B-1-cells. IL-10 has no decisive function for the induction of antibody production and development of B-cell memory during the interaction of T_H2 and B-cells. IL-10 deficient mice (IL-10T) develop chronic enterocolitis / inflammatory bowel disease. They are growth retarded and develop anemia but no differences can be observed in T- and B-cell subsets in thymus, spleen, bone marrow and peritoneum. Furthermore, no differences in antibody production or class beteween IL-10T and normal mice are found. IL-10 up-regulates monocyte phagocytosis in the presence of IL-4 and IFNγ; it increases FcγRI expression (not RII and RIII) and FcγR-mediated cytotoxic activity of monocytes. IL-10 down-regulates MHC class II molecules on monocytes up-regulated by IFNγ or by IL-4 but not if up-regulated by GM-CSF + IL-4. IL-10 does not down-regulate MHC class II expression on B-cells. IL-10 protects mice from lethal LPS- and staphylococcal enterotoxin B (SEB)-induced shock but it is not involved in endotoxin tolerance [13]. Endogenous IL-10 protects mice from death during septic peritonitis. IL-10 inhibits osteoclastogenesis by inhibiting differentiation of osteoclast progenitors into pre-osteoclast-like cells (rat bone marrow). IL-10 depresses splenocyte functions in murine endotoxemia: proliferation, IL-2, IL-6 and IFNγ release. This implicates a dampening of Ag-driven cellular immune responses which may augment susceptibility to repeated or continuous invasion of microorganisms. **Phase I studies:** [93] No adverse effects with up to 50 μg/kg. Peripheral blood mononuclear cells from IL-10-treated volunteers: lower levels of IL-1, IL-6, and TNFα production for 48 h after injection of IL-10. No changes in serum-Ig levels up to 96 h after injection.	
[Refs. 13, 32, 44, 60, 66, 121, 139, 168, 177]		[Ref. 138]					

[a] Abbreviations: aa, amino acid; T_c, cytotoxic T cell; max., maximum; PGE_2, prostaglandin E_2; PAF, platelet-activating factor; CFU-E, erythroid colony-forming units; BFU-E, erythroid burst-forming units; Ag, antigen; PBMNC, peripheral blood mononuclear cells.

TABLE 12. IL-11[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-11 AGIF [Refs. 100, 147]	Interleukin-11 Adipogenesis inhibitory factor Bone-marrow-derived stromal growth factor Multifunctional hematopoietic cytokine	IL-11R. α-chain (h): 151 kDa, 422 aa, 83% aa homology between human and murine chain, K_d = 350 pM, chromosome 9p13 (h), 4 (m). β-chain: gp130 / CD130 (shared with IL-6, LIF, CNTF). An unidentified third chain is involved in IL-11 signal transduction. [Ref. 45]	Fibroblasts (stromal cells), trophoblasts, bone marrow stromal cells, fetal lung.	hIL-11: 24 kDa single polypeptide, chromosome 19q13.3-q13.4. Specific activity hrecIL-11: 2.1×10^6 U/mg. Belongs to the IL-6, LIF, CNTF, OSM and CT-1 cytokine family (based on aa-sequence similarity). Bioassay: T11 proliferation assay (h). T11 is a subline of the IL-6 dependent murine plasmacytoma cell line T1165.85.1.	h: 199 aa including 21 aa leader. hIL-11 is biologically active in mice and rats.	**as IL-6 (LIF and OSM).** **Activates:** Megakaryocyte colony formation (synergistically with IL-3), platelet and neutrophil precursors. **Stimulates:** Myelopoiesis, erythropoiesis, lymphopoiesis, Ig production by B-cells, acute phase protein synthesis, production of IL-6 mRNA in T_H-cells and monocytes. **Shortens:** G_0 in early progenitor cells. **Inhibits:** Preadipocyte differentiation, proliferation of untransformed small intestinal IEC18 cells (reversible). No inhibition of transformed SW260 or HT29 colonic cell lines. Inhibitory response is lost during carcinogenic transformation. Thus, IL-11 is involved in normal growth control of intestinal epithelium. **Enhances:** Proliferation of IL-6-dependent plasmacytoma cells, proliferation and differentiation of hematopoietic progenitor cells synergistically with IL-3 and IL-4. ***In vivo* effects:** Limits chemo/radiation therapy-induced intestinal mucosal cytotoxicity. Enhances gastrointestinal absorption of iron in rats. Does not induce IL-6.	IL-1. Leustroducsin-B.

[a] Abbreviations: aa, amino acid; K_d, dissociation constant; CNTF, ciliary neurotrophic factor.

TABLE 13. IL-12 and IGIF[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-12 NKSF (NKCF) TSF CLMF [Refs. 15, 26, 44, 49, 87, 121, 125, 176, 177, 186, 187, 205]	Interleukin-12 NK cell stimulatory factor T-cell stimulating factor Cytotoxic T-lymphocyte maturation factor EBV-transformed B-cell line factor Cytotoxic lymphocyte maturation factor	hIL-12R: 110 kDa, homologous to β-chain of IL-6R (gp130) but no binding of IL-12 to gp130 or of IL-6 to IL-12R. Relative low affinity of IL-12 for IL-12R suggests involvement of other chains to form high affinity receptor. IL-12R on PBMC from leukemic patients is upregulated by anti-CD3 monoclonal antibody (activation). IL-12Rβ2 is the binding and signal transducing component of the IL-12R. Expressed on Th_1 cells (not T_H2). Induced by IL-12 and type I interferons [161]. Continuous stimulation with antigen is required to maintain expression of the IL-12Rβ2 chain; thus, the default is loss of the IL-12Rβ2 chain and thus T_H2 development [67]. [Ref. 26]	Monocytes / macrophages, NK cells, phagocytic cells, B-cells, keratinocytes, Langerhans cells (dendritic APCs). Production of IL-12 by monocytes in response to LPS depends on the presence of leukocytes. IL-12 production is down-regulated by cAMP and PGE_2.	hIL-12 / mIL-12: disulfide-linked heterodimer of p35 (35 kDa) and p40 (40 kDa) glycosylated subunits, homologous to IL-6 / IL-6R. Bioactivity linked to p40 (p70 dimer). Level of bioactive p70 (LPS - mono's) is determined by level of p35 expression. p40 found on monocytes / macrophages and B-cells (highly regulated) while p35 is more ubiquitously and constitutively expressed. m p40: chromosome 11A5-B2. m p35: chromosome 6C. Bioassay: Stimulation of proliferation of PHA-activated human T-lymphoblasts (h). Immunoassay: p75 ELISA.	h p35: 219 aa. h p40: 328 aa. homologies (aa): m - h p35: 70%. m - h p40: 60%. mIL-12 active on murine and human lymphocytes, whereas hIL-12 is active only on human cells. Species specificity linked to p35.	**Activates:** CD4 T-cells: T_H1 induction and maturation, IFNγ production (synergizes with IL-2) → cell-mediated immunity [99]. NK cell induction, growth and IFNγ production (enhances lysis by NK and LAK cells). **Enhances:** Cytolytic activity of CTL, NK cells, LAK cells and macrophages, FasL-mediated cytotoxicity of murine Th_1 cells. IL-10 gene expression and IL-2R expression [99]. **Inhibition:** IL-4 induced IgE synthesis from B-cells. **Induces:** IFNγ production by NK cells and T-cells (optimal with IL-1β, TNFα, or B7 costimulation), differentiation of T_H1 cells from naive Th cells, IL-2Rα expression on T_H1 cells. Acts synergistically with other growth factors to enhance proliferation of hematopoietic stem cells. Regulation of cytokine synthesis and proliferation of T- and NK cells, differentiation of $CD8^+$ cells. ***In vivo* effects:** IL-12 is a costimulatory cytokine for leukemic $CD3^+$ large granular lymphocytes activated by the TCR. IL-12 functions as adjuvant for heat-killed *L. monocytogenes* and the generation of an antigen-specific T-cell response and protective immunity against *L. monocytogenes* [15]. IL-12 has proven to be of therapeutic value in a variety of mouse tumor and infectious disease models but on the other hand IL-12 plays a role in some forms of immunopathology including endotoxin-induced shock and autoimmune diseases associated with aberrant T_H1 activity. IL-12 is associated with the development of diabetes mellitus in non-obese diabetes mice. *In vivo* antiviral activity mediated by IFNγ. IL-12 protects normal and SCID mice against *Cryptosporidium parvum* infection (IFNγ-dependent protective effect) [15]. IL-12 strongly amplifies the influence of MHC class I antigens on mixed lymphocyte reaction-induced IFNγ production. IL-12 expression is enhanced in gastric mucosa of *Helicobacter pylori* infected patients.	LPS. Antigens (bacterial and parasitic). Bacterial double stranded DNA. Microbial heat shock proteins. Crude bacterial extracts. Bacterial superantigens. Yeast extracts. IFNγ. Phagocytosis + bacterial components. Inhibited by: IL-4, IL-10, IL-13 and TGFβ.
IGIF IL-1γ IL-18 [Ref. 133, 150]	IFNγ Inducing Factor Interleukin-1γ Interleukin 18	Signaling possibly involves IL-1R subunits. [Ref. 150]	Kupffer cells, activated macrophages.	hIGIF: 18-19 kDa. Protein structure shows similarities to IL-1α, IL-1β and IL-1ra. Precursor protein cleaved by ICE [134].	Precursor 192 aa including 35 aa leader sequence (h).	Activity broadly similar to IL-12. IGIF and IL-12 are synergistic but mechanistically independent (no homology). Augments NK-activity in spleen cells and induces IFNγ production by T-cells (more potently than IL-12 and through a separate pathway). Furthermore, IGIF induces IL-2 and GM-CSF production and thus enhances T-cell proliferation through an IL-2 dependent pathway. IGIF enhances Th_1 cytokine production and inhibits the production of IL-10 by concanavalin A-stimulated peripheral blood mononuclear cells. Enhances FasL-mediated cytotoxicity of murine T_H1 cells. IGIF may be involved in development of T_H1 cells and in mechanisms of tissue injury in inflammatory reactions.	

[a] Abbreviations: EBV, Epstein-Barr virus; PBMC, peripheral blood mononuclear cells; APCs, antigen-presenting cells; PGE_2, prostaglandin E_2; aa, amino acid; ELISA, enzyme-linked immunosorbent assay; ICE, IL-1β converting enzyme; SCID, severe combined immunodeficiency; LAK, lymphokine-activated killer cells; NK cells, natural killer cells; CTL, cytotoxic T lymphocytes.

TABLE 14. IL-13[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducing condition
IL-13 P-600 [Refs. 47, 102, 121, 137, 192]	Interleukin-13	hIL-13R consists of 3 subunits: 130 kDa, 75 kDa and 65 kDa. hIL-4R and hIL-13R are similar but distinct and the IL-13R is also a functional receptor for IL-4. The IL-13R is structurally different on various cell types. Murine NR4 encodes IL-13Rα which binds IL-13 with low affinity but does not bind IL-2, -4, -7, -9, and -15. This is the primary binding subunit for IL-13 and may be a component of the IL-4R. Binding induces the high-affinity IL-13R. [Ref. 47, 149]	Human activated T-cells: $CD4^+$, $CD8^+$, $CD45RA^+$, $CD45RO^+$, activated T_H2-cells (mouse and human), mast cells. Optimal production by T-cells with anti-CD28 and PMA. Additional ligation of CD3 inhibits IL-13 production. Cyclosporine enhances IL-13 production by $CD4^+$ and $CD8^+$ T-cells.	hIL-13: 10 kDa, non-glycosylated, chromosome 5. mIL-13: 10-12 kDa, chromosome 11. Bioassay: (h + m) proliferation of human TF-1 cells (human erythro-leukemic cell line). hIL-13 and mIL-13 are equally active on human cells, but mIL-13 is the preferred agent for mouse cells.	132 aa (h). Relatively high aa homology with IL-4. 58% aa homology between hIL-13 and mIL-13. 30% aa homology between hIL-13 and hIL-4.	**Promotes:** B-cell growth and differentiation (IgE, IgG_4 production), IL-1ra production by monocytes, IL-1RII expression and release by human neutrophils, production of 15-HETE (IFNγ mediated), MHC class II expression on monocytes (down-regulated by IL-10), CD23 expression on B-cells (CD23 expression and sCD23 secretion by B chronic lymphocytic leukemia cells), CD11b, CD11c, CD18, CD29, CD49e, CD13, and CD23 expression on monocytes, differentiation of dendritic cells from circulating precursors in concert with GM-CSF. **Inhibits:** IL-1α, IL-1β, IL-6, IL-8, IL-10, IL-12 p35+p40, MIP-1α, GM-CSF, G-CSF, IFNα, and TNFα production by monocytes. CD64 (FcγRI), CD32 (FcγRII), CD16 (FcγRIII), and CD14 expression on monocytes. IFNγ production by IL-2 activated NK cells, IL-2-induced proliferation of chronic lymphocytic leukemia B-cells, bone resorption through inhibition of PGE_2 synthesis in osteoclasts,cyclooxygenase-2 (COX2)-dependent PGE_2 synthesis in osteoclasts. Regulates phenotype and function of human monocytes [50, 192].	Activation of T_H2 cells.

[a] Abbreviations: aa, amino acid; PGE_2, prostaglandin E_2; PMA, phorbol myristate acetate.

TABLE 15. IL-14 and LMW-BCGF[a]

Acronym, or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducing condition
IL-14 HMW-BCGF [Refs. 1, 2, 121]	Interleukin-14 High molecular weight B-cell growth factor	Not defined.	T-cells.	60 kDa (h).	468 aa (h).	**Induces:** Differentiation and proliferation of activated B-cells (not resting B-cells). **Inhibits:** Ig secretion of mitogen-stimulated B-cells.	Activation of T-cells (mitogen).
LMW-BCGF BSF-I [Ref. 172]	Low molecular weight B-cell growth factor B-cell stimulatory factor BCGF of 12 kDa		T-cells.	12-15 kDa (h + m). pI = 6.3 - 6.6.	124 aa (h).	**Stimulates:** Growth of activated B-cells.	Activation of T-cells (mitogen).

[a] Abbreviation: aa, amino acid.

TABLE 16. IL-15[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducing condition
IL-15 IL-T [Refs. 6, 29, 58, 72, 77, 121, 128, 148]	Interleukin-15 Interleukin-T	IL-15Rα (cytoplasmic domain dispensable for mitogenic signaling). IL-2Rβ. IL-2Rγ. (see: IL-2Rs). IL-2 ~ IL-2Rβγ forms a much more stable receptor ligand complex than IL-15 ~ IL-2Rβγ. [Refs. 6, 48, 63, 72, 77]	Monocytes, T-cells (NOT produced by IL-2 producing activated T-cells), fibroblasts, endothelial cells, epithelial cells, muscle cells (myocytes), placental tissue, kidney cells (mRNA), bone marrow stromal cells.	14-18 kDa (h), chomosome 4q31. IL-15 mRNA production is selectively resistant to down-regulation by IL-4, IL-13 and TGFβ and is increased by IL-10.	73% aa homology between hIL-15 and mIL-15. No significant sequence homology with IL-2.	**as IL-2** (T-cell chemoattractant). **Activates:** T-cells and NK cells. **Stimulates:** Proliferation and activity of $CD3^+$ T-cells and $CD56^+$ NK cells, IFNγ production by NK [29] cells synergistically with hrecIL-12, GM-CSF and TNFα production by NK cells, co-stimulation of proliferation and differentiation of B-cells activated by anti-IgM, locomotion and chemotaxis of normal T-cells. **Induces:** Development of LAK cells. **Promotes:** Growth of epidermal γδ T-cells mediated by the β and γ_c chains of the IL-2R, growth of murine γδ T-cells induced by *Salmonella* infection [148]. **Enhances:** B-cell expansion and antibody production, production of NK cell-derived cytokines including IFNγ, GM-CSF, and TNFα.NK cell cytotoxicity, antibody-dependent cell-mediated cytotoxicity, recruitment and activation of T-cells into synovial membrane [128]. ***In vivo:*** Enhanced IL-15 protein and mRNA in granulomata of patients with granulomatous leprosy in contrast to lepromatous leprosy. Blood monocytes of both types of patients are equally capable of IL-15 production *in vitro* in response to *Mycobacterium leprae*. Therefore, IL-15 may be involved in immunomodulation of T-cell responses in intracellular infection [97].	Cell activation. Bacterial infection.

[a] Abbreviations: aa, amino acid; TGF, transforming growth factor; NK cells, natural killer cells; LAK cells, lymphokine-activated killer cells.

and it is therefore not surprising that endothelial cells can also produce IL-8.

It is obvious that IL-8 plays an important role during infection (40, 79, 194). This can be demonstrated by the correlation between IL-8 and survival in septic patients, disease severity in patients with meningococcal infection, and endotoxin-induced pleurisy. In contrast, patients with *Pseudomonas pseudomallei* sepsis have a poor prognosis when IL-8 levels rise above 100 pg/ml, and in an animal model of parasitic infection (*Plasmodium berghei*), IL-8 appears to have a deleterious effect (194).

IL-9

Whereas murine IL-9 was isolated and identified in 1988 from culture supernatants of T-cell clones that contained an unusual autocrine growth factor, human IL-9 was obtained by expression cloning of factors produced by a human T-cell lymphotropic virus type 1-transformed T-cell line. This factor was named P40/TGFIII (Table 10) and could support the long-term growth of certain T-cell clones in the absence of IL-2, IL-4, or antigen. Two years later, a factor obtained from pokeweed mitogen-stimulated spleen cells was found to have a mast cell growth-enhancing activity and appeared to be identical to IL-9. Apart from its effect on T cells and mast cells, IL-9 has been found to enhance the production of IgG and IgE in synergism with IL-4 (159). Of special interest is its role in the differentiation of hippocampal progenitor cells, indicating links between the central nervous system and the immune system (130).

The role of IL-9 as an autocrine growth factor for T cells implies that it has therapeutic value in T-cell lymphomas. Indeed, blockade of IL-9 expression and IL-9-Rs has led to a subsequent growth arrest of Reed-Sternberg cells in Hodgkin's lymphoma, although IL-9 is probably not involved in the pathogenesis of most peripheral B- and T-cell lymphomas (131).

IL-10

In 1989, Fiorenzo et al. (65) found that a factor produced by activated T cells was able to inhibit cytokine production by T_H1 T-cell clones. After cloning, it became apparent that this factor exerted a large number of effects on different cell types (Table 11) (139), and it was subsequently named IL-10. Some years earlier it had become clear that the reason why strong immune responses are often biased towards either cellular or humoral reactivity is the functional dichotomy of T-helper cells (138, 139). The development of an immune response often results in a shift towards either a T_H1 or T_H2 type response. T_H1 responses are predominantly cellular, whereas T_H2 responses are characterized by strong humoral reactivity. Interestingly, these T-helper cell subsets can be distinguished by their cytokine production profile. IL-10 is typically produced by T_H2 cells and may therefore steer a developing immune response towards the humoral side. In line with this is the potent stimulatory effect of IL-10 on B cells, especially with respect to antibody production.

Effects of IL-10 on other cell types include the inhibition of proinflammatory cytokine production by activated monocytes/macrophages (32, 60), and IL-10 may therefore be involved in the negative regulation or control of the inflammatory response that is otherwise characterized by several autoamplifying loops. Enhanced proliferation of mast cells and inhibition of IFN-γ production by NK cells are two other major effects of IL-10 (44).

Because of the suppressive effects of IL-10, there are several promising clinical applications (138, 139). Its suppressive effect

TABLE 17. IL-16[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-16	Interleukin-16	CD4 on T-cells ($CD4^+$ T-cells).	$CD8^+$ T-cells: in lysate of unstimulated $CD8^+$ cells and secreted by histamine-stimulated $CD8^+$ cells → constitutively synthesized and stored in $CD8^+$ cells.	hIL-16: 14-17 kDa, chromosome 15q26.1 (80 kDa precursor protein).	130 aa.	**Suppresses:** $CD4^+$ T-cells: replication of HIV and SIV (transcription), mixed lymphocyte reaction, antigen-induced proliferation.	Mitogen / antigen.
ISL	Immunodeficiency virus suppressing lymphokine			Biological activity linked to 56 kDa homotetrameric form.	Human and green monkey (*Ceropithecus aethiops*) IL-16 differs in 7 non-clustered aa changes.	**Induces:** $CD4^+$ T-cells: adhesion, CD25 (IL-2Rα) and HLA-DR expression, cytokine synthesis, G_0 to G_1 cell-cycle change (no cell division), migration [153].	Histamine (asthma).
LCF	Lymphocyte chemoattractant / lymphotactic factor		$CD4^+$ T-cells: constitutive mRNA and 80 kDa precursor protein. Bioactive protein release after 18-24 h following activation.	pI 9.1.		CD4-dependent intracytoplasmic signaling in lymphocytes. Rises in intracellular Ca^{2+} and inositol (1,4,5)-triphosphate.	Serotonin ($CD8^+$ T-cells).
			GM-CSF-treated cosinophils.	hrecIL-16: bioactivity 10^{-9} - 10^{-12} M (peak 10^{-9} - 10^{-10} M).		**Miscellaneous:** Chemoattractant for $CD4^+$ T-cells, monocytes and eosinophils.	
[Refs. 30, 115]		[Refs. 30, 115]	Tracheal epithelial cells and T-cell clones from asthma patients within 4 h after histamine stimulation. mRNA determined in human brain, thymus, spleen, blood leukocytes and pancreas.				

[a] Abbreviations: aa, amino acid; SIV, simian immunodeficiency virus.

TABLE 18. IL-17[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IL-17 CTLA8 vIL-17 / HVS13 [Refs. 203, 204]	Interleukin-17 Murine T-cell derived molecule (mIL-17) viral IL-17 / *Herpes virus saimiri* gene 13 (57% homologeous to CTLA8)	IL-17R (h). 97.8 kDa / 864 aa. pI = 4.85. N-terminal signal peptide with cleavage site after aa 31 (Ala) followed by a 291 aa extracellular domain, a 21 aa transmembrane domain and a 521 aa cytoplasmic tail. Eight potential N-linked glycosylation sites in the extracellular domain. No significant homologies with any known nucleotide and protein sequences. Also binds HVS13. IL-17R mRNA found in: fetal liver epithelial cells (D11), fibroblasts (3T3), rat intestinal epithelial cells (IEC6), splenic B-cells, muscle cells (BB4), mast cells (H7), triple negative thymus cells ($CD3^-CD4^-CD8^-$) (TN), pre-B-cells (70Z/3), T-cell thymoma (EL4) and T-cell clones 7C2 and D10. [Ref. 204]	Activated (primarily $CD4^+$) T-cells.	hIL-17: 15-20 kDa. Forms disulfide-linked dimers (30-38 kDa). mIL-17: 17-21 kDa, glycosylated, chromosome 6.	155 aa (m & h). *N*-terminal signaling sequence. 77% aa homology between hIL-17 and HVS13 and 63% aa homology with rat CTLA8. rCTLA8 and HVS13 57% aa homology.	**Acts on many cells and tissues in a pro-inflammatory way.** **Activates:** T-cells. **Induces:** IL-6 (fibroblasts) and IL-8 production. **Enhances:** ICAM-1 expression on human fibroblasts. **Stimulates:** Co-stimulates T-cell proliferation (with PHA).	Mitogen. anti-CD3. anti-CD28. Ionomycin.

[a] Abbreviations: aa, amino acid; r, rat; PHA, phytohemagglutinin.

TABLE 19. NF-α, TNF-β, and LT-β[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
TNFα	Tumor necrosis factor-α Cachectin	TNF-R55 / CD120a / TNF-R1 / p55 / TNF-Rβ (K_d 500 pM). TNF-R75 / CD120b / TNF-R2 / p75 / TNF-Rα (K_d 100 pM). Members of TNF-R / NGF-R superfamily (such as Fas antigen and CD40). TNF-Rs present on almost all nucleated cell types. TNF-R1 is ubiquitously expressed whereas TNF-R2 is found predominantly on hematopoietic and endothelial cells and shows a tightly regulated expression. *In vivo* analysis of TNF-R deletions has revealed a more severe phenotype of TNF-R1 compared with TNF-R2 knockout. TRADD = TNF-R1-associated signal transducer. TNF activated cell signaling primarily through TNF-R1 and to a lesser extend by TNF-R2. Transmembranous form of TNFα is superior to sTNF in activating TNF-R2 in various systems such as T-cell activation, thymocyte proliferation and GM-CSF production. Diversity of TNFα effects can be controlled through differential sensitivity of TNF-R2 for 2 soluble forms of TNFα suggesting an important physiological role for TNFα in local inflammatory responses. Both TNF-R's display differential cooperation. The ability of TNF-R2 to cooperate with TNF-R1 in TNF-R1-mediated cytotoxicity could be mapped to the binding site for TNF-R-associated factor 2 (TRAF2) [199]. TRAF1 and TRAF2 form heterodimeric complexes and associate with the cytoplasmic domain of TNF-R2. A third member is CD40bp (CRAF1,	Monocytes / macrophages, activated alveolar macrophages, T-cells (T_H1), large granular lymphocytes, B-cells, keratinocytes, neutrophils, NK cells, astrocytes, endothelial cells, smooth muscle cells, mast cells, fibroblasts, mesangial cells (kidney), germinal center and man-tle zone B-cells. PGE_2 inhibits the release of TNFα from LPS-stimulated macrophages via a feedback mechanism involving IL-10. IL-10, IL-1 and IL-6 are potent inhibitors of TNFα synthesis by PBMC. TNFα is produced by $CD4^+$ cells in the presence of MHC class-II^+ cells in response to superantigens and exotoxins ($CD8^+$ cells produce only small amounts of TNFα under the same circumstances). Peritoneal macrophages of mice produce increasing amounts of TNFα with increasing age.	h + m TNFα: 17 kDa. Expressed as 26 kDa trans-membranous precursor protein from which 17 kDa subunit is released after proteolytic cleavage. Biologically active as non-covalently linked homotrimer and as precursor (precursor is not secreted). Membrane associated form is presumably also trimeric and is active on both receptors. Chromosome 6p (h), linked to MHC gene. hTNFα only interacts with mTNF-R55 and not with mTNF-R75. Bioassay: cytolysis of L929 mouse fibrosarcoma cells. New TNFα originates from: - small intracellular pool of mRNA. - newly transcribed mRNA. IFNγ controls TNFα synthesis at the translational level. mRNA synthesis peaks 90 min. after LPS injection. Pentoxifylline inhibits TNFα synthesis (20-500 μg/rat after 1 μg LPS).	157 aa. Synthesized as large precursor (233 aa).	TNF is a potent paracrine and endocrine mediator of inflammatory and immune functions; it modulates endothelial cell functions and protects against infection in general. **Activates:** Macrophages, lymphocytes, neutrophils (enhances FcγR & CR3 expression), eosinophils, endothelial cells, fibroblasts, chondrocytes, osteoclasts, and nerve cells. **Induces:** Fever and shock-like symptoms, IL-1 and IL-6 in many cell types, parathyroid hormone-related protein (PTHrP), infection-induced malnutrition, MHC class II expression on monocytic cell line C119/9 (derived from U937), expression of adhesion molecules (VCAM-1 and E-selectin through p55), bactericidal/permeability increasing protein (B/PI) release in whole blood, NFκB activation and apoptosis through TNF-R1, IL-1ra production by human neutrophils synergistically with IL-10 and IL-4. **Cytotoxic for:** Transformed and virus-infected cells, tumor cell lines and endothelial cells. **Enhances:** CD14 expression on polymorphonuclear cells, PGE_2 synthesis of mesangial cells (kidney), IL-10 production in response to LPS, oxidative burst by neutrophils, verotoxin receptor (Gb3) expression on human umbilical cord vascular endothelial cells, proliferation and differentiation of human B-cells, primary antibody response to T-cell-dependent Ag but not to T-cell-independent Ags, alloreactive cytotoxic T-cell responses, FcγR-mediated phagocytosis by human PMN, virus-specific IgG response after primary and secondary immunization with inactivated rabies vaccine. **Stimulates:** Late shedding of TNF-R2 from human monocytes, not TNF-R1. **Regulates:** Activated synovial T-cell growth by driving them into S-phase. **Inhibits:** Collagen synthesis in human and rat granulation tissue fibroblasts. **Miscellaneous:** Increase in cAMP suppresses TNFα production and increase in cGMP increases TNFα production. TNFα is involved in control of the monocyte-mediated regulation of cytokine production by T-cells, i.e., TNFα enhances the monocyte's ability to induce IFNγ production and TNFα is also involved in LPS-induced apoptosis of $CD4^+CD8^+$ thymocytes (mouse). TNFα overcomes PGE_2-induced down-regulation of peritoneal macrophage activation. TNFα plays a critical role in non-steroidal anti-inflammatory drug-induced gastric injury.	LPS and other bacterial products (such as DNA and *Klebsiella pneumoniae* K1 and K3 capsular antigens). Viruses. *Candida* species. *Aspergillus* species. Antigen / mitogen. Superantigens. Cytokines. Immune complexes. *Mycoplasma* membrane lipoproteins (monocyte) through a mechanism distinct of LPS (involves post-translational events and critically depends on tyrosine phosphorylation). Neuropeptide substance P (aa region 4-11). Lignin derivatives increase TNFα mRNA. sCD23 (in monocytes, inhibited by IL-4 and IL-10). GM-CSF primes monocytes for TNFα & TNF-R production in response to LPS. Listeriolysin-O causes sustained transcription of the TNFα gene and production of TNFα by macrophages *in vitro*. TNFα mRNA is inhibited by tenidap, corticosteroids, and pentoxifylline. Indomethacin increases LPS-induced TNFα plasma levels in rats whereas LPS-induced TNFα is inhibited by

[Refs. 9, 10, 14, 19, 22, 46, 78, 83, 97, 185, 193, 196]		LAP1 or TRAF3) that associates with the cytoplasmic domain of CD40. [Refs. 10, 22, 78, 81, 83, 97]	T-cells (T_H1), B-cells, mononuclear phagocytes (small quantities), astrocytes. Coordinately produced with IFNγ.	hTNFβ: 20-180 kDa, x3-n polymer, chromosome 6p. Soluble or secreted form: homotrimer. Biologically active as homotrimer.		as **TNFα** (with certain exceptions). Endogenous pyrogen, stimulates catabolism, activates peripheral blood lymphocytes and vascular endothelial cells. Wide variety of effects on diverse cell types due to modulation of gene expression for growth factors, cytokines, transcription factors, cell surface receptors and acute phase proteins. Plays important role in host defense against infection and tumor growth and plays key role in lymph node development. Is not readily detected in circulation → locally acting paracrine factor.	PGE_2, dexamethasone and pentoxifylline. Platelets (autologous). Antigen / mitogen. LPS (B-cells). Pyrogenic exotoxin A (high levels TNFβ).
TNFβ LTα [Refs. 9, 10, 14, 193]	Tumor necrosis factor-β Lymphotoxin-α	As for TNFα: homotrimer binds to TNF-R1 and TNF-R2. [Refs. 10, 22, 80, 81]					
LTβ [Refs. 10, 193]	Lymphotoxin-β	Heterotrimers LT(α),$(\beta)_2$ bind to LTβ-R (= TNF-Rtp = TNF-R related protein, member of TNF-R / NGF-R superfamily). hLTβ-R and mLTβ-R: 66% aa homology. mLTβ-R gene is located very close to the TNF-R1 gene on chromosome 6. [Refs. 10, 38, 81, 145]	T-cells.	hLTβ: 33 kDa, glycosylated, chromosome 6p. Integral membrane LT. Forms hetero-trimeric complexes with LTα: α1:β2 and α2:β1.		as **TNFα / LTα**. Surface LTαβ complex is required for development of peripheral lymphoid organs.	As LTα.

[a] Abbreviations: K_d, dissociation constant; NGF, nerve growth factor; PGE_2, prostaglandin E_2; PBMC, peripheral blood mononuclear cells; aa, amino acid; VCAM-1, vascular cell adhesion molecule 1; Ag, antigen; PMN, polymorphonuclear leukocyte.

on T_H1 cells may be of use in the prevention of transplant rejection and T-cell-mediated autoimmune diseases such as multiple sclerosis and type I diabetes. Furthermore, its anti-inflammatory effect could be beneficial in sepsis, rheumatoid arthritis, and psoriasis. The observation that enhanced IL-10 production is deleterious in several intracellular parasitic infections in which macrophage- or cell-mediated immunity is involved in protection (i.e., leishmaniasis, schistosomiasis, and trypanosomiasis) implies therapeutic value for IL-10 antagonism. Furthermore, antagonism of IL-10 may be expected to have beneficial effects during the polyclonal B-cell activation and hyperglobulinemia observed in AIDS patients because IL-10 is a potential factor influencing dysregulation of B-cell growth.

IL-11

In 1989 a protein with multifunctional activity was detected in the conditioned medium of a primate bone marrow stromal cell line, and this was followed by the cloning of the human cDNA from a human fetal lung fibroblast cell line. This protein, initially called bone marrow-derived stromal growth factor, was shown in vitro to influence lymphohematopoietic stem cell and megakaryocyte progenitor cell proliferation and differentiation, erythroid progenitor cell proliferation, B-lymphocyte maturation, hepatocyte acute-phase protein synthesis, and adipogenesis (Table 12) (100, 147). This protein, now named IL-11, has a unique and slightly unusual structure but nevertheless shares some functional activities with IL-6 and even induces IL-6 mRNA synthesis in T-helper cells and monocytes. Directly or through IL-6 induction, IL-11 can enhance antibody production in primary as well as secondary antigen-specific responses and therefore can play a significant regulatory role in Ig production (147). As described for IL-9, IL-11 is involved in the differentiation of hippocampal progenitor cells, thereby linking immune and neural network development (130). The multiple activities of IL-11 in vitro prompted further investigation in nonhuman primates. Administration of IL-11 to normal primates, especially in combination with IL-3 and GM-CSF, results in increased platelet and neutrophil levels. Interestingly, in none of these studies were side effects such as fever observed. These preclinical studies imply that IL-11 may be a promising candidate for treatment of thrombocytopenia and leukopenia (i.e., as an adjunct to chemotherapy or bone marrow transplantation) (75, 76, 147).

IL-12 and IGIF

A factor produced by a human Epstein-Barr virus-transformed B lymphoblastoid cell line was found to mediate several biological effects on human T and NK cells (Table 13). Unlike other cytokines, this factor appears to be composed of two different proteins (p35 and p40) encoded by separate genes. The production of this cytokine is particularly complex because the expression of both genes is required to produce biologically active IL-12. Produced predominantly by macrophages and B lymphocytes in response to a variety of stimuli, its main effect appears to be the regulation of T-cell and NK cell functions (cytotoxicity) (187). In contrast to IL-4 and IL-10, IL-12 has been implicated in polarizing the maturation of T cells to the T_H1 phenotype (186), which through production of IL-2, lymphotoxin, and IFN-γ orchestrates the cellular immune response (26, 176). It is therefore not surprising that IL-12 produced early during infection is critically involved in protection against an array of intracellular pathogens (*Leishmania major*, *Toxoplasma gondii*, *Schistosoma mansoni*, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Cryptococcus neofor-*

TABLE 20. Interferon[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
IFNα1/α2 (>20 subtypes of IFNα) [Refs. 7, 37, 121]	Interferon-α Leukocyte interferon	IFNαβ-R / CD118 (h) 51 kDa, forms homodimers, shared with IFNβ, member of IFN receptor family. [Ref. 7]	T-cells, B-cells, NK cells, monocytes / macrophages, fibroblasts, lymphoblastoid cells.	hIFNα: 16-27 kDa, chromosome 9q.	165 / 166 aa (h).	Activates macrophages, NK cells, T_C and B-cells + other cells. Modulates MHC class I and II expression. Antiviral and antiparasitic activity. Enhances Ig synthesis. Inhibits proliferation of certain tumor cells and IL-5 production by human $CD4^+$ T-cells. Inhibits IL-12 and IFNγ production. ***In vivo* effects (human):** Decreases total cholesterol, HDL-C, LDL-C and Apo-A1 and increases Apo-B100, Apo-B100 / Apo-A1, total cholesterol / HDL-C ratio, triglyceride levels and Lp(a).	Viruses. Double-stranded RNA. Bacteria. LPS (in macrophages).
IFNβ (= IFNβ1) [Refs. 7, 37, 121]	Interferon-β Fibroblast interferon	IFNαβ-R / CD118 (h). 51 kDa, see IFN-α. [Ref. 7]	Many virus-infected cells, fibroblasts, epithelial cells, macrophages.	hIFNβ: 20 kDa, chromosome 9q. Significant homology to IFN-α's.	166 aa.	**Similar to IFNα.** Activates macrophages and NK cells. Modulates MHC class I and II expression. Antiviral activity. Inhibits IL-12 and IFNγ production. Interrupts IL-6-dependent signaling events in myeloma cells.	Microorganisms. Double-stranded RNA. Cytokines.
IFNγ	Interferon-γ Type II interferon Immune interferon	IFNγ-R / CD119 (h). 90 kDa. 2 chains: - binding chain: human chromosome 6. murine chromosome 10. - signal transduction chain. IFNγ-Rα is required for JAK-1 binding and is therefore critical for signal transduction. IFNγ produced during the generation of the $CD4^+$ T_H1 subset extinguishes expression of the IFNγ-R β-subunit resulting in T_H1 cells that are unresponsive to IFNγ. This loss also occurs in IFNγ-treated T_H2 cells. These effects define a mechanism of cellular desensitization where a cytokine down-regulates expression of a receptor subunit required primarily for	T-cells (T_H0, T_H1, and T_C), CD8 > CD4. $CD8^+$ and IL-2-producing $CD4^+$ T-cells (only CD45 RO^+ cells, not $CD45RA^+$ cells), large granular lymphocytes, endothelial cells, smooth muscle cells, NK cells, dendritic cells, B-cell lines ($CD5^+$), macrophage (cell lines), myelomonocytic cells, astrocytoma cell lines, tumor cells of non-lymphoid origin, mouse embryo fibroblasts, L929 cells (low levels). PGE_2 inhibits acquisition of ability to produce IFNγ by naive $CD4^+$ T-cells. Peripheral blood mononuclear cells produce increased amounts of IFNγ (in response to PHA) after	hIFNγ: 17-25 kDa, glycosylated, pI 8.6 -8.7, chromosome 12q. mIFNγ: 26-25 kDa, glycosylated, chromosome 10. Larger forms (38-80 kDa) due to aggregation. Noncovalent homodimer formation. No structural relation to IFN-α/β. Species specific biological action.	166 aa (h), 23 aa hydrophobic signaling sequence. 136 aa (m). Contains one cysteine which may result in a disulfide bond (implied by its decreased thermolability compared to hIFNγ).	Antiviral activity (weak). **Activates:** Monocytes, macrophages, neutrophils, NK cells, vascular endothelium (with promotion of $CD4^+$ T-cell adhesion), fibroblasts, smooth muscle cells (vasoconstriction), T_S and B-cells (differentiation). MHC class I and MHC class II expression (on many cells).ICAM-1 gene activation. Primes IL-12 p40 gene promoter in monocytic cells. **Inhibits:** General inhibition of cell growth, IL-4-induced B-lymphocyte proliferation and Ig synthesis, growth of CD_4^+ IL-4 producing T_H2 population, tumor growth. **Down-regulates:** Surface CD14 expression on purified monocytes. **Induces:** IFNγ mRNA (its own message), growth and differentiation of $CD4^+$, IFNγ, and IL-2-producing T_H1 population, IL-2R expression on mitogen-activated T-cells, TNF-R and VLA-1 ($\alpha_1\beta_1$-integrin) expression on monocytes, high-affinity FcγR expression on polymorphonuclear neutrophils, synthesis of enzymes that mediate respiratory burst (directly), rapid	Superantigens. Microorgansims. Antigen / mitogen, augmented by IL-2. IL-12 increases IFNγ production by CD45 RO^+ and $CD45RA^+$ cells. mRNA in response to inducers for IFNα/β (poly ICLC, Newcastle disease virus). mRNA inhibited by tenidap.

	signaling and not ligand binding.	cryo-preservation, monocyte and NK cell elimination or irradiation. This results from the inactivation of cryosensitive suppressor monocytes. These monocytes exert their effect through a subset of radiosensitive immuno-downregulatory T-cells.			andextensive differentiation of human neuroblastoma cells combined with TNFα [157]. **Stimulates:** Immune (T-cell) cytotoxicity (synergistically with TNFα), expansion and recruitment of early myeloid progenitors. **Enhances:** Macrophage killing of intracellular pathogens, antiviral effect of IFNα/β, antigen-specific T_H cell activity, MHC class II expression on antigen presenting cells, IL-12 production from phagocytic cells, TNFα synthesis at transcriptional level, superoxide production and pathogen killing by neutrophils (as cofactor in combination with LPS or TNF). **Miscellaneous:** Possible B-cell-specific survival/growth factor. Necessary for T-cell apoptosis in response to anti-CD3-stimulation in the absence of accessory cells. Depending on cytokine expression in a localized micro-environment, IFNγ can have opposite effects on specific T-cell subpopulations; with IFNγ by itself, apoptosis occurs, but in combination with other stimuli, proliferation and differen-tiation occur. Overcomes PGE_2-induced down-regulation of peritoneal macrophage activation. Plays a key role in human mixed-lymphocyte reaction (MLR).
[Refs. 7, 44, 63, 96, 121, 177]	[Refs. 7, 62, 121, 177, 206]				

[a] Abbreviations: aa, amino acids; T_c, cytotoxic T cell; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo, apolipoprotein; T_s, suppressor T-cell; PGE_2, prostaglandin E_2; VLA, very late appearing antigen; NK cell, natural killer cell.

mans) (15, 87, 125). Most, if not all, of these protective effects are mediated by IFN-γ. The present evidence suggests that IL-12 represents a bridge between innate resistance and adaptive immune responses and that the bias of the immune system to either a T_H1 or T_H2 response is regulated by the balance of IL-12 and IL-4 early during the immune response (15, 126).

Preclinical studies have shown that in vitro treatment of depressed NK cells from HIV-seropositive patients with IL-12 results in up-regulation of cytotoxicity within a few hours. In addition, the cytotoxicity of IL-12-treated peripheral blood leukocytes (PBL) from HIV-infected patients was also efficiently enhanced with respect to tumor-derived target cells as well as to cytomegalovirus-infected cells, and this cytotoxicity was at least as high as in PBL from healthy donors. In conclusion, the central role of IL-12 in the biology of immune responses suggests possibilities for therapeutic use in infectious diseases, allergic diseases, tumors, and immunodeficiencies and as an adjuvant in vaccinations (126). IL-12 antagonism may be beneficial in autoimmune diseases (15, 87).

A protein with effects broadly similar to those of IL-12 has recently been isolated from Kupffer cells of the liver of mice injected with *Propionibacterium acnes* followed by a challenge with lipopolysaccharide (LPS) which leads to toxic shock. This protein, named IL-γ, or IFN-γ-inducing factor (IGIF), proved to protect these mice against liver damage. Indeed, its IL-12-like activities appeared to be stronger than those of IL-12 itself, especially with respect to induction of IFN-γ production by T_H1 and NK cells (150). Its actions are independent of IL-12, but synergism with IL-12 has been observed. Its effects on T_H1 cells indicate a regulatory function in the development of immune reactions. Based on structural and functional differences from any known cytokines, it was recently proposed that this cytokine be designated IL-18 (133).

IL-13

Discovered in 1993, human IL-13 (the homolog of murine P-600) was first reported as a cytokine with IL-4-like activities and the potential to regulate inflammatory and immune responses (Table 14) (137). Like IL-4 and IL-10, human IL-13 is predominantly produced by $CD4^+$ T cells with T_H2 characteristics. Its stimulatory effect on B cells together with its effects on monocytes led to its inclusion in the IL family of cytokines (47). IL-13 inhibits the production of a large array of cytokines by monocytes in response to LPS (IL-1α, IL-1β, IL-6, IL-8, IL-10, IL-12 p35 and p40, macrophage inflammatory protein 1α [MIP-1α], GM-CSF, granulocyte CSF [G-CSF], IFN-α, and TNF-α) and increases the production of IL-1ra; therefore, IL-13 can be regarded as an anti-inflammatory cytokine (50). Apart from inhibition of cytokine production, it also induces significant changes in the phenotypes of monocytes (50, 192). The effects of IL-13 on B cells are in part also found with IL-4 (e.g., the switch to IgG4 and IgE). The fact that IL-4 and IL-13 share a large number of biological effects without noticeable synergism implies that these cytokines may have common receptor components (but not the IL-4-R-binding protein) (149). However, IL-13 acts independently of IL-4, because the activities of IL-13 cannot be blocked by anti-IL-4 neutralizing antibodies. Differences between IL-4 and IL-13 include the inability of IL-13 to support the proliferation of mitogen-induced blasts or T-cell clones and the lack of induction of CD8α expression on $CD4^+$ T-cell clones.

IL-14 and LMW BCGF

Enhancement of B-cell proliferation has been ascribed to many lymphokines, including IL-1, IL-2, IFN, and several BCGFs or B-cell-stimulatory factors. One of the human

TABLE 21. CSF[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
GM-CSF [Refs. 35, 80, 119]	Granulocyte macrophage colony-stimulating factor	GM-CSF-R / CDw116 (h). α-chain 85 kDa, glycosylated. β-chain (KH97) 130 kDa, shared with IL-3Rα and IL-5Rα. Both members of hemato-poietic cytokine receptor superfamily. hGM-CSF-Rα: cytoplasmic domain activates β-subunit. hGM-CSF-Rβ: signal transduction. Soluble hGM-CSF-R present. [Refs. 5, 94, 111]	T-cells (T_H2), fibroblasts, endothelial cells, mono-cytes / macrophages (low level of expression), mast cells, neutrophils, eosinophils (C5a, FMLP), mantle zone B-cells.	h: 14-22 kDa, glycosylated, chromosome 5q. m: 23 kDa, glycosylated. Species-specific biological action.	144 aa (h) - 118 aa (m). hGM-CSF and mGM-CSF share 54% aa homology.	**Activates and differentiates:** Multipotential hematopoietic progenitor cells, T-lymphocytes, monocytes, neutrophils and precursors, eosinophils, megakaryocytes. **Enhances:** Function of mature monocytes / macrophages, physiological activity of eosinophils and neutrophils, CR3 expression on granulocytes, CD14 expression on PMN, expression and secretion of TNF-R p55 & p75 and biologically active TNFα by monocytes, oxidative burst by neutrophils, IL-3Rα expression on neutrophils and thereby enhances MHC class II expression (HLA-DR), dendritic cell maturation and migration as well as immunostimulatory function, tumor antigen presentation by epidermal antigen presenting cells, IL-12 production from phagocytic cells, endothelial cell proliferation and migration. **Down-regulates:** Surface CD14 on purified monocytes. **Antagonizes:** TGFβ-induced CD16 expression on human monocytes. **Inhibits:** Neutrophil migration and apoptosis of polymorphonuclear cells.	Antigen / mitogen. LPS. Cytokines. sCD23 (monocytes). Leustroducsin-B (bone marrow stromal cells).
G-CSF GM-DF CSF-β [Refs. 5, 41, 80, 119]	Granulocyte CSF Granulocyte macrophage differentiation factor	G-CSF-R (h): single 150 kDa subunit protein. mG-CSF-R: 150 kDa, 62% protein similarity to h-G-CSF-R. Two membranous forms generated by alternative splicing. Member of hematopoietic cytokine receptor superfamily. On human neutrophils: K_d = 250 pM, 560/cell. [Refs. 5, 41]	Monocytes / macrophages, fibroblasts, endothelial cells, T-cells (low level of expression), neutrophils, germinal center B-cells, large granular lympho-cytes.	hG-CSF: 18-22 kDa, pI 5.5, glycosylated, chromosome 17q. mG-CSF: 24-25 kDa, glycosylated. hG-CSF and mG-CSF show biological cross-reactivity.	207 aa (h). hG-CSF and mG-CSF: 75% aa homology.	**Activates and differentiates:** Neutrophils and granulocytes and their precursors (colony formation), macrophages *in vitro*. **Enhances:** Physiological activity and survival of mature neutrophils, CD14 expression on peripheral mononuclear cells, oxidative burst and alkaline phosphatase synthesis by neutrophils, production of TNFα, solTNF-R1 & 2, and IL-1ra by LPS-stimulated human monocytes, antigen-dependent cytotoxicity, proliferation and migration of endothelial cells. Polarizes T-cells of mice towards T_H2 cytokine production and attenuates graft versus host disease.	LPS. Cytokines. Leustroducsin-B.
M-CSF CSF-1 [Refs. 5, 80]	Macrophage CSF.	M-CSF-R / CDw115 (h), found on virtually all mononuclear phagocytes, K_d = 30 pM. 165 kDa tyrosine kinase capable of auto-phosphorylation. [Ref. 5]	Monocytes / macrophages, fibroblasts, endothelial cells, granulocytes, lymphocytes, epithelial cells.	hM-CSF: 61 kDa precursor protein, glycosylated, secreted as 70-90 kDa homodimer, chromosome 5q or 1p. Different sizes due to alternative splicing. May also exist as integral membrane protein.	554 aa precursor / 189 aa mature protein (h). hM-CSF is reactive on murine cells, but mM-CSF is not reactive on human cells.	**Activates and differentiates:** Monocytes / macrophages and precursors. **Induces:** Cytokine synthesis by monocytes / macrophages. **Enhances:** Function of mature macrophages, production of monocytes, antibody-dependent cell-mediated cytotoxicity by monocytes and macrophages. **Inhibits:** Bone resorption by osteoclasts.	LPS. Cytokines. $Fc_\gamma R$ ligation (mRNA).

[a] Abbreviations: FMLP, formyl-Met-Leu-Phe; aa, amino acid; PMN, polymorphonuclear leukocytes; K_d, dissociation constant.

TABLE 22. Classification of chemokines

ELR-containing CXC chemokines		Non-ELR containing CXC chemokines		CC chemokines	
IL-8	Interleukin-8, see Table 9	**MIG**	Monokine induced by IFNγ	**MCP-1/2/3/4**	Monocyte chemotactic protein
GCP-2	Granulocyte chemotactic protein 2	**PF4**	Platelet factor 4	**MIP-1α/β**	Macrophage inflammatory protein
GROα/β/γ	Growth regulated oncogene	**IP-10**	IFNγ-inducible protein	**HCC1**	Hemofiltrate C-C chemokine 1
ENA-78	Epithelial neutrophil activating protein 78	**SDF-1α/β**	Stromal cell-derived factor-1	**CCF18**	CC chemokine F18
PBP	Platelet basic protein			**RANTES**	Regulated on activation, normal T-expressed and secreted
CTAP III	Connective tissue activating protein III			**I 309**	
NAP-2	Neutrophil activating protein 2			**Eotaxin**	
LAPF4	Low-affinity platelet factor 4				
β-Thromboglobulin					

TABLE 23. CXC chemokines[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
GROα MGSA [Ref. 33, 70]	Growth regulated oncogene Melanoma growth stimulating activity.	GROαR / CXC-CR1 and CXC-CR2: low and high affinity receptors on neutrophils.	Fibroblasts, chondrocytes, epithelial cells, monocytes/ macrophages, neutrophils (in response to LPS, TNFα or IgG-opsonized yeasts), platelets.	8 kDa (h).	73 aa (h). GROβ and GROγ share 93 and 82% identity with GROα at nucleotide level.	Chemotactic factor for neutrophils. Activates neutrophils. Stimulates proliferation of melanoma cells. GROγ induces myeloperoxidase release from cytochalasin-B treated neutrophils.	Infection.
ENA-78 [Ref. 33, 113]	Epithelial neutrophil activating peptide 78		Human pulmonary epithelial cells (A549).	8.3 kDa (h).	78 aa (h). 4 cysteines positioned identical to those of IL-8. 53% sequence homology with NAP-2 and 52% with GROα.	Shares several properties of neutrophil activation with NAP-2 and IL-8. **Induces:** Chemotactic activity in neutrophils. **Induces:** Release of elastase from cytochalasin-B pretreated neutrophils. Cytosolic Ca^{2+} -release.	TNF-α. IL-1β.
IP-10 [Refs. 24, 33, 129, 164, 182, 183]	IFNγ-inducible Protein-10		T-cells, monocytes, endothelial cells, keratinocytes.	8.5 kDa (h)		Chemotactic factor for monocytes and T-cells. **Stimulates:** Transendothelial chemotaxis of $CD3^+$ T-cells. **Promotes:** T-cell adherence to endothelial cells.	

[a] Abbreviation: aa, amino acids.

TABLE 24. CC chemokines[a]

Acronym or synonym	Full Name	Receptors	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
MIP-1α SCI LD-78 pAT464 GOS19 [Refs. 24, 33]	Macrophage inflammatory protein-1α Stem cell inhibitor	CC-CKR1 (also receptor for MCP-3 and RANTES, found on monocytes > neutrophils > eosinophils). CC-CKR4. CC-CKR5. [Ref. 24]	T-cells, B-cells, monocytes, mast cells, fibroblasts, neutrophils.	8.0 kDa (h), non-glycosylated. hMIP-1α is active on mMIP-1α cells.	69 aa (h). 75% aa similarity between h and mMIP-1α.	**Chemotactic for:** Monocytes (activates for IL-1, IL-6 and TNF production), T-cells, neutrophils, eosinophils. **Induces:** Expression of β_1-integrins on endothelial cells, endogenous pyrogen (not inhibited by cyclooxygenase inhibitors). **Inhibits:** Proliferation of early hematopoietic stem cells. **Augments:** CTL and NK cell cytolytic responses.	Infection. Endotoxin.
MIP-1β ACT-2 [Refs. 24, 33]	Macrophage inflammatory protein-1β	CC-CKR1. CC-CKR5.	T-cells, B-cells, monocytes, mast cells, fibroblasts, neutrophils.	8 kDa (h), glycosylated.	69 aa (h).	**Chemotactic for:** Monocytes (activates for IL-1, IL-6 and TNF production), T-cells. **Induces:** Expression of β_1-integrins on endothelial cells. **Stimulates:** Adhesion of T-lymphocytes to endothelial cells. **Augments:** CTL and NK cell cytolytic responses. MIP-1β can counteract the ability of MIP-1α to suppress stem-cell growth.	Infection. Endotoxin.
MIP-1γ [Refs. 24, 33, 157]	Macrophage inflammatory protein-1γ	Same receptor as for MIP-1α on neutrophils. Most other CC chemokine receptors. [Refs. 24, 156]	Expressed constitutively by a wide variety of tissues in mice. Therefore, most CC chemokine receptors in the vascular compartment are occupied. In blood compartment of normal mice: ~1 μg/ml (90 nM).	10 kDa (h).	100 aa (h).	Pyrogenic activity if injected intracerebrally.	Infection.
RANTES hSISδ [Refs. 33, 168]	Regulated on activation, normal T-expressed and secreted	CC-CKR1. CC-CKR3. CC-CKR4. CC-CKR5. Duffy blood-group antigen.	T-cells, platelets, renal epithelium, mesangial cells.	8 kDa (h), non-glycosylated.	68 aa (h). Expression down-regulated by T-cell activation.	**Chemotactic for:** Monocytes, $CD4^+CD45RO^+$ T-cells, eosinophils, and basophils (and enhances histamine release). **Augments:** CTL and NK cell cytolytic responses.	

MCP-1 MCAF [Refs. 33, 141, 156, 158]	Monocyte chemotactic protein-1 Monocyte chemotactic and activating factor	CC-CKR2a. CC-CKR2b. Duffy blood-group antigen. [Ref. 156]	Monocytes / macrophages, fibroblasts, B-cells, endothelial cells, keratinocytes, smooth muscle cells, neoplastic cells.	8-10 kDa, glycosylated, chromosome 17 (h).	99 aa precursor including 23 aa amino terminal signaling sequence (h). Mature form: 4 cysteine residues.	Chemotactic factor for monocytes (induces macrophage infiltration). Induces release of lysosomal enzymes and superoxide anion. Augments cytostatic activity. Stimulates histamine release from basophils. Regulates cytokine production in monocytes and expression of adhesion molecules on macrophages. MCP-1 increased during sepsis. Enhanced during infection and inflammation characterized by leukocyte infiltration.	$Fc_\gamma R$ ligation (mRNA). TNFα and IL-1.
MCP-2 [Refs. 33, 156, 158]	Monocyte chemotactic protein-2			8.5 kDa (h).	74 aa (h).	Stimulates eosinophils and basophils. Increased during sepsis.	
MCP-3 [Refs. 33, 36, 156, 158]	Monocyte chemotactic protein-3	CC-CKR1. CC-CKR2a. CC-CKR2b. CC-CKR3. [Refs. 36, 156]		8.5 kDa (h).	76 aa (h).	**Activates:** Monocytes, lymphocytes, NK cells, basophils, eosinophils, neutrophils, and dendritic cells.	
MCP-4 [Ref. 69]	Monocyte chemotactic protein-4	CC-CKR2 CC-CKR3	Epithelial cells, endothelial cells. Produced by mucosal epithelial cells from patients with T_H2 allergic and T_H1 non-allergic sinusitis.			Chemoattractant for monocytes and eosinophils. Stimulates histamine release from basophils.	TNFα, IL-1 (IFNγ and IL-4 synergize with TNFα and IL-1 in increasing MCP-4 mRNA in epithelial and endothelial cells).

[a] Abbreviation: aa, amino acid.

BCGFs that is capable of stimulating the growth and differentiation of activated B cells only (by antigen or cross-linking of surface membrane Ig) was purified and characterized in 1985 (2). With a molecular weight of 60,000 and homology to the murine low-molecular-weight (LMW) BCGF (12 kDa), it was initially named high-molecular-weight (HMW) BCGF and was later designated IL-14 (Table 15) (1). HMW-BCGF activity was first identified in culture supernatant of mitogen-stimulated acute lymphocytic leukemia T cells and Namalva (human B-cell lymphoma) cell lines (2). Its BCGF activity was reported to be completely independent of the presence of other BCGFs. Apart from being secreted, HMW BCGF may also be a putative intracellular precursor for another mature BCGF (1).

Human LMW BCGF was isolated in 1987 and represents the predominant molecular species released by normal lectin-activated human T cells. LMW BCGF has been defined by its comitogenic effect on activated T-cells. Studies performed by Sharma et al. (172) indicate the possibility that the BCGF gene either belongs to a multigene family or represents a differentially spliced single gene.

IL-15

Being purified from the culture supernatant of a simian kidney epithelial cell line, IL-15 represents a cytokine with biological actions similar to those of IL-2 (Table 16) (72). In fact, IL-15 activity was first determined with the assay for murine IL-2 (IL-2-dependent T-cell line CTLL). Human IL-15 was obtained by using the simian gene sequence to probe a cDNA library from the human stromal cell line IMTLH (77); murine IL-15 was obtained by similar techniques. Although human IL-2 and IL-15 share several biological effects, no significant sequence homologies were found. In contrast to IL-2, the most abundant sources of IL-15 appear to be nonlymphoid cells (i.e., muscle and placenta). No expression of IL-15 can be detected in (activated) peripheral T cells, but abundant mRNA levels were found in monocytes (29, 47), epithelial cells, muscle cell lines, and stromal cell lines derived from bone marrow and thymus. The IL-15-R is composed of three subunits, and the β and γ chains are shared with the IL-2-R and are necessary for signal transduction (6, 48, 72). The IL-15-Rα chain is unique for IL-15, and the differences in distribution compared with IL-2 imply that IL-15 may have unique roles in the development and activation of some lymphocyte subpopulations as well as additional activities outside the immune system (72, 128).

In animal models, IL-15 appears to contribute to the pathogenesis of rheumatoid arthritis by recruitment of IL-15-responsive T cells into the synovial membrane (128), whereas in humans IL-15 may be involved in modulation of immune reactivity during intracellular infection (e.g., leprosy) (97).

IL-16

Originally called lymphocyte chemoattractant factor (30), IL-16 appeared to be biologically active only in its tetrameric form, which is composed of 14- to 17-kDa chains. Although expression of the IL-16 precursor mRNA is found in $CD4^+$ as well as $CD8^+$ T cells, fully assembled bioactive tetrameric protein is present only in $CD8^+$ T cells. Structurally, IL-16 bears no resemblance to other cytokines or chemokines. The sequence and structure of the secreted form appear to be strongly conserved across species, and the predicted amino acid homology of murine IL-16 (mIL-16) with human IL-16 (hIL-16) is >85% (secreted peptide). Furthermore, mIL-16 has chemoattractant bioactivity for human $CD4^+$ T cells (153), and this activity is inhibited by antibody to human recombinant IL-16 (hrecIL-16).

Although IL-16 is predominantly secreted by $CD8^+$ T cells it is not clear yet whether these cells are classic cytotoxic lymphocytes or other $CD8^+$ subsets (115). IL-16 displays a variety of effects on $CD4^+$ T cells, monocytes, and eosinophils (Table 17). The chemotactic effect of IL-16 leading to tissue infiltration by $CD4^+$ T cells has been investigated in several disease states (30). In asthmatics, IL-16 secretion by airway epithelial cells is augmented by histamine, which suggests that IL-16 is involved in the full development of inflammatory responses. Moreover, IL-16 appears to be the only lymphocyte chemoattractant factor in the airways of persons with atopic asthma. IL-16 also appears to be involved in granulomatous inflammatory responses such as delayed-type hypersensitivity granuloma formation, sarcoidosis, and *Mycobacterium tuberculosis*-induced granuloma formation. This effect implies a possible role for IL-16 inhibitors in suppressing diseases in which IL-16 plays a prominent part. In addition, its ability to inhibit HIV replication together with the priming effect of $CD4^+$ T cells (for IL-2-induced proliferation) suggests possibilities for IL-16 in treatment of HIV infection (153).

IL-17

A protein named CTLA8 was first cloned (rodent cDNA sequence) and described in 1993, and its predicted amino acid sequence showed 57% homology with that of HVS13 of *Herpesvirus saimiri*. Recombinant HVS13 and mCTLA8 exhibit similar activities on a variety of cell types (Table 18), which was the basis for terming them viral IL-17 and mIL-17, respectively. In 1995 human IL-17 was cloned and described by Yao et al. (204). IL-17 is produced almost exclusively by activated $CD4^+$ T cells and is able to induce production of IL-6 and IL-8 by and expression of intercellular adhesion molecule-1 (ICAM-1) on human foreskin fibroblasts. The biologic activities of IL-17, its role in immune regulation, and its mechanism of action remain to be determined.

TNF AND LT

More than 20 years ago it was found that an endotoxin-induced serum factor was able to cause hemorrhagic necrosis of tumors. Isolation and characterization of two factors capable of tumor necrosis, TNF-α and LT-α (also called TNF-β), occurred 10 years later. It then became evident that TNF-α was identical to the macrophage-secreted factor cachectin, a factor first described as a lipoprotein lipase-suppressing hormone secreted by endotoxin-induced RAW 264.7 cells. Both TNF-α and LT-α are biologically active as homotrimers. LT-β is a cytokine with actions similar to those of LT-α; in fact, LT-β is bioactive as a heterotrimeric protein composed of one LT-α and two LT-β molecules or as a complex of two LT-α and one LT-β subunits. Whereas TNF-α and LT-α are mostly secreted, LT-β is strictly a transmembrane protein that acts chiefly through cell-to-cell contact. The two LT are produced mainly by T cells, whereas TNF-α is secreted predominantly by monocytes in response to inflammatory stimuli (Table 19). TNF-α and LT-α have the same receptors, TNF-RI and TNF-RII (9, 10, 22), whereas LT-β binds to its own unique receptor, LT-β-R, also named TNF-R-related protein (38, 145). The receptors initiate signals for cell proliferation and apoptosis, and these signals are required for the normal development and function of the immune system. Excessive signaling can cause severe inflammatory reactions and tissue injury and may even lead to shock. In contrast, mutations in the receptor or ligand genes can cause characteristic disturbances of lymphocytes, derangement of the immune response, or autoimmune disease (81, 83). The role of TNF-α during infection has been described in numerous studies (185). TNF-α-dependent resistance to infections has been demonstrated (e.g., *Listeria monocytogenes* infection) but, on the other hand, TNF-α has also been implicated in the pathogenesis of diseases such as endotoxic shock. Due to its high toxicity for animals as well as humans, TNF-α did not fulfill initial expectations for therapeutic application in the treatment of cancer, for example. Extensive clinical trials have been conducted to test TNF-α-neutralizing antibodies in the treatment of septic shock, but no substantial benefit was observed (185). In patients with rheumatoid arthritis, anti-TNF-α treatment has proved to lessen pain, joint swelling, anemia, and erythrocyte sedimentation rates. Potential problems for this antibody-based therapy are the lack of neutralization of LT-α, the antigenicity of murine monoclonal antibodies that prevents long-term therapy, the formation of TNF-α–anti-TNF-α immune complexes that may be harmful, and the requirement for high doses of anti-TNF-α antibodies for neutralization of TNF-α (81). A different, more promising approach for inhibition of TNF-α-mediated effects in vivo is the development of chimeric inhibitor molecules in which the extracellular domain of the TNF-R is spliced to an Ig heavy-chain fragment. Such molecules are as stable as Igs and are minimally antigenic because they are composed of two nonantigenic elements. In addition, they block the effects not only of TNF-α but also of LT-α, since their binding domain is the receptor, which has the added advantage of a higher affinity for the ligand than monoclonal antibodies.

IFN

Type I, or viral, IFN (IFN-α, or leukocyte-derived IFN, and IFN-β or fibroblast-derived IFN) were originally described as factors capable of inducing RNA and protein in target cells. They are produced during viral or bacterial infection and have significant structural and functional homologies. Type II, or immune, IFN (IFN-γ) is primarily produced by T lymphocytes in response to antigen or mitogen and has a higher molecular weight than type I IFN (Table 20) (7, 63).

Although initial clinical studies with IFN-α suggested therapeutic activity against malignant melanoma, osteosarcoma, and various lymphomas, subsequent trials demonstrated significant activity only against less common tumor histiotypes such as hairy cell leukemia, chronic myelogenous leukemia, and a few types of lymphoma. Despite IFN-α's activity against some specific leukemias and lymphomas, it has limited activity against solid tumors.

IFN-γ plays a critical role in the immune response and is the earliest detectable cytokine at the site of immunization with protein antigens. It plays a major role in the generation and regulation of the immune response and is one of the T_H1-specific cytokines that promote T_H1 responses and inhibit T_H2 responses. Enhancement of MHC class II expression on antigen-presenting cells leading to more efficient antigen presentation is also ascribed to IFN-γ. Apart from these effects, IFN-γ priming and activation of macrophages lead to enhanced production of proinflammatory cytokines in response to several stimuli. Furthermore, IFN-γ displays some adjuvant properties and plays a significant role in the control of several infections (e.g., *M. tuberculosis* and *L. major*). Apart from its value in cancer chemotherapy (157), IFN-γ has also proved effective for treatment of a variety of other diseases, such as rheumatoid and psoriatic arthritis (117), chronic granulomatous disease (170), and hepatitis B. One difficulty of the use of IFN-γ in therapy is the side effects produced (117, 170).

TABLE 25. C chemokine[a]

Acronym or synonym	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects
Lymphotactin [Refs. 33, 101]	T-cells.	10 kDa (h).	92 aa (h).	Chemotactic factor for T-cells.

[a] Abbreviation: aa, amino acid.

CSF

The major CSF comprise GM-CSF (119), M-CSF (80), G-CSF (119), and multi-CSF. The last, better known as IL-3, is described above.

In general, GM-CSF acts on bipotential stem cells to produce granulocytes and mononuclear phagocytes (119), G-CSF acts on the bone marrow to induce granulocyte colony formation (41), and M-CSF induces mononuclear phagocyte colony formation (80) (Table 21).

GM-CSF and G-CSF have proven to be of therapeutic value in the treatment of neutropenia arising from various causes (e.g. cancer chemotherapy, bone marrow transplantation, or infectious diseases), and generally, the duration as well as degree of neutropenia is reduced (120). In patients with myelodysplastic syndrome, recombinant GM-CSF has proven to increase not only numbers of monocytes and eosinophils but also numbers of killer T cells and nonactivated T-helper cells (phase I/II clinical trial) (68). On the other hand, the therapeutic benefit of M-CSF seems to be more modest. It had only slight effects on circulating-leukocyte levels when given to leukopenic patients. Beneficial effects of M-CSF, such as activation of host defenses against viral, bacterial, parasitic, and fungal infections, can be expected because of its enhancement of monocyte function. In addition, M-CSF induced the terminal differentiation of peripheral blood blast cells from some patients with acute myeloid leukemia in vitro and may therefore hold promise for treatment of leukemia (140).

CHEMOKINES

Basically, chemokines can be considered proinflammatory cytokines with chemotactic properties. They are involved in the initiation and propagation of inflammatory responses that are characterized by sequestration of neutrophils at the site of infection or tissue injury (113, 135). The chemokines have been divided into two groups of related polypeptides (supergene families) based on structural similarities in their primary amino acid sequences: CXC, or α, chemokines and CC, or β, chemokines. The CXC and CC chemokine genes cluster on chromosomes 4 and 7, respectively, except the gene for CXC chemokine stromal-cell-derived factor-1, which is located on chromosome 10 (16).

Over 12 different CXC chemokines, most of which have strong neutrophil chemotactic and activating properties, have been described. This property appears to be based on a specific amino acid sequence immediately preceding the first cysteine, the so called ELR motif (Glu-Leu-Arg) (33, 164). Indeed, chemokines lacking this motif (MIG, PF4, and IP-10 [see Table 22]) have relatively weak neutrophil-activating capacities. Table 22 lists the CXC and CC chemokines, and Tables 23 and 24 describe the properties of some representatives of CXC and CC chemokines, respectively. The members of the CC supergene family (Table 24) have relative specificity for the elicitation of mononuclear cells (macrophages and T cells), and some members appear to be potent chemotactic factors for eosinophils and basophils.

Lymphotactin is a structurally unique chemokine that bears only minor similarities to some CC chemokines. In contrast to the other chemokines it is mainly produced by T lymphocytes and is a strong chemotactic factor for T cells (Table 25). Due to its effects and structure it may represent a third supergene family of chemokines (C chemokines) (101).

MISCELLANEOUS CYTOKINES

Cytokines involved in the development and regulation of immune responses that cannot easily be categorized in other groups are summarized in Table 26.

CYTOKINE RECEPTORS

Characteristic features of cytokines are their functional pleiotropy and redundancy. This can in part be explained by the molecular biology of the cytokine receptor systems (45, 62, 85, 122). Most cytokine receptors consist of two or more membrane proteins, and generally only one of these subunits displays specific binding properties (private ligand-specific receptor). The others have no ability to bind the ligand but are associated with signal generation and transduction (public class-specific signal transducer). Binding of the ligand to the ligand-specific subunit leads to oligomerization of the subunits, which juxtaposes their cytoplasmic domains and allows the receptor to engage the intracellular signaling machinery. Several cytokine receptor systems use a common signal transducer; e.g., gp130 is used by IL-6, leukemia-inhibitory factor (LIF), oncostatin M (OSM), and IL-11. Therefore, different cytokines can mediate similar functions on various tissues, or a tissue-specific effect can be realized by different cytokines. With few exceptions (e.g., IL-8-R, M-CSF-R, and TGF-β-R), cytokine receptors do not contain classical signaling domains and hence do not use signaling pathways such as cyclic AMP (cAMP)-protein kinase A, inositol lipid hydrolysis with Ca^{2+} mobilization followed by protein kinase C activation, cGMP-protein kinase G, or receptor tyrosine kinase activation. Instead, dimerization of the cytokine receptor components results in the activation of receptor-associated cytoplasmic protein tyrosine kinases, the so-called JAKs (Janus family of tyrosine kinases [95]), that in turn activate members of the STAT family (signal transducers and activators of transcription) or induce the Ras–mitogen-activated protein kinase cascade (95). Several review articles on cytokine receptors (5, 10, 45, 62, 105, 111, 118, 122, 136, 143, 200, 201) and cytokine signal transduction (21, 89, 95, 98, 106, 107, 142, 145, 151, 155, 169, 171) have been published recently.

Based on structural similarities, cytokine receptors can be divided into several superfamilies: the Ig receptor superfamily (e.g., IL-1-R), the hematopoietin receptor superfamily (e.g., IL-2-R, -4-R, -5-R, -6-R, and -9-R, GM-CSF-R, LIF-R, and OSM-R), the TNF receptor superfamily (e.g., TNF-R, LT-α-R, and LT-β-R), the G-protein-coupled receptor superfamily (e.g., IL-8-R and many other chemokine receptors), the

TABLE 26. Miscellaneous cytokines[a]

Acronym or synonym	Full Name	Receptor(s)	Producers	Biochemistry	Molecular biology and miscellaneous information	Major effects	Inducers
TGFβ [Refs. 32, 127, 175]	Transforming growth factor β Cartilage inducing factor A Cartilage inducing factor B	TGF-RI (53-65 kDa). TGF-RII (83-110 kDa), contains functional kinase. TGF-RIII (250-310 kDa, β-glycan), no signaling motive and may function as reservoir for surplus TGFβ or as regulator of ligand-binding ability or surface expression of RI or RII. TGF-RIV (60 kDa, only on pituitary cells). TGF-RV (400 kDa). On most cells TGF-R's I, II, III and V are co-expressed. The loss of cellular response to TGFβ correlates with loss of type I and / or type II receptors.TGF-RII contains functional kinase. [Ref. 127]	Megakaryocytes / platelets, monocytes / macrophages, activated alveolar macrophages, subsets of T-lymphocytes, fibroblasts, chondrocytes, osteoblasts / osteoclasts, endothelial cells, smooth muscle cells.	12.5 kDa (h), chromosome 19q, 14q. Biologically active as dimer. Three homodimer isoforms in human: $TGF\beta_1$, $TGF\beta_2$ and $TGF\beta_3$. Bioassay: proliferation of Mv1Lu or HT-2 cells.	112 aa (h).	**Induces:** Isotype shift in B-cells (IgA_1 and IgA_2 production) together with IL-10, CD16 (FcγRIII) expression on human monocytes. **Activates:** Osteoblasts and inflammatory cells. **Chemotactic for:** Fibroblasts. **Inhibits:** Macrophage killing of intracellular parasites, endothelial cell proliferation, NK cell activity, TNFα- or IL-1β- or LPS-induced expression of IL-6 and IL-8 in human umbilical vein endothelial cells [32]. **Inhibits growth of:** Osteoclasts, NK cells, hepatocytes, epithelial cells, T- and B-cells (and functions). **Stimulates:** Growth of cells of mesenchymal origin in general, osteoblasts, formation of extracellular matrix, adhesion of intra-epithelial lymphocytes (IEL) to epithelial cells by up-regulation of CD103 ($\alpha_E\beta_7$ integrin) α_E chain on IEL (ligand E-cadherin). Enhances macrophage ability to produce IL-10 in normal and tumor-bearing mice. Interacts with EGF, FGF, TGF-α, PDGF and IL-2.	Infection.
LIF HILDA DSF DIF DIA HSF III CNDF MLPLI [Refs. 5, 132, 191]	Leukemia inhibitory factor Human interleukin for DA cells Differentiation stimulating factor Differentiation inducing factor Differentiation inhibition activity for murine embryonic stem (ES) cells hepatocyte stimulating factor III Cholinergic neuronal differentiation factor Melanoma-derived lipoprotein lipase inhibitor	LIF-R (120 and 250 kDa form). gp130 / CD130 / β chain. Expressed on hematopoietic cells and cell lines originating from bone marrow, thymus spleen liver, placental tissue and peritoneum. Additionally on blood mononuclear cells except lymphocytes, NK cells, granulocytes, erythrocytes or platelets. [Ref. 5, 94]	Bone marrow stromal cells, fibroblasts, T-cells, monocytes / macrophages, astrocytes.	50-58 kDa glycoprotein (h), chromosome 22q. At least half of its weight is composed of oligosaccharides. Belongs to the IL-6, CT-1, CNTF, OSM and IL-11 cytokine family (based on aa-sequence similarities). Bioassay: proliferation of TF-1 cell line (h), proliferation of M1 cell line (m).	179 aa (h). 79% aa homology between h and mLIF.	**as IL-6 (IL-11 and OSM).** **Promotes survival of:** Sensory neurons (shifts from adrenergic to cholinergic phenotype). **Activates growth of:** Fibroblasts. Kaposi sarcoma cells in AIDS. **Suppresses:** Differentiation of pluripotent hematopoietic stem cells and of murine M1 myeloid leukemia cell line. **Potentiates:** IL-3 dependent proliferation of hematopoietic progenitor cells. **Stimulates:** Production of acute phase proteins by hepatocytes. **Induces:** Macrophage differentiation, IL-6 expression, cachexia, excessive bone formation, *in vivo* expansion of bone marrow progenitor cells. **Miscellaneous:** Plays an important role (along with IL-6 and G-CSF) in regulation of hematopoietic stem cells. Important in the release of Ca^{2+} from bone tissue.	TNFα. IL-1. Leustroducsin-B.
OSM	Oncostatin M	OSM-R (150 kDa). gp130 / CD130.	T-cells, monocytes / macrophages, histiocytic lymphoma cells.	26 kDa (h). Thermostable at	226 aa (h). Structurally related to LIF,	**Inhibits:** Growth of melanomas (A375) and carcinomas (certain solid tumors) and synergizes with TGFβ1 in this effect, endothelial	LPS. Leustroducsin-B.

[Ref. 25]		[Ref. 25, 94]		56°C) and resistant to pH 2-11. Bioassay: proliferation of TF-1 cells. Belongs to the IL-6, LIF, CNTF, CT-1, and IL-11 cytokine family.	G-CSF, IL-6, and CNTF.	cell plasminogen activator synthesis, IL-1-induced expression of IL-8 and GM-CSF by synovial and lung fibroblasts. **Stimulates:** Growth of normal fibroblasts and AIDS-related Kaposi's sarcoma-derived cells, LDL receptor expression and uptake by hepatoma cells, IL-6 production by cultured human endothelial cells, growth of IL-6-dependent plasmacytomas. **Induces:** IL-6 production by human endothelial cells, fibroblasts and Kaposi's sarcoma cells.	
MIF [Ref. 27]	Migration inhibitory factor		Activated T-cells, monocytes / macrophages and anterior pituitary gland. Rat: constitutively expressed in lung, liver, kidney, spleen, adrenal gland and skin. Significant quantities of MIF protein present in various cell types and MIF is readily released after LPS stimulation.	12 kDa.		Activates monocytes / macrophages (inhibits migration). Induces IL-1 and TNFα. Potentiates lethal endotoxemia. Counter-regulates the inhibitory effects of glucocorticoids on inflammatory cytokine production (controls steroid axis).	Infection, stress, and glucocorticoids.
PDGF [Refs. 86, 163, 195]	Platelet derived growth factor	PDGF-R (170-180 kDa), tyrosine kinase. Dimers consisting of α and β subunits which may combine to form one of three non-covalently associated complexes [$(\alpha)_2$, $(\beta)_2$, or $(\alpha)_1(\beta)_1$]. The α subunit binds either A or B chain whereas the β subunit binds only the B chain. Therefore, different isoforms bind to different receptor classes and this would determine the differential activity of PDGF isoforms on various cell types. [Ref. 86]	Platelets, endothelial cells, smooth muscle cells, monocytes / macrophages, fibroblasts, neurons, cytotrophoblasts.	28-32 kDa (h), chromosome 7 (A), 22 (B). Dimers composed of combinations of 2 different gene products (16 kDa A chain and 14 kDa B chain): 3 different forms (AA, BB and AB). Bioassay: proliferation of Swiss 3T3 cells or NR6-3T3 fibroblasts.	A chain: 160 aa. B chain: 110 aa.	**Activates:** Glial cells, vascular smooth muscle cells (vasoconstrictor), endothelial cells, epithelial cells, glial cells and chondrocytes. Granule release from neutrophils and monocytes. Potent mitogen for (dermal and tendon) fibroblasts (collagen synthesis). **Inhibits:** NK cell activity. **Chemotactic for:** Fibroblasts, smooth muscle cells, neutrophils, monocytes, epithelial and endothelial cells. **Stimulates:** Degranulation by neutrophils and monocytes, collagen synthesis, mitogenesis of mesoderm-derived cells, extracellular matrix synthesis.	Clotting.
SCF SF KL MGF [Ref. 202]	Stem cell factor Steel factor *c-kit* ligand Mast cell growth factor	SCF-R / CD117 (145 kDa). [Ref. 202]	Bone marrow stromal cells, endothelial cells, fibroblasts, Sertoli cells.	18.5 kDa (h). Forms glycosylated homodimers. Glycosylation not essential for biological activity. Soluble and membrane-bound forms. Bioassay: proliferation of TF-1 cells.	237 aa precursor (h).	**Activates and differentiates:** Multipotential progenitor cells, mast cells (proliferation and survival and differentiation into connective tissue mast cells). **Enhances:** IL-7R expression on γδ intra-epithelial lymphocytes., thymocyte proliferation with IL-2 and IL-7. **Miscellaneous:** Synergizes with other hematopoietic growth factors (G-CSF, M-CSF, GM-CSF, IL-3, IL-6) to stimulate myeloid, lymphoid and erythroid progenitor cells. Plays an important role in survival, proliferation or migration of primordial germ cells and melanoblasts.	
CT-1 HSF	Cardiotrophin-1 Hepatocyte stimulating factor	Signal transduction through gp130.			Belongs to the IL-6, LIF, CNTF, OSM and IL-11 cytokine family (based on aa-sequence similarity).	**Induces:** Liver acute phase response: hepatoma cells - fibrinogen mRNA expression (rat). - haptoglobin mRNA (human). - α_2-macroglobulin mRNA (rat).	

TABLE 26—*Continued*

[Ref. 160]		[Ref. 160]			Cardiac myocyte hypertrophy.	
EBI-3	Epstein Barr virus induced gene 3		B-cells (expression and on plasma membrane after EBV infection). PBMNC (after pokeweed mitogen stimulation). *In vivo* expressed by: scattered cells in inter-follicular zone of tonsils, cells associated with sinusoids in perifollicular areas of the spleen, and placental syncytiotropho-blasts (high expression).	34 kDa, glycosylated, chromosome 19p. Related to p40 subunit of IL-12 and to CNTF-R. EBI3 is retained in the ER in an endoglucosidase-H sensitive form associated with molecular chaperone calnexin and a novel 60 kDa protein.	Lacks membrane anchoring motive and is therefore suggested to be secreted.	**Regulates:** Cell-mediated immune responses.	EBV. Pokeweed mitogen.
[Refs. 49, 71]						

[a] Abbreviations: aa, amino acids; EGF, epidermal growth factor; FGF, fibroblast growth factor; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; EBV, Epstein-Barr virus; PBMNC, peripheral blood mononuclear cells; ER, endoplasmic reticulum.

TGF-β-R superfamily (e.g., TGFβ-R), and the IFN receptor superfamily (IFN-α-R, IFN-β-R, and IFN-γ-R).

Not only are the biological actions of cytokines regulated by cytokine or receptor expression, but also the presence of soluble receptors (23, 85, 198) can influence the effects of a specific cytokine; e.g., sIL-6-Rα (the extracellular portion of IL-6-Rα) enhances IL-6 activity by transporting IL-6 to the IL-6-Rβ (198). Furthermore, not all receptors are capable of signal transduction; e.g., IL-1-RII is devoid of signaling and may act as a decoy receptor, thereby attenuating the effects of IL-1β (55). In addition, naturally occurring autoantibodies to cytokines may affect cytokine actions (12, 82).

Remarkable discoveries that linked cytokine receptors to HIV infection were made in 1996 and have been extensively reviewed by Fauci (64). Apart from the induction or suppression of HIV expression by numerous individual cytokines, it appears that several receptors for CC and CXC chemokines can act as coreceptors for HIV; i.e., T-tropic (T-cell-tropic) HIV strains use CXC-CKR4 (also known as LESTR or fusin), M-tropic (monocyte- or macrophage-tropic) HIV-1 strains use CC-CKR5, and M-tropic and dually tropic HIV-1 strains use CC-CKR2b and CC-CKR3 as coreceptors (57, 64). As a consequence, the chemokines RANTES (regulated on activation, normal T expressed, and secreted), MIP-1α, and MIP-1β suppress M-tropic viral replication while stromal-cell-derived factor-1 suppresses T-tropic viral replication (16). Furthermore, people with a defect in the gene encoding CC-CKR5, leading to a truncated version of the receptor that is not expressed on the cell surface, have been shown to be partially protected against certain strains of HIV.

CONCLUSIONS

Over the last 2 decades our understanding of the biology and biological significance of cytokines has dramatically increased and some cytokines have been introduced into clinical practice (e.g., IFN-γ and G-CSF). Apart from cytokines, one may expect that treatment with cytokine inhibitors, anticytokine antibodies, receptor antagonists, or substances that inhibit cytokine signaling (171) may be of therapeutic value. Treatment with such biological response modifiers generally means modulating an array or cascade of events. Therefore, in-depth investigation of possible effects and accurate determination of the optimal immunomodulatory doses of these modifiers are absolutely necessary. However, many questions on cytokine biology remain unanswered. Until the mechanisms responsible for the control of cytokine biological activities are further elucidated, clinical trials should be designed carefully and the results obtained should be interpreted and evaluated with caution. Basic and animal research on cytokines must be continued in addition to investigations of therapeutic applications in clinical trials.

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