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# Cytokines, Chemokines and Their Receptors

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## Introduction

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The immune system is skilled in communication and designed to respond quickly, specifically and globally to protect an organism against foreign invaders and disease. The cytokine superfamily of proteins is an integral part of the signaling network between cells and is essential in generating and regulating the immune system. Much progress has been made recently in interpreting how the immune system communicates with, or is mediated by, cytokines and chemotactic cytokines (chemokines). These interacting biological signals have remarkable capabilities, such as influencing growth and development, hematopoiesis, lymphocyte recruitment, T cell subset differentiation and inflammation. This chapter provides brief synopses for a comprehensive list of immune-related cytokines and chemokines. Information such as gene cloning and mapping details, protein characteristics and expression, receptor usage, source and target cells, major biological functions and knockout phenotype is described for each cytokine and chemokine. With an approach that organizes cytokines and chemokines into interacting groups with related physical and/or functional properties, this chapter aims to highlight the capability of this system to maintain widespread impact and functional complementation while not sacrificing regulation and specificity of action. A more complete understanding of these properties may lead to more advanced means of correcting improper cytokine- or chemokine-mediated immune responses, such as those causing autoimmune disease.

Detailed and reliable communication must occur through a complex system of network connections to accomplish a task at a modern workstation. In parallel, the immune system is an interdependent biological network charged with developmental tasks and the responsibility of protecting its host against injury and infection. An immune cell within a given microenvironment can respond to signals received through its receptors with its own protein-based language that will influence the cell itself (autocrine effect) or other cells throughout the organism (paracrine effect). The language of cytokines is critical in this communication. Cytokines are small soluble factors with pleiotropic functions that are produced by many cell types as part of a gene expression pattern that can influence and regulate the function of the immune system.

The term cytokine was proposed by Cohen et al in 1974[1] to replace lymphokine, a term coined in the late 1960's to denote lymphocyte-derived soluble proteins that possess immunological effects.[2] Since the latter designation misleadingly suggested that lymphocytes were the only source for these secreted proteins, the term cytokine slowly became preferred. Following the introduction of this general term, the Second International Lymphokine Workshop held in 1979 proposed the interleukin (IL) system of nomenclature to simplify the growing list of identified cytokines. Ironically, this partially adopted system introduced confusion in that the interleukins, presently numbering at least 23, affect many cell types but their name implies that they act only among leukocytes. As a result, modern cytokine nomenclature is a mix of the widely accepted, but slightly misleading, interleukin designations and other proteins still known by their original names. A good

As this chapter unfolds, repeated mention of a number of cytokines and chemokines will make it clear that these proteins can be part of a bigger immune program, e.g., T cell subset differentiation. Mature CD4 and CD8 T cells leave the thymus with a naive phenotype and produce a variety of cytokines. In the periphery, these T cells encounter antigen presenting cells (APCs) displaying either major histocompatibility complex (MHC) class I molecules (present peptides generated in the cytosol to CD8 T cells) or MHC class II molecules (present peptides degraded in intracellular vesicles to CD4 T cells). Following activation, characteristic cytokine and chemokine secretion profiles allow the classification of CD4 T helper (Th) cells into two major subpopulations in mice and humans.[3-7] Th1 cells secrete mainly IL-2, interferon-γ (IFN-γ) and tumor necrosis factor-β (TNF-β), whereas Th2 cells secrete mainly IL-4, IL-5, IL-6, IL-10 and IL-13. Th1 cells support cell-mediated immunity and as a consequence promote inflammation, cytotoxicity and delayed-type hypersensitivity (DTH). Th2 cells support humoral immunity and serve to downregulate the inflammatory actions of Th1 cells. This paradigm is a great example of an integrated biological network and is very useful in simplifying our understanding of typical immune responses and those that turn pathogenic. For example, the failure to communicate “self” can lead to a loss of tolerance to our own antigens and prompt destructive immune responses to self-tissues and autoimmune disease. Autoimmunity, the major focus of this book, is the underlying mechanism of a set of conditions, such as type 1 diabetes mellitus, multiple sclerosis and rheumatoid arthritis. Autoimmune diseases may be caused in part by cytokine- and chemokine-mediated dysregulation of Th cell subset differentiation. The main factors affecting the development of Th subsets, aside from the context in which the antigen and costimulatory signals are presented, are the cytokines and chemokines in the stimulatory milieu. A better understanding of the properties and interactions of the individual cytokines and chemokines that play a role in Th cell activation may lead to more advanced treatments for autoimmune disease.

The proceeding sections will introduce many of the currently identified cytokines and chemokines, along with their receptors. You will find that cytokines and chemokines with related structure and/or function are clustered into groups of interdependent homologues, e.g., the IL-1-like cytokines. A particular group of cytokines or chemokines can exhibit functional redundancy with, and widespread impact on, other groups of cytokines or chemokines, e.g., IL-1-like cytokines and IL-6-like cytokines. Interestingly, this can occur while maintaining several regulatory features, such as internal checkpoints and specificity of action. It is therefore hoped that this chapter may serve as more than a brief catalogue of the field of cytokines, chemokines and their receptors, but may also highlight the remarkable capabilities of this interacting network of biological signals.

## Cytokines, their Receptors and their Genes

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Table 1 introduces the human cytokines and lists some of their properties, such as receptor usage and physical characteristics. Each human cytokine described in Table 1 has a murine counterpart so the basic list can be used interchangeably in regards to terminology. Hundreds of cytokines have been identified. In the interest of conciseness the table includes only common cytokines with recognized immune function, many of which are discussed in more detail below. Excluded are the ‘growth factors’, neurobiological proteins and ‘trophins’, for example. It is also beyond the scope of this chapter to describe how cytokines signal through their receptors in any detail. One popular cytokine signaling mechanism used by cytokines such as IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15 and the interferons, however, begins with dimerization of the appropriate receptor chains upon ligand binding. Following this, different types of receptor-associated Janus family tyrosine kinases (Jak) are activated which phosphorylate the receptor chains and allow the recruitment and activation of other kinases and transcription factors, such as those of the signal transducer and activator of transcription (Stat) family. This promotes the rapid translocation of these proteins to the nucleus and stimulation of target


Common human cytokines and their receptors[1].

### IL-1-Like Cytokines

Firstly, the interleukins are comprised mostly of hematopoietic growth factors and can be further divided into groups of proteins as shown in Table 1. The IL-1-related group of pro-inflammatory cytokines consists of IL-1α, IL-1β, IL-1 receptor antagonist (IL-1RA) and IL-18. IL-1α and IL-1βare produced mainly by mononuclear and epithelial cells upon inflammation, injury and infection.[10] These two proteins are of primary importance to the outcome of these challenges to the immune system in that they trigger fever, induce a wide variety of acute phase response (APR) genes and activate lymphocytes.[10] IL-1α and IL-1β arise from two closely linked genes that, along with the IL-1RA gene, lie on human (and mouse) chromosome 2.[10,11]The two forms of IL-1 are quite similar in function since they both signal through the IL-1 type 1 receptor (IL-1-R1/CD121a).[12] Both proteins can also bind to the IL-1 type 2 receptor (IL-1-R2/CDw121b) which does not appear to be involved in signaling, except as a possible decoy.[13] The IL-1 receptor genes are located on human chromosome 2 along with their ligands, albeit at a distance.

Murine knockout studies confirm the importance of IL-1 in fever responses and the APR. While at least three studies involving the IL-1β knockout mouse demonstrate that fever development is suppressed upon turpentine or lipopolysaccharide (LPS) challenge,[14-16]one study demonstrates that the role of IL-1β as a pyrogen is not obligatory and that its absence can in fact exacerbate an induced fever response.[17] The latter conflicting result may stem from differences in experimental protocol or reagents.[14] Knockout studies also show that while both forms of IL-1 can induce fever responses, fever induction is not reduced in IL-1α knockout mice, indicating that IL-1βcan compensate for IL-1α but not vice versa.[14] The role for IL-1 in the APR (a series of cellular and cytokine cascades in reaction to trauma or infection that help limit damage) was confirmed in a localized tissue damage model of turpentine injection where challenged IL-1β-deficient mice did not develop an APR.[18] Accordingly, IL-1R1 knockout mice are irresponsive to IL-1 in the induction of IL-6, E-selectin and fever.[18] These mice also have a reduced APR to turpentine.[19]

IL-1RA is produced by virtually any cell that can produce IL-1 and is similar in structure to IL-1β but lacks its agonist activity.[20] The different species of IL-1RA, a secreted form with a signal peptide and at least two intracellular forms, arise from alternative splicing of different first exons on chromosome 2.[20,21] IL-1RA represents an intriguing example of a naturally occurring cytokine receptor antagonist. IL-1RA may be an acute phase protein that may serve to regulate the agonist effects of IL-1 during chronic inflammatory and infectious disease because its expression is influenced by cytokines, viral and bacterial products, bound antibody and acute phase proteins, such as IL-1, IL-4, IFN-γ and LPS.[20] Consistent with this notion are two studies of IL-1RA-deficient mice which exhibit growth retardation, an exacerbated fever response to turpentine injection, increased lethality following LPS injection and decreased susceptibility to *Listeria monocytogenes*.[14,22]These observations verify the importance of balance in the IL-1 system in mediating these immune challenges.

IL-18, initially termed interferon-γ inducing factor (IGIF), is a pro-inflammatory cytokine that is encoded on human chromosome 11 and mouse chromosome 9.[23] IL-18 has been placed in the IL-1 group of interleukins because it bears structural homology to IL-1α and β, is converted into a mature form by IL-1β converting enzyme (ICE) along with IL-1β and binds to the IL-18 receptor (IL-18R or IL-1R related protein).[23] The IL-18R resembles the IL-1R and transduces IL-1R signaling.[23] IL-18 shares biological function with IL-12 in that it induces IFN-γ secretion (in synergy with IL-12), enhances natural killer (NK) cell activity and promotes inflammatory Th1 cell responses.[23] Accordingly, when IL-18[24] or its receptor[25] is knocked out, mice exhibit defective NK cell activity and Th1

certain situations.

### Common γChain Cytokines

Cytokines that utilize the common γ chain (γc/CD132) in their receptor comprise the next group of interleukins, namely IL-2, IL-4, IL-7, IL-9, IL-13 and IL-15. These diverse cytokines invoke lymphocyte activation and differentiation (the outcome of which can vary) and possess some redundancy in biological function because of their common receptor subunit.[29] The γc itself cannot bind cytokines; however, new evidence suggests that it can be shed as a soluble negative modulator.[30] Indeed, γc-deficient mice are severely immunocompromised, as are humans with γc defects.[31,32]

IL-2 is expressed from a gene on human chromosome 4 or mouse chromosome 3 and is mainly secreted by activated T cells. IL-2 and the heteromultimeric IL-2 receptor (IL-2R) complex (combinations of IL-2Rα/CD25, IL-2Rβ/CD122 and γc) are upregulated on T cells following antigenic or mitogenic stimulation leading to clonal expansion. As such, IL-2 is commonly regarded as an autocrine or paracrine T cell growth factor but it actually has effects on many cell types, such as B cells, NK cells, macrophages and neutrophils.[29,33,34]The IL-2 knockout mouse exhibits immune dysregulation caused by defects in T cell responsiveness in vitro; however, only delays in normal T cell functionality were found in vivo.[35,36] Interestingly, IL-2Rα-[37] and IL-2Rβ-deficient[38] mice exhibit loss of T cell regulation and autoimmunity, indicating that proper IL-2 signaling may be required to induce regulatory T cells and/or eliminate abnormally activated T cells via the reversal of T cell anergy or apoptosis (programmed cell death) induction, respectively.[39]

The IL-4 gene is located on human chromosome 5 (along with the IL-3, IL-5, IL-9, IL-13 and granulocyte macrophage colony stimulating factor (GM-CSF) genes) and murine chromosome 11 (along with the IL-3, IL-5, IL-13 and GM-CSF genes). Short or long isoforms of IL-4 can exist arising from alternative splicing.[40] IL-4 is produced by activated T cells, mast cells, basophils and NKT cells and targets many cell types, including B cells, T cells, macrophages and a wide variety of hematopoietic and nonhematopoietic cells.[29,41] Physiologic signal transduction via IL-4 depends on heterodimerization of the IL-4 receptor α chain (IL-4Ra/CD124), with γc and possibly the IL-13 receptor α chain (IL-13Ra/CD213a1).[42] IL-4 is the principal cytokine required by B cells to switch to the production of immunoglobulin (Ig)E antibodies, which mediate immediate hypersensitivity (allergic) reactions and help defend against helminth infections.[41] IL-4 also inhibits macrophage activation and most of the effects of IFN-γ on macrophages. However, the most important biological effect of IL-4 with respect to immune modulation is the growth and differentiation of Th2 cells. As described earlier, Th2 cells support humoral immunity and serve to downregulate the inflammatory actions of Th1 cells. Moreover, stimuli that favour IL-4 production early after antigen exposure favour the development of Th2 cells.[3] IL-13 is also associated with this subset of T cells.[43] Like IL-4, and along with the fact that it maps closely to IL-4 and shares receptor α subunits with IL-4, IL-13 is expressed by activated T cells, induces IgE production by B cells and inhibits inflammatory cytokine production.[44] These properties of IL-4 and IL-13 have been convincingly demonstrated in mice lacking the IL-4 or IL-13 gene. [45-48] These mice are deficient in the development and maintenance of Th2 cells.

The remaining γc cytokines, IL-7, IL-9 and IL-15, are potent hematopoietic factors expressed from genes on human chromosome 8 and mouse chromosome 3, human chromosome 5 and mouse chromosome 13, and human chromosome 4 and mouse chromosome 8, respectively. IL-7, expressed by stromal and epithelial cells, stimulates immature B cells, thymocytes and mature T cells via its receptor consisting of the IL-7 receptor α chain (IL-7Rα/CD127) and the γc.[49-51] Knocking out IL-7 or IL-7Rα/CD127 causes severe defects in thymic T cell and B cell development consistent with the critical roles that IL-7 and its receptor play in maturation of the immune system.[51-56] IL-9 promotes the growth of mast cells, B

activated monocytes, epithelial cells, and a variety of tissues, shares biological activities with IL-2 in that it stimulates NK cells, B cells and activated T cells.[29,59-61] The IL-15 receptor (IL-15R) consists of combinations of IL-15Rα, IL-2Rβ/CD122 and γc. Similarities in function between IL-2 and IL-15 are partially due to receptor subunit sharing. A recent study, however, provides evidence that IL-2 and IL-15 control different aspects of primary T-cell expansion in vivo. IL-15 is critical for initiating T cell divisions, whereas IL-2 can limit T cell expansion by decreasing γc expression and rendering cells susceptible to apoptosis.[62] The α chain ligand specificity and broad cellular expression range of IL-15 allows for differential activity even outside of the immune system.[29] IL-15- and IL15Ra-deficient mice were recently generated. Initial studies confirm the role of IL-15 in NK cell stimulation and indicate a role for IL-15 in peripheral CD8 T cell maintenance upon immune challenge.[63,64]

### Common *β* Chain Cytokines

Cytokines that utilize the common β chain (βc/CDw131) in their receptor comprise the next group of interleukins, namely IL-3, IL-5 and GM-CSF. The genes for IL-3, IL-5 and GM-CSF are closely linked and lie on human chromosome 5 and mouse chromosome 11.[65] Like the γc cytokines, these associated (but not particularly homologous at the amino acid sequence level) βc cytokines overlap in biological function because of their common receptor subunit.[65] When the βc is mutated, normal hematopoiesis is noted but impaired immune responses can be observed that are most likely due to a loss of responsiveness to IL-5 and GM-CSF, rather than IL-3.[66,67]

IL-3, originally termed multicolony stimulating factor (multi-CSF), is produced by activated T cells and stimulates both multipotential hematopoietic cells (stem cells) and developmentally committed cells such as granulocytes, macrophages, mast cells, erythroid cells, eosinophils, basophils and megakaryocytes.[68-70]The human IL-3 receptor consists of CD123 and βc/CDw131. The mouse IL-3 receptor has an additional β chain called $\beta_{IL-3}$, the function of which can be compensated for by CD123 if knocked out.[67] Knocking out CD123 itself also has little effect on hematopoiesis.[71] On the other hand, if IL-3 is knocked out, mast cell and basophil development upon challenge is affected,[66] as well as some forms of DTH,[72] confirming a role for IL-3 in host defense and expanding hematopoietic effector cells.

IL-5, originally identified as a B cell differentiation factor, is produced mainly by activated T cells (especially Th2 cells) and aids in the growth and differentiation of eosinophils and late-developing B cells.[73-75]When IL-5 or CDw125 is absent, mice exhibit developmental defects in certain B cells (CD5/B-1 B cells) and a lack of eosinophilia upon parasite challenge.[76,77]

Lastly, GM-CSF, as its name suggests, was originally found to stimulate granulocytes and macrophages. GM-CSF has since been found to be expressed by many cell types, including macrophages and T cells, and shares many of the functions of IL-3 in stimulating a variety of precursor cells, including macrophages, neutrophils and eosinophils.[78-80]Interestingly, GM-CSF-deficient mice have normal hematopoietic development but suffer from pulmonary disease perhaps caused by a lack of lung surfactant clearance by alveolar epithelial cells or macrophages.[81]

### IL-6-Like Cytokines

IL-6 is the prototype cytokine representing the next group of interleukins. Most of the members of this group utilize the glycoprotein 130 (gp130) or CD130 receptor. IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), granulocyte colony-stimulating factor (G-CSF) and IL-12 have partially overlapping functions and are key mediators in various immune processes including hematopoiesis and the APR. CD130-deficient mice exhibit embryonic lethality, a finding that appears to be linked to a significant role for CD130-dependent signaling in homeostasis.[82]

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