Current perspectives

Interleukins, from 1 to 37, and interferon-γ: Receptors, functions, and roles in diseases

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Advancing our understanding of mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumor development, organ transplantation, and chronic infections could lead to effective and targeted therapies. Subsets of immune and inflammatory cells interact via ILs and IFNs; reciprocal regulation and counter balance among T_H and regulatory T cells, as well as subsets of B cells, offer opportunities for immune interventions. Here, we review current knowledge about ILs 1 to 37 and IFN-γ. Our understanding of the effects of ILs has greatly increased since the discoveries of monocyte IL (called IL-1) and lymphocyte IL (called IL-2); more than 40 cytokines are now designated as ILs. Studies of transgenic or knockout mice with altered expression of these cytokines or their receptors and analyses of mutations and polymorphisms in human genes that encode these products have provided important information about IL and IFN functions. We discuss their signaling pathways, cellular sources, targets, roles in immune regulation and cellular networks, roles in allergy and asthma, and roles in defense against infections. (J Allergy Clin Immunol 2011;127:701-21.)

Key words: Cytokines, interleukins, T cells, B cells, dendritic cells, adaptive immune response, humoral immune response, allergy and asthma

Abbreviations used	
APC:	Antigen-presenting cell
CSF:	Colony-stimulating factor
DC:	Dendritic cell
FoxP3:	Forkhead box protein 3
γc:	γ-Chain
G-CSF:	Granulocyte colony stimulation factor
IBD:	Inflammatory bowel disease
IL-1F:	IL-1 family
IL-1RI:	IL-1 type I receptor
IL-1RII:	IL-1 type II receptor
IL-1Ra:	IL-1 receptor antagonist
IL-1RacP:	IL-1 receptor accessory protein
MS:	Multiple sclerosis
NK:	Natural killer
NKT:	Natural killer T
Poly I:C:	Polyriboinosinic:polyribocytidylic acid
R:	Receptor
RA:	Rheumatoid arthritis
Tbet:	T-box expressed in T cells
TLR:	Toll-like receptor
Tr1:	Type 1 regulator T
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

Since the discovery of IL-1 in 1977, approximately 200,000 published articles have referred to ILs. Secreted proteins that bind to their specific receptors and play a role in the communication among leukocytes are named ILs. The nomenclature is continuously evolving, and there have been proposals for the assignment of new members to the IL-1 family.[1] ILs are assigned to each family based on sequence homology and receptor chain similarities or functional properties (Fig 1). CD4$^+$ T_H cells are divided into distinct subsets according to cytokine profile. The profile of cytokine expression depends on the adjuvanicity of the molecules presented with the antigen and the status of the T cells, along the types of antigen-presenting cells (APCs) and cytokines in the microenvironment. CD4$^+$ naive T cells can differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, and T-follicular effector cells. On the basis of their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T-cell subsets can promote different types of inflammatory responses (Fig 2). During the development of allergic disease, effector T_H2 cells produce IL-4, IL-5, IL-9, and IL-13[2,3]; their production of IL-25, IL-31, and IL-33 contributes to T_H2 responses and inflammation.[4-7] These cytokines have roles in production of allergen-specific IgE, eosinophilia, and mucus. T_H1 cells, however, produce the cytokine IFN-γ, which protects against intracellular pathogens and plays a role in activation-induced death of skin keratinocytes, mucosal epithelial cells, and T cells.[8,9]
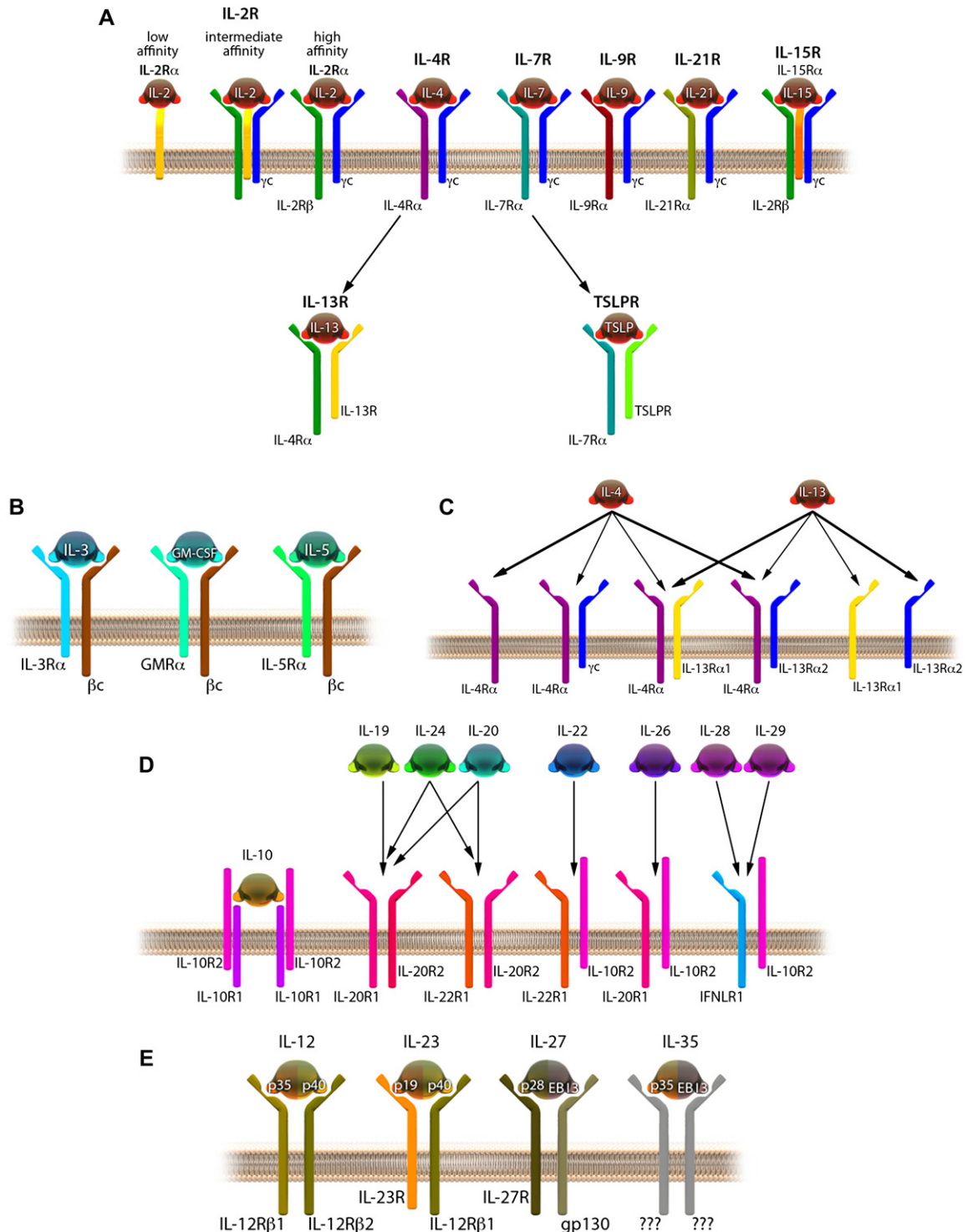
FIG 1. A, The receptors of the IL-2 family, which is composed of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Receptors contain the common cytokine receptor γ chain (CD132, γc). IL-13R shares IL-4Rα with IL-4, and TSLPR shares IL-7R with IL-7. B, The receptors for IL-3, IL-5, and GM-CSF *(GMR)* are heterodimers of a unique α-chain and the common β-chain (βc, CD131) subunit. C, The receptors for IL-4 and IL-13 consists of 2 receptor chains, the IL-4Rα (CD124) and the common γc. IL-4 and IL-13 bind to IL-4R, which consists of the IL-4Rα and the IL-13Rα1 chain. IL-13R consists of 2 subunits, IL-13Rα1 and IL-13Rα2, and signaling occurs via the IL-4R complex type II that consists of the IL-4Rα and IL-13Rα. D, On the basis of similarities in their intron-exon structure, conserved secondary protein structures, and similar types of receptors, the following cytokines have been classified as IL-10 family members: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29. They share common receptor subunits shown. E, IL-12R consist of 2 subunits, IL-12Rβ1 and IL-12Rβ2.A heterodimer of IL-12Rβ1 and IL-23R bind IL-23. IL-12Rβ2 shows homology to the gp130 subunit of IL-27R. *EBI3,* Epstein-Barr virus-induced.
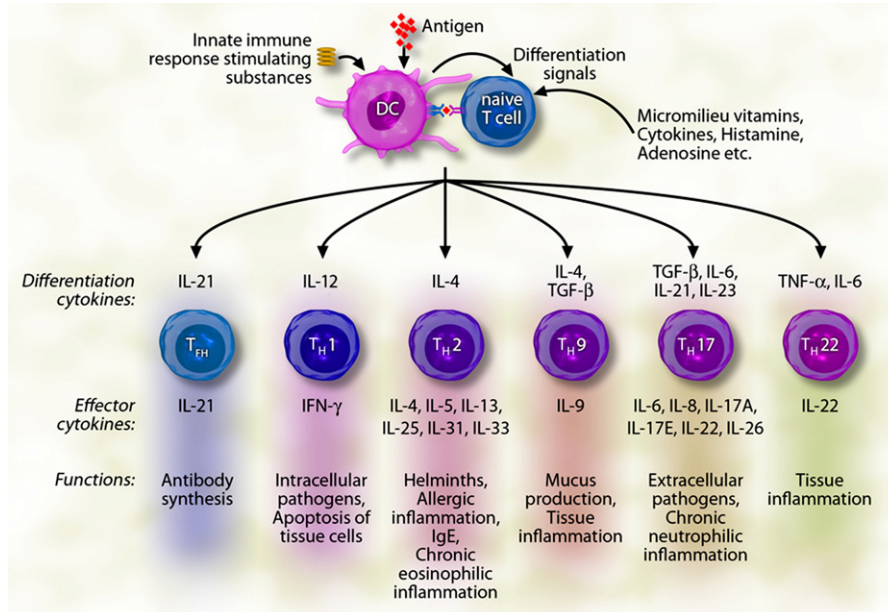
FIG 2. Antigen presentation by DCs to naive T cells and other factors (innate immune response substances, vitamins, cytokines in the environment) induces the T cells to produce ILs and differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, or follicular T_H (T_{FH}) cells. These T-cell subsets can promote different types of inflammatory responses on the basis of their respective cytokine profiles, responses to chemokines, and interactions with other cells.

The discovery of the T_H17 has improved our understanding of inflammatory processes. T_H17 cells are characterized by their expression of IL-17A, IL-17F, IL-6, IL-8, TNF-α, IL-22, and IL-26.[10,11] The combination of TGF-β and IL-4 reprograms differentiation of T_H2 cells so that they become T_H9 cells, which produce IL-9 and IL-10.[12] T-follicular helper cells provide helper functions to B cells; they represent one of the largest and most important subsets of effector T cells in lymphoid tissues.[13] Subsets of regulatory T (Treg) cells regulate and counterbalance the immune response; they have distinct phenotypes and mechanisms of action and include $CD4^+CD25^+$Forkhead box protein 3 $(FoxP3)^+$ Treg cells, which are selected in the thymus, and type 1 Treg (Tr1) cells, which are induced.[14,15] Subsets of $CD8^+$ T cells, γδ T cells, IL-10–producing B cells, IL-10–producing natural killer (NK) cells, dendritic cells (DCs), and macrophages might contribute to immune suppression or regulation.[16] Investigations of the mechanisms of immune and inflammatory cell functions have identified a growing list of ILs and interactions among different cell types that contribute to their effector and suppressive functions (Table I). Detailed information on all cytokines is provided in this article's Online Repository at www.jacionline.org.

IL-1 FAMILY
IL-1 and the IL-1 receptor antagonist

IL-1 was first described as a protein that induced fever and was called *human leukocytic pyrogen*, which is made up of 2 major proteins, IL-1α and IL-1β.[17,18] There are now 11 members of the IL-1 family. Although IL-1α and IL-1β have minimal sequence homology, they have similar biological properties. However, there are fundamental differences in their localization, maturation, and secretion. IL-1α is translated into a biologically active form, whereas IL-1β is translated as pro–IL-1β and has no biological activity until it is processed by caspase-1. IL-1α and IL-1β exert similar effects by binding to the IL-1 type I receptor (IL-1RI). They can also bind to the IL-1 type II receptor (IL-1RII), which acts as a decoy receptor and is not involved in signal transduction. IL-1 is a potent proinflammatory cytokine that acts as an endogenous pyrogen. It has diverse potentiating effects on cell proliferation, differentiation, and function of many innate and specific immunocompetent cells. IL-1 mediates many inflammatory diseases by initiating and potentiating immune and inflammatory responses.

The IL-1 receptor antagonist (IL-1Ra) is synthesized and released in response to the same stimuli that lead to IL-1 production.[19] The IL-1Ra lacks the IL-1 receptor accessory protein interacting domain, so that binding of the IL-1Ra to IL-1RI inhibits IL-1 signaling.[18] There are at least 4 isoforms of the IL-1Ra; 3 isoforms localize within the cell, and the fourth has a signal peptide—it is generally secreted without a requirement for maturation. Therapies under development for some inflammatory disorders involve neutralization of IL-1 activity by administration of IL-1Ra and anti–IL-1 neutralizing mAbs.[20] IL-1Ra–deficient mice spontaneously develop chronic inflammatory polyarthropathy. Balance among the expression levels of IL-1, IL-1Ra, IL-1RI, and IL-1RII is decisive in generation of proinflammatory and/or homeostatic functions.[21]

IL-18

IL-18 is a member of the IL-1 family that is expressed by a range of cell types, including macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes, and DCs.[22] IL-18 shares structural features with IL-1 and it is synthesized as a 24-kd, biologically inactive precursor that requires cleavage by

TABLE I. Characteristics of cytokines

Cytokine	Structure	Size molecular weight	Receptors	Cell sources	Cell targets	Major functions	Disease association
IL-1α, IL-1β	Heterodimer	17 kd	IL-1RI, IL-1RII	Macrophages, monocytes, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts, synovial lining cells	T cells, fibroblasts, epithelial and endothelial cells	Induction of proinflammatory proteins, hematopoiesis, differentiation of T_H17 cells	Wide range of autoimmune and inflammatory diseases, RA, IBD, psoriasis
IL-1Ra (antagonist)	Heterodimer	16.1-20 kd	IL-1RI, IL-1RII	Monocytes, macrophages, fibroblasts, neutrophils, endothelial and epithelial cells, keratinocytes	T cells, fibroblasts, epithelial and endothelial cells	Antagonism of IL-1	Wide range of autoimmune and inflammatory diseases, RA, IBD, psoriasis
IL-2	Monomer	15.5 kd	IL-2R	$CD4^+$ and $CD8^+$ activated T cells, DCs, NK cells, NKT cells	$CD4^+$ and $CD8^+$ T cells, NK and B cells	Proliferation of effector T and B cells, development of Treg cells, differentiation and proliferation of NK cells and growth factor for B cells	T-cell–mediated autoimmune and inflammatory diseases, X-linked severe combined immunodeficiency 1
IL-3	Monomer	15 kd	IL-3Rα + β c (CD131)	T cells, macrophages, NK cells, mast cells, eosinophils, stromal cells	Erythroid progenitors, granulocyte-macrophages progenitors, $CD34^+$ progenitor cells, basophils, eosinophils	Hematopoietic growth factor, activation of basophils and eosinophils	Role in allergic diseases, different types of cancers, lymphocytic and acute myeloid leukemias
IL-4	Monomer	15 kd	IL-4R type I, IL-4R type II	T_H2 cells, basophils, eosinophils, mast cells, NKT cells, γ/δ T cells.	T and B cells	Induction of T_H2 differentiation, IgE class switch, upregulation of class II MHC expression on B cells, upregulation of CD23 and IL-4R, survival factor for B and T cells, role in tissue adhesion and inflammation	Inflammatory and autoimmune diseases (allergy/ asthma and diabetes mellitus), chronic lymphocytic leukemia diseases
IL-5	Dimer	15 kd	IL-5R	T_H2 cells, activated eosinophils and mast cells, Tc2 cells, γ/δ T cells, NK and NKT cells, $CD4^-$ ckit$^-$ CD3ε$^-$ IL2Rα$^-$ (Peyer patches)	Eosinophils, basophils, and mast cells	Differentiation and function of myeloid cells, increment of chemotactic activity and adhesion capacity on eosinophils, remodeling and wound healing	Allergy/asthma, hypereosinophilic syndrome
IL-6	Homodimer	19-26 kd	IL-6R, (sIL-6R) gp130	Endothelial cells, fibroblasts, monocytes/ macrophages	Hepatocytes, leukocytes, T cells, B cells, hemopoietic cells	Liver: synthesis of acute phase proteins; leukocytes: trafficking, activation; T cell: differentiation, activation, survival; B cell: differentiation, production of IgG, IgM, IgA hematopoiesis	Autoimmune disease, chronic inflammatory disease, B-cell malignancy, SLE, Castleman disease, plasmacytoma/ multiple myeloma

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size molecular weight	Receptors	Cell sources	Cell targets	Major functions	Disease association
IL-7	Monomer	25 kd	IL-7R and sIL-7R	Epithelial cells, keratinocytes, DCs, B cells, and monocytes/ macrophages	B, T, and NK cells	Proliferation of pre-B and pro-B cells (mice), megakaryocytes maturation, VDJ recombinations, naive T-cell survival, synthesis induction of inflammatory mediators in monocytes	Allergy/ autoimmunity and psoriasis
IL-8	Homodimer	16 kd	CXCR1 and CXCR2	Monocytes, macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, fibroblasts, keratinocytes, chondrocytes, synovial cells, hepatocytes	Neutrophils, NK cells, T cells, basophils, eosinophils, endothelial cells	Chemoattractant for neutrophils, NK cells, T cells, basophils, eosinophils; mobilization of hematopoietic stem cells; angiogenesis	Increased levels during inflammatory diseases (RA, psoriasis, bacterial and viral infections)
IL-9	Monomer	14 kd	IL-9R	T_H2, T_H9, mast cells, and eosinophils	B, T, and mast cells	T and mast cells growth factor, inhibition of T_H1 cytokines, proliferation of $CD8^+$ T cells and mast cells, IgE production, chemokine and mucus production in bronchial epithelial cells	Helminth infections, Hodgkin lymphoma, asthma, food allergy
IL-10	Homodimer	20.5 kd, predicted size of precursor protein; 18.6 kd, predicted size mature protein, monomer	IL-10R1/IL-10R2 complex	T cells, B cells, monocytes, macrophages, DCs	Macrophages, monocytes, T cells, B cells, NK cells, mast cells, DC and granulocytes	Immune suppression	Cancer, autoimmunity, allergy
IL-11	Monomer	19 kd	IL-11Rα + gp130	Stromal cells: fibroblasts, epithelial cells, endothelial cells, vascular smooth muscle cells, synoviocytes, osteoblasts	Myeloid, erythroid, and megakaryocyte progenitors, osteoclasts, epithelial cells, hepatocytes, macrophages, neurons	Growth factor for myeloid, erythroid, and megakaryocyte progenitors; bone remodeling; protects epithelial cells and connective tissue; induction of acute-phase protein; inhibition of macrophage activity; promotion of neuronal development	Increased during allergic asthma
IL-12 (p35/p40)	Heterodimer	IL-12a p35, 35 kd; IL12b p40, 40 kd	IL-12Rb1 and IL-12Rb2	Monocytes, macrophages, neutrophils, microglia, DCs, B cells	T cells (Th1 cells), NK cells	Induce T_H1-cell differentiation and cytotoxicity	Impaired T_H1 r esponse with higher susceptibility to intracellular pathogens, use as anticancer agent

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size molecular weight	Receptors	Cell sources	Cell targets	Major functions	Disease association
IL-13	Monomer	10 kd	IL-13Rα1 and IL-13Rα2	T, NKT, and mast cells, basophils, eosinophils	B cells, mast cells, epithelial cells, eosinophils, smooth muscle cells and macrophages	Switching to IgG$_4$ and IgE, upregulation of CD23, MHC-II on B cells, induction of CD11b, CD11c, CD18, CD29; CD23, and MHC-II on monocytes, activation of eosinophils and mast cells, recruitment and survival of eosinophils, defense against parasite infections	Asthma, allergic rhinitis, fibrosis
IL-14	Monomer	53 kd	IL-14R	T cells, T-cell clones, B-lineage and T-lineage lymphoma cell lines	B cells, certain leukemia cells	Proliferation of activated B cells	Autoimmunity, lymphoma genesis
IL-15	Monomer	14-15 kd	IL-15R	Monocytes, activated CD4$^+$ T cells, keratinocytes, skeletal muscle cells	T, NK, and NKT cells	T-cell activation, proliferation and activation of NK cells, differentiation of γ/δ T cells, suppression of IL-2 induced AICD of T cells, homeostasis of CD8$^+$ memory, NK and NKT cells, enhancement of T$_H$2 differentiation and suppression of allergic rhinitis	Autoimmune and inflammatory diseases
IL-16	Homotetramer	56 kd	CD4	T cells, eosinophils, mast cells, eosinophils, monocytes, DCs, fibroblasts, epithelial cells	T cells, monocytes, macrophages, eosinophils	Chemotaxis, modulation of T-cell response	Increased during various inflammatory and infectious diseases including atopic eczema, allergic asthma, Crohn disease, RA, hepatitis C infection, tuberculosis; inhibits HIV infection
IL-17A	Cysteine knot, homodimer or heterodimer	35 kd	IL-17RA (=IL-17R)	T$_H$17 cells, CD8$^+$ T cells, NK cells, NKT cells, $\gamma\delta$ T cells, neutrophils	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment of neutrophils	RA, MS, IBD, psoriasis, allergic asthma, atopic dermatitis, contact hypersensitivity
IL-17B,C,D	Cysteine knot, homodimer	41 kd, 40 kd, 52 kd	For IL-17 B, IL-17RB (=IL-17H1, IL25R); for IL-17C and D, not known	IL-17B: neuronal cells, chondrocytes; IL-17C: immune cells under certain conditions; IL-17D: resting B and T cells	Monocytes, endothelial cells, myofibroblasts	Induction of proinflammatory cytokines, chemokines, and metalloproteases; IL-17B: chondrogenesis and osteogenesis	RA, allergic asthma, inflammatory cardiomyopathy, Wegener granuloma
IL-17F	Cysteine knot, homodimer or heterodimer	44 kd	IL-17RA (=IL-17R) and IL-17RC (=IL-17RL)	T$_H$17 cells, CD8$^+$ T cells, NK cells, NKT cells, $\gamma\delta$ T cells, neutrophils	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment of neutrophils	IBD, psoriasis, allergic asthma

TABLE I. *(Continued)*

Cytokine	Structure	Size molecular weight	Receptors	Cell sources	Cell targets	Major functions	Disease association
IL-18	Heterodimer	22.3 kd	IL-18R	Wide range of cells, mainly macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes, DCs	Variety of cells, T cells, NK cells, macrophages, epithelial cells, chondrocytes	Induction of IFN-γ in presence of IL-12, enhances NK cell cytotoxicity, promoting T_H1 or T_H2–cell responses depending cytokine milieu	Autoimmune diseases or inflammatory disorders, RA, psoriasis, MS, type I diabetes
IL-19	Monomer	20.5 kd, predicted size of precursor; 17 kd, predicted size of mature protein; 35-40 kd, found in transfected cells, glycosylated	IL20R1/IL-20R2	Monocytes, keratinocytes, airway epithelial cells and B cells	Keratinocytes	Unknown	Psoriasis
IL-20	Monomer	20 kd, predicted size of precursor; 17.5 kd, predicted size of mature protein	IL-20R1/IL-20R2 and IL-22R1/IL-20R2	Monocytes, keratinocytes, epithelial and endothelial cells	Keratinocytes, monocytes	Role in skin biology	Psoriasis, RA, atherosclerosis
IL-21	4-Helix bundle, monomer	15 kd	IL-21R	T cells (predominantly T_H17), NKT cells	CD4$^+$ T cells, CD8$^+$ T cells, B cells, DCs, macrophages, keratinocytes	Regulation of proliferation, differentiation, apoptosis, antibody isotype balance, cytotoxic activity	Cancer, SLE, RA
IL-22	6 Antiparallel α-helices, monomer	23 kd	IL-10R2 chain and IL-22R1 chain	Activated T cells (predominantly T_H17), NKT cells (NK-22)	Tissue cells like keratinocytes, subepithelial myofibroblasts	Pathogen defense, wound healing, tissue reorganization	Psoriasis, IBD, cancer
IL-23 (p19+p40)	Heterodimer	IL-12b p40, 40 kd; IL-23 p19, 19 kd	IL-12Rb1 and IL-23R	Macrophages, activated DCs	T cells (T_H17 cells) and macrophages	Stimulate production of proinflammatory IL-17 and promote memory T-cell proliferation	Susceptibility to extracellular pathogens, exacerbate organ-specific autoimmune inflammation
IL-24	Homodimer and monomer	23.8 kd, predicted size of unprocessed precursor; 18 kd, unglycosylated mature protein; 35 kd, observed size of secreted IL-24, glycosylated	IL20R1/IL-20R2 and IL-22R1/IL-20R2	Melanocytes, T cells, monocytes	Cancer cells	Tumor suppression	Melanoma, psoriasis
IL-25 (IL-17E)	Homodimer	17 kd	IL-17RA and IL-17RB	T_H2 cells, mast and epithelial cells, eosinophils and basophils from atopic individuals	T_H2 memory cells	Induction of T_H2 responses, IgE, IgG$_1$, IL-4, IL-5, IL-13, and IL-9 production	Gastrointestinal disorders, asthma
IL-26	6 α-Helices, homodimer	38 kd	IL-10R2 chain and IL-20R1 chain	Activated T cells (predominantly T_H17), NKT cells	Epithelial cells	Activation and regulation of epithelial cells	IBD
IL-27 (p28+EBI3)	Heterodimer	IL-27a p28, 28 kd; IL-27b EBI3, 25.4 kd	WSX-1 and gp130	Activated DCs, macrophages, epithelial cells	T cells, NK cells	Induction of Tbet promoting T_H1-cell differentiation, inhibition of T_H17-cell response via STAT1	Immune pathology because of uncontrolled inflammatory response
IL-28A/B/IL-29 (IFN λ family)	Monomer	IL-28A, 22.3 kd; IL-28B, 22.2 kd; IL-29, 21.9 kd	IL-28R1/IL-10R2	Monocyte-derived DCs	Most cell types	Antiviral immunity	Role in allergic and autoimmune diseases
IL-30 (p28 subunit of IL-27)							

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size molecular weight	Receptors	Cell sources	Cell targets	Major functions	Disease association
IL-31	4-Helix bundle	24 kd	IL-31RA/OSMRβ	Activated CD4^{+} T cells (mainly T_H2) and CD8^{+} T cells	Keratinocytes, epithelial cells, monocytes, eosinophils, basophils	Induction of IL-6, IL-8, CXCL1, CXCL8, CC chemokine ligand 2, and CC chemokine ligand 8 production in eosinophils, upregulates chemokine mRNA expression in keratinocytes, expression of growth factors and chemokines in epithelial cells, inhibition of proliferation and apoptosis in epithelial cells	Atopic dermatitis, allergic contact dermatitis, prurigo nodularis, chronic spontaneous urticaria, nonatopic eczema, asthma, other inflammatory disorders
IL-32	Unknown	14.9-26.6 kd	Unknown	Monocytes, macrophages, NK cells, T cells, epithelial cells	Macrophages, DCs, T cells, PBMCs, monocytes	Induction of TNF-α, IL-8, and IL-6, apoptosis	RA, IBD, autoimmune diseases
IL-33	β-Trefoil fold	30 kd (active form, 18 kd)	ST2	Necrotic cells and nuocytes	Basophils, mast cells, eosinophils, NK cells, NKT cells, T_H2 cells, DCs, nuocytes	Transcriptional repressor activity, induction of T_H2 inflammation on mucosal tissues	Autoimmune and cardiovascular diseases, asthma, gastrointestinal tract and lung disorders
IL-34	Homodimer	39 kd monomers	CSF1R	Heart, brain, liver, kidney, spleen, thymus, testes, ovary, small intestine, prostate, colon, most abundant in spleen	Monocytes, macrophages	Proliferation	
IL-35 (p35+EBI3)	Heterodimer	60 kd	Unknown	Treg cells	Different T-cell subsets	Proliferation of Treg cells and inhibition of T_H17-cell function, suppression of inflammatory responses	IBD, collagen-induced arthritis
IL-37	Unknown	17-24 kd	IL-18Rα ?	Monocytes, tonsil plasma cells, breast carcinoma cells	Intracellular mechanism manner and DC	Suppression of proinflammatory cytokines and inhibition of DC activation	RA
IFN-γ	Homodimer	34 kd	IFNGR1/IFNGR2	NK and NKT cells, macrophages, myelomonocytic cells, T_h1 cells, CTL and B cells	Epithelial cells, macrophages, DCs, NK cells, T and B cells	Antiviral properties, promotes cytotoxic activity, T_H1 differentiation, upregulation of MHC class I and II, inhibition of cell growth, proapoptotic effects and control of AICD, regulation of local leukocyte-endothelial interaction, and enhancement of microbial killing ability	Susceptibility to intracellular pathogen infection and tumor development, type 1 diabetes, RA, experimental autoimmune encephalomyelitis

AICD, Activation-induced cell death; *CTL,* cytotoxic T lymphocyte; *NK,* natural killer; *OSMRβ,* oncostatin-M receptor β; *sIL-6R,* soluble IL-6 receptor; *STAT1,* signal transducer and activator of transcription 1.

caspase-1 to become a biologically active molecule.[23] The IL-18 receptor (R) complex consists of a heterodimer that contains 2 chains. Although it was originally discovered as an inducer of IFN-γ production, IL-18 alone induces only small amounts of IFN-γ, whereas its combination with IL-12 induces high levels of IFN-γ production by T cells. The biological activity of IL-18 can be neutralized by the IL-18–binding protein, which binds mature IL-18 with a high affinity. IL-18 expression correlates with activities of rheumatoid arthritis (RA) and Crohn disease.[23] IL-18–deficient mice are more susceptible to bacterial infections than normal mice and have uncontrolled disease progression that is accompanied by reduced responses of T_H1 cells (Table II).[24]

IL-33

As part of the IL-1 family, IL-33 is a potent inducer of T_H2 responses via its receptor, ST2.[25] Binding of IL-33 to ST2 causes its homodimerization and recruitment of the IL-1R accessory protein (IL-1RacP).[26] *In vitro*, polarized T_H2 cells produce increased amounts of T_H2 cytokines in the presence of IL-33. The soluble form of ST2 is released by fibroblasts, macrophages, and monocytes in the presence of LPS, TNF-α, IL-1, or T_H2 cell clones; soluble ST2 inhibits binding of IL-33 to its receptor and is a negative regulator of its activity.[27] Levels of soluble ST2 are increased in individuals with inflammatory conditions such as SLE, RA, idiopathic pulmonary fibrosis, asthma, progressive systemic sclerosis, Behçet disease, Wegener granulomatosis, severe trauma, and sepsis. ST2-deficient mice have normal maturation of T_H2 cells but altered antigen-specific T_H2 type responses, increased rates of ventricular fibrosis, and cardiomyocyte hypertrophy in response to ventricular pressure overload.

IL-37

Some IL-1 family (IL-1F) members were given an IL-1F designation but might be designated as individual ILs because of different functions. IL-37 was originally defined as IL-1 family member 7 (IL-1F7).[28] IL-37 transcripts are detected in lymph nodes, thymus, bone marrow, placenta, lung, testis, and uterus.[28,29] The protein is found in monocytes, tonsil plasma cells, and breast carcinoma cells.[30,31] IL-37 has 5 different splice variants (IL-1F7a-e).[32] IL-37b (IL-1F7b) is the largest isoform and shares significant sequence homology with IL-18; it binds to the IL-18 receptor α-chain (IL-18Rα) and does not appear to be an antagonist of IL-18.[31] TGF-β and several Toll-like receptor (TLR) ligands induce production of high levels of IL-37 by PBMCs; proinflammatory cytokines such as IL-18, IFN-γ, IL-1β, and TNF moderately increase IL-37 levels.[33] IL-37b transgenic mice are protected from LPS-induced shock via reductions in proinflammatory cytokines and the inhibition of DC activation (Table II).[33]

COMMON γ-CHAIN CYTOKINE FAMILY

The common γ-chain (γc) family consists of ILs 2, 4, 7, 9, 15, and 21 and was named for binding of these factors to the common γc receptor (CD132; Fig 1). They act mainly as growth and proliferation factors for progenitors and mature cells and also have roles in lineage-specific cell differentiation.

IL-2

IL-2, discovered more than 30 years ago in supernatants of activated T cells, is mainly produced by $CD4^+$ and $CD8^+$ T cells, and to a lesser extent by activated DCs and NK and NK T (NKT) cells.[34] The IL-2R consists of 3 subunits: the ligand-specific α chain IL-2Rα (CD25), the β-chain IL-2Rβ (CD122, which is also part of the IL-15R complex), and the common γc (Fig 1). All 3 subunits are required for the assembly of the high-affinity IL-2R. On T-cell activation, IL-2Rα is rapidly induced and participates in formation of a high-affinity quaternary complex, which activates multiple signal transduction pathways.[35] IL-2 is essential for the development of Treg cells. IL-2 also acts as a B-cell growth factor, stimulates antibody synthesis, and promotes proliferation and differentiation of NK cells to increase their cytolytic functions.[36] Recombinant human IL-2 is used in immunotherapy for cancer and AIDS associated with HIV. Anti–IL-2Rα inhibits the immune response in patients with autoimmune diseases and prevents rejection of transplanted organs.[37]

IL-4

IL-4 is a 15-kd monomer (129 amino acids) produced by T_H2 cells, basophils, mast cells, and eosinophils. There are 2 types of IL-4Rs (Fig 1). Type I IL-4R binds only IL-4 and consists of 2 receptor chains: IL-4Rα (CD124) and the common γc (CD132). Type II IL-4R binds IL-4 and IL-13 and consists of the IL-4Rα and the IL-13Rα1 chains.[35] A pleiotropic cytokine, IL-4 regulates allergic conditions and the protective immune response against helminths and other extracellular parasites.[38] IL-4 is the major stimulus of T_H2-cell development (Fig 2); it also suppresses T_H1-cell development and induces IgE class-switching in B cells. IL-4 increases the expression of class II MHC molecules in B cells, upregulates B-cell receptors, increases expression of CD23, prolongs lifespans of T and B cells in culture, and mediates tissue adhesion and inflammation. IL-4 and IL-4Rα knockout mice have defects in T_H2-cell differentiation and reduced serum levels of IgG_1 and IgE.[39]

IL-7

IL-7, also known as pre–B-cell growth factor or lymphopoietin-1, is a homeostatic cytokine.[40] The IL-7R is present on most T cells, progenitors of B cells, and bone marrow macrophages; it consists of the IL-7Rα (CD127) chain and the common γc (CD132) (Fig 1).[35] Because γc is ubiquitously expressed on lymphocytes, IL-7 responses are determined by the expression of IL-7Rα, which is shared with thymic stromal lymphopoietin (TSLP) receptor. IL-7 signaling contributes to survival and proliferation of thymocytes and development of naive and memory B and T cells, mature T cells, and NK cells. Studies of IL-7 and IL-7Rα knockout mice have shown that IL-7 is important for homeostatic T-cell and B-cell development.[41] IL-7 or reagents that block IL-7 signaling might be used to treat patients with HIV-associated immunodeficiency and immunodeficiency secondary to chemotherapy, autoimmune diseases, and lymphoid malignancies.

IL-9

IL-9 was first discovered in mice, where it was found to be a potent, antigen-independent growth factor for T cells[42] and mast cells.[43] T_H2 cells are the main source of IL-9 production; mast

TABLE II. *In vivo* phenotype related to cytokines

Cytokine	Phenotype of cytokine KO mice	Phenotype of receptor chain KO mice	Phenotype of certain transgenics	Phenotype of human poly-morphisms and mutations
IL-1α, IL-1β	Resistance to fever induction, impaired acute-phase response	Normal vigor, no overt phenotype	Transgenic mice overexpressing IL-1α in basal keratinocyte show spontaneous inflammatory skin lesions	Polymorphisms associated periodontal diseases
IL-1ra (antagonist)	High susceptibility to develop collagen-induced arthritis, autoimmunity, arteritis	Normal vigor, no overt phenotype	Protected from collagen-induced arthritis	Polymorphism associated with ulcerative colitis, lupus erythematosus, osteoporosis, and viral infections
IL-2	Reduction of polyclonal T-cell responses, changes of the isotype levels in serum immunoglobulins, absence of secondary antiviral T-cell responses, and reduced NK-cell activity	Enlargement of peripheral lymphoid organs associated with polyclonal T-cell and B-cell expansion, development of lymphoproliferative and autoimmune disorders	Treg-cell deficiency	Development of X-linked severe combined immunodeficiency
IL-3	Abnormal seminal vesicle development; hydrocephaly	Normal hematopoiesis, growth, development, and longevity; diminished immunity to parasites (reduced numbers of mast cells)	Transgenic mouse expressing antisense IL-3 RNA: death after 3-6 mo of age because of pre–B-cell lymphoproliferative syndrome or neurologic dysfunction	Ser27Pro: protective effect on the development of asthma
IL-4	Severe trouble on T_H2 differentiation, decreases in IgE and IgG_1 serum levels	Severe trouble on T_H2 differentiation, decreases in IgE and IgG_1 serum levels	Allergic airways inflammation and remodeling	Development of X-linked severe combined immunodeficiency
IL-5	Resistant to induction of experimental asthma	IL-5Rα$^{-/-}$: low IgM and IgG_3 serum concentrations	Prolonged wound healing because of increased eosinophilic invasion into the wound areas	
IL-6	Normal (viable, fertile), impaired regulation of T-cell trafficking, abnormalities in acute-phase response	IL-6R: decreased production of serum amyloid A, 1/3 fewer T cells gp130$^{-/-}$ embryos: dead at 12.5 days post coitus, decreased number of pluripotential and hematopoietic progenitors in liver, decreased number of T cells in the thymus	IL-6 transgenics: increase of IgG_1, monoclonal transplantable plasmacytoma	Low bone mineral density, juvenile RA
IL-7	High lymphopenia, impaired transition to pre–B cells, reduction of B-cell numbers in thymus and spleen	General reduction of thymic and peripheral lymphoid cellularity	T-cell and early B-cell expansion, lymphoproliferative skin disorders, chronic colitis	Development of X-linked severe combined immunodeficiency
IL-8	Impaired neutrophil infiltration but normal function	CXCR2$^{-/-}$: increased susceptibility to various pathogens; impaired wound healing; impaired angiogenesis; neurologic defects; altered growth of induced and implanted tumors	Excessive accumulation of neutrophils, decreased L-selectin expression on circulating neutrophils	IL-8: -251 (IL-8 promoter region): AA genotype increases the risk of atrophic gastritis and gastric cancer because of elevated IL-8 levels and neutrophils infiltration; CXCR1: M300R and R142C: reduced efficiency of HIV infection because of reduced CD4 expression

(Continued)

TABLE II. *(Continued)*

Cytokine	Phenotype of cytokine KO mice	Phenotype of receptor chain KO mice	Phenotype of certain transgenics	Phenotype of human poly-morphisms and mutations
IL-9	Mucus overproduction, mast cell proliferation, complete inhibition of allergic airways inflammation and remodeling	Reduction of the number of thymocytes, critical role in early T-cell development	Development of thymic lymphomas, asthma	Development of X-linked severe combined immunodeficiency, Hodgkin disease, large cells anaplastic lymphomas
IL-10	Mice have growth retardation, anemia, and chronic enterocolitis; they demonstrate elevated T_H1 responses leading to accelerated clearance of infections; elevated T_H2 responses leading to exaggerated allergic response	IL-10R2$^{-/-}$ mice grow normally and are fertile but develop chronic colitis and splenomegaly after 12 wk of age	IL-10 overexpression results a defect in α/β T-cell maturation	Polymorphisms in the promoter region of the *IL-10* gene leading to variations in IL-10 expression have been associated with several diseases including cancer, autoimmunity, and allergy
IL-11	No obvious abnormalities	IL-11Ra$^{-/-}$: no overt hematologic abnormalities, but increased bone volume; females are infertile because of impaired placenta development	Induce survivin and antiapoptotic proteins in endothelial cells and increased fibroblasts and remodeling in lung	
IL-12 (p35/p40)	p40 KO: immunocompromised, susceptible to infection with several intracellular pathogens p35KO: defect in T_H1 cells response and are highly susceptible to EAE and CIA	No obvious developmental abnormalities, impaired IFN-γ secretion, T_H1 differentiation, and NK cytolytic activity, which results in higher susceptibility to intracellular pathogens	p40: develop inflammatory skin lesions	Psoriasis, susceptibility to poorly pathogenic mycobacterial and *Salmonella* infection
IL-13	Decreased levels of IL-4, IL-5, and IL-10	Upregulation of IL-13Rα2 and IL-13, higher amount of CD4$^+$ T_H2 cells, increased frequency of eosinophils in granuloma, decrease in severity of hepatic fibrosis, decrease in IgE serum levels	Asthmalike lung inflammation	Associated with bronchial asthma
IL-14		Defects restricted to appendicular skeleton	Hypergammaglobulinemia (IgG, IgA, and IgM autoantibodies)	SLE and Sjögren syndrome
IL-15	Reduced numbers of NK, NK T, and CD8$^+$ T cells, almost a total lack of memory CD8$^+$ T cells	Reduced numbers of NK, NK T, and CD8+ T cells, almost a total lack of memory CD8$^+$ T cells	Increase of CD8$^+$ T cells and lymphomas, inhibition of IL-2–induced activation-induced cell death, inhibition of allergic inflammation in asthma model, elimination of colon-carcinoma cells	Development of X-linked severe combined immunodeficiency
IL-16		CCR5-deficient mice show reduced binding of IL-16 to the cell surface and diminished T-cell migration		-295 (IL-16 promoter region): TT genotype is associated with Crohn disease; CC genotype is associated with contact dermatitis
IL-17A	Profound defects in host protection, resistance to several inflammatory diseases	Profound defects in host protection, resistance to several inflammatory diseases	Inflammation and destruction of the tissue, neutrophilia	

(Continued)

TABLE II. *(Continued)*

Cytokine	Phenotype of cytokine KO mice	Phenotype of receptor chain KO mice	Phenotype of certain transgenics	Phenotype of human polymorphisms and mutations
IL-17F	Profound defects in host protection, enhanced T_H2 cytokine production and eosinophil function	Profound defects in host protection, resistance to several inflammatory diseases	Pathological phenotype in lung	SNP (His161Arg) associated with protection against asthma and chronic fatigue syndrome
IL-18	Increased susceptibility to *Leishmania major* infection accompanied by decreased T_H1-cell response, more susceptibility to viral infections with impairment of NK-cell activity			
IL-19	Mice exhibit epidermal hyperplasia in response to intradermal IL-23 treatment		No phenotype of transgenics described	Polymorphisms in the *IL-19* gene have been associated with psoriasis
IL-20	No KOs described	IL-20R2$^{-/-}$ mice are unresponsive to skin alterations induced by intradermal IL-23 injection	Overexpression leads to skin abnormalities and death within a few days after birth	Polymorphisms in the *IL-20* gene have been associated with psoriasis
IL-21	Reduced numbers of T_H17 cells, reduced EAE progression	Reduced serum IgG$_1$ levels, increased IgE levels, reduced numbers of T_H17 cells, reduced EAE progression	CD8$^+$ memory T-cell accumulation, elevated serum IgM and IgG$_1$	
IL-22	Defects in host protection, increased intestinal epithelial damage		—	Viral clearance, antiviral defense
IL-23(p19+p40)	p40 KO: immunocompromised p19 KO: can still generate T_H1 cells and IFN-γ, defect in delayed type hypersensitivity response, resistant to developing EAE and CIA	No obvious developmental abnormalities, impaired IFN-γ secretion, T_H1 differentiation, and NK cytolytic activity, which results in higher susceptibility to intracellular pathogens	p40: Develop inflammatory skin lesions p19: Develop systemic inflammatory diseases	Ulcerative colitis, psoriasis, ankylosing spondylitis and myocardial infarction, psoriasis, arthritis
IL-24	Epidermal hyperplasia induced by intradermal injection of IL-23, a major cytokine implicated in psoriasis, was shown to be mediated by both IL-19 and IL-24		Share many of the phenotypic features with IL-20 and IL-22 transgenics including epidermal hyperplasia, neonatal lethality, and abnormal keratinocyte differentiation	
IL-25	Constant expression of T_H2 cytokines and higher levels of IgE, increases in mast cells in parasitic infections	Lack of production of IL-5 and IL-13 by splenocytes, lower number of eosinophils, neutrophils, lymphocytes	Splenomegaly, lymphadenopathy, and increases in eosinophils and B cells in the periphery, growth retardation and pronounced inflammations of organs, T_H2-like reactions in the lung	
IL-26				Associated with protection from MS and RA

TABLE II. *(Continued)*

Cytokine	Phenotype of cytokine KO mice	Phenotype of receptor chain KO mice	Phenotype of certain transgenics	Phenotype of human poly-morphisms and mutations
IL-27(p28+EBI3)	EBI3: early defect in T_H1-cell response during *L major* infection, resistant to oxazolone-induced colitis	gp130: Severe developmental defects WSX-1: increased T_H1, T_H2, or T_H17 cell response in several models of infection and inflammation	Aberrant inflammatory response in the GI tract	COPD, asthma
IL-28A/B/IL-29 (IFN-δ family)	No knockouts described		No phenotype of transgenics described	None described
IL-31		Significant enhancement of T_H2-type response and granuloma formation in models with *Schistosoma mansoni*	Alopecia, chronic pruritus, skin lesions, conjunctivitis and swelling around eyes, inverse T-cell:B-cell ratio	
IL-32			Overexpression of human IL-32, more TNF-α, IL-1, IL-6 in response to LPS, increased collagen-induced arthritis	
IL-33		Altered antigen-specific T_H2 responses, lack of pulmonary granuloma formation in the lung, absence of endotoxin tolerance		
IL-37			Protected from LPS-induced shock	
IFN-γ	Defects in T_H1 cytokine-induced functions, susceptibility to intracellular pathogens, tumor development, enhanced EAE	Defect in resistance to bacterial and viral infections		Susceptibility to pulmonary tuberculosis, MS, myasthenia gravis, and arthritis manifestations

CIA, Collagen-induced arthritis; *COPD*, Chronic obstructive pulmonary disease; *EAE*, Experimental autoimmune encephalomyelitis; *GI*, gastrointestinal; *KO*, knockout; *SNP*, single nucleotide polymorphism.

cells (mainly within the airways of subjects with asthma) and eosinophils secrete IL-9 to a lesser extent. IL-9 inhibits cytokine production by T_H1 cells, promotes IgE production by B cells, induces chemokine and mucus secretion by bronchial epithelial cells, and promotes proliferation of mast cells.[43] The IL-9R consists of the ligand-specific α-chain (IL-9Rα) and the common γc (Fig 1). The IL-9Rα chain is sufficient to bind IL-9 with high affinity but does not mediate any signal by itself. IL-9 has important roles in pathogenesis of asthma and allergies and in fighting helminth infections. A new population of T cells, T_H9 cells that produce IL-9 and IL-10, have been proposed to contribute to inflammation (Fig 2).[12]

IL-15

IL-15 is structurally homologous to IL-2 and was discovered for its ability to induce T-cell proliferation like IL-2.[44] Many of the biological actions attributed to IL-2 can also be induced by IL-15. The IL-15R consists of the IL-15Rα chain, the IL-2Rβ chain, and the common γc (Fig 1).[35] IL-15 is produced by nonimmune cells (keratinocytes and skeletal muscle cells) and immune cells (monocytes and activated CD4+ T cells) in response to signals that induce innate immunity. Although IL-15 shares some functions with IL-2, such as activation of T cells, stimulation of NK-cell proliferation, and cytolytic activity, differences in their

biological functions have been identified on the basis of differences observed between phenotypes of IL-2 and IL-15 knockout mice.[45]

IL-21

IL-21 is produced by T cells, NKT cells,[46] and the T_H17 subset of CD4+ T cells.[47,48] The receptor for IL-21 is expressed on various cells, indicating a broad spectrum of action. IL-21 affects B-cell functions by regulating antibody isotype balance, proliferation, apoptosis, and differentiation into plasma cells. Cytotoxic activity and proliferation of CD8+ T cells, NK cells, and NKT cells increase on stimulation with IL-21.[49,50] IL-21 has been tested as an anticancer drug, and first clinical trial results are promising by slowing down tumor progression in metastatic melanoma.[51] In contrast with its anticancer effects, IL-21 also contributes to inflammation in several disorders, as expected for a T_H17-related cytokine.

IL-10 FAMILY
IL-10

IL-10 is an anti-inflammatory factor that is an important regulator of several aspects of immune responses. The *IL-10*

gene maps to a cytokine cluster that includes the genes *IL-19, IL-20, IL-24*, and *IL-26* on chromosome *1q31-32*.[52] IL-10 is produced mainly by monocytes, T cells (mainly Tr1 cells), B cells, NK cells, macrophages, and DCs.[53] Mast cells can also produce IL-10, which limits the rate of leukocyte infiltration, inflammation, and skin disorders such as contact dermatitis or after chronic ultraviolet B irradiation.[54] IL-10 is secreted as a homodimer that consists of 2 subunits, each of 178 amino acids with a molecular weight of ~18 kd.[55] The receptor complex for IL-10 is made up of 2 IL-10R1 and 2 IL-10R2 chains (Fig 1).[56] IL-10 directly affects APC functions by downregulating the expression of MHC class II and costimulatory molecules on the surface of macrophages and monocytes.[57] IL-10 inhibits the expression of many proinflammatory cytokines, chemokines, and chemokine receptors[58] and mediates allergen tolerance in allergen-specific immunotherapy and after exposure to high doses of allergen.[14,59] In addition to these indirect effects, IL-10 directly affects T-cell activation by suppressing CD28, CD2, and signaling of the inducible T-cell costimulator via the tyrosine phosphatase SHP-1.[60] In contrast with its inhibitory effects on T cells, IL-10 promotes survival, proliferation, and differentiation of human B cells and increases the production of IgG$_4$.[57] Several mouse models demonstrate the importance of IL-10 in regulation of the inflammatory response. IL-10 knockout mice develop normal lymphocyte and antibody responses but have reduced growth, are anemic, and spontaneously develop chronic colitis.[61]

IL-19

IL-19, first isolated from an EBV-transformed, B-cell library is secreted as a 35 to 40–kd glycosylated protein and functions as a monomer.[62] IL-19 binds to a heterodimeric receptor made up of IL-20R1 and IL-20R2. This complex also binds IL-20 and IL-24.[56] IL-19 is expressed by LPS-stimulated monocytes, and low levels have been observed in B cells.[62] Mouse IL-19 stimulates production of IL-6 and TNF-α and induces apoptosis and production of reactive oxygen species in monocytes, indicating a role in proinflammatory responses.[63] IL-19 might promote T$_H$2-cell responses because it induces expression of IL-4, IL-5, IL-10, and IL-13 by activated T cells.[64] Increased levels of IL-19 have been observed in patients with asthma, whereas lower circulating levels and increased epidermal expression of IL-19 were observed in patients with psoriasis.[65]

IL-20

The human *IL-20* gene encodes a 176 amino acid protein that is secreted as a functional monomer.[66] IL-20 can signal through a complex of IL-20R1 and IL-20R2 (also binds IL-19 and IL-24) or a complex of IL-22R1 and IL-20R2 (also binds IL-24; Fig 1).[56] IL-20 is mainly produced by LPS-stimulated monocytes and DCs but is also produced by epithelial and endothelial cells as well as keratinocytes. IL-20 has important functions in skin. Transgenic overexpression in mice caused skin abnormalities that include hyperkeratosis, a thickened epidermis, and a compact stratum corneum; the mice are retarded in growth and die within the first days after birth.[66] Together with IL-19, IL-20 appears to have a role in the pathogenesis of psoriasis—their mRNA was detected in psoriatic lesions but not in uninvolved skin from the same subjects. Moreover, the expression of all receptor chains involved in IL-20 and IL-19 binding is upregulated in psoriatic skin.[67] In addition to its

potential role in psoriasis, IL-20 has been associated with RA, atherosclerosis, and angiogenesis.[68] It was shown to be an angiogenic factor in a rat model of ischemic disease and might be used to treat patients with ischemic disorders.[69]

IL-22

IL-22 was identified in mice as a gene that is induced by IL-9 in T cells.[70] It binds to a complex of IL-22R1 and IL-10R2 (Fig 1).[70,71] IL-22 is expressed by activated T cells and, at lower levels, by activated NK cells[72]; specifically, it is produced by T$_H$17 and T$_H$22 cells[73] and by NK-22 cells.[74] The IL-10R2 chain, which is shared with other cytokine receptors, is ubiquitously expressed. The IL-22R1 chain, in contrast, is not detected on immune cells but in kidney, small intestine, liver, colon, lung, and particularly pancreas and skin.[75] IL-22 induces genes that are involved in the antimicrobial defenses of keratinocytes.[73] IL-22 is upregulated during bacterial infection,[74] psoriasis, and atopic dermatitis.[76,77] Although IL-22 has been associated with inflammatory disorders, it might also have anti-inflammatory effects.[78-80]

IL-24

IL-24 was first described as *melanoma differentiation-associated gene-7*.[81] Secreted human IL-24 undergoes extensive N-linked glycosylation and has an apparent molecular weight of ~35 kd.[82] IL-24 binds to complexes made up of IL-22R1 and IL-10R2 or IL-20R1 and IL-20R2 (Fig 1).[82] IL-24 is expressed by normal melanocytes, T cells, and monocytes.[81,83] IL-24 specifically inhibits tumor growth.[84] In a phase I clinical trial, intratumoral injections of a nonreplicating adenovirus vector that carried *IL-24* were well tolerated and induced apoptosis in large volumes of tumor tissue.[85]

IL-26

IL-26 was discovered in a study of phenotypic changes in human T cells after transformation by *Herpesvirus saimiri*.[86] Interestingly, mice and rats do not have the *IL-26* gene, although zebrafish, chickens, and frogs do; evolutionary conservation is limited.[87] Expression of IL-26 seems to be restricted to memory T cells, NK cells, and T$_H$17 cells.[72,88] The receptor for IL-26 consists of the IL-10R2 chain, which is part of other receptors in this cytokine family, and the IL-20R1 chain (Fig 1).[89] In contrast with IL-10R2, IL-20R1 has not been detected in immune cells, but IL-20R1 is expressed on several types of epithelial cells and skin, testis, heart, placenta, salivary gland, and prostate cells.[66,83] Partly because mice do not carry *IL-26*, there have been few studies of its physiological function or role in disease processes. However, because IL-26 is expressed by T$_H$17 cells, it could have proinflammatory effects in disorders such as Crohn disease.[90]

IL-28A, IL-28B, and IL-29

IL-28A, IL-28B, and IL-29 (alternatively termed IFN-λ2, IFN-λ3, and IFN-λ1, respectively) have homology with type I IFNs, although the intron-exon structure of their genes more closely resembles that of the IL-10 family.[91,92] IL-28A, IL-28B, and IL-29 all signal through the same receptor complex, which is composed of a single IL-28R1 chain and an IL-10R2 chain (Fig 1). Expression of IL-28 and IL-29 is induced by exposure of cells to polyriboinosinic:polyribocytidylic acid (poly I:C) or viral

infection, indicating their antiviral activities.[92] IL-28 and IL-29 inhibit replication of hepatitis B and C viruses, so they might be used to treat patients infected with these viruses.[93] Interestingly, IL-28 and IL-29 might also promote the development of tolerogenic DCs.[94]

IL-12 FAMILY

IL-12, IL-23, IL-27, and IL-35 share receptor and ligand chains (Fig 1). However, their functions differ with their expression on different cell types and combinations of different receptor chains. IL-30 is the alternative designation for the p28 subunit of IL-27.

IL-12

IL-12, first described as NK stimulating factor, is a heterodimer that consists of a 35-kd light chain (p35) and a 40-kd heavy chain (p40).[95] It is produced by activated monocytes, macrophages, neutrophils, microglia, and DCs. IL-12p70 consists of p35 and p40 subunits and binds to a heterodimeric receptor composed of IL-12Rβ1 and IL-12Rβ2.[96] Each receptor subunit is expressed by activated T cells and NK cells, along with DCs and B-cell lines.[97] IL-12 mediates development and maintenance of T_H1 cells by inducing production of IFN-γ by T_H1 and NK cells. IL-12 indirectly activates the antimicrobial, antiparasitic, and antitumor activity of macrophages and promotes cytolytic activity of NK cells and lymphokine-activated killer cells.[98] Reduced production of IL-12 impairs T_H1 responses and increases susceptibility to infection with intracellular pathogens.

IL-23

IL-23 includes the IL-12p40 subunit and a distinct IL-23p19 subunit (Fig 1).[99] IL-23 is mainly produced by phagocytic cells, macrophages, and activated DCs from peripheral tissues including the skin, intestinal mucosa, and lungs. Because they use the same p40 subunit, IL-23 and IL-12 have the IL-12Rβ1 subunit in their receptor complexes. A second subunit (called IL-23R) is required for specific recognition of p19; this heterodimer forms the high-affinity IL-23R. Activated and memory T cells express high levels of the IL-23R, along with NK and NKT cells, eosinophils, monocytes, macrophages, DCs, and epithelial cells.[99,100] A population of innate lymphoid cells responds to IL-23 and mediates intestinal immune pathology; these might be involved in pathogenesis of inflammatory bowel disease (IBD).[101]

IL-27

IL-27 is a heterodimeric cytokine that consists of the p28 and EBI3 subunits. The p28 chain is related to IL-12p35, whereas the EBI3 is related to IL-12p40 and structurally resembles the soluble IL-6R (Fig 1).[102] IL-27 is expressed predominantly by APCs (including DCs and macrophages) and endothelial cells. IL-27 mediates its effect through a heterodimeric receptor composed of IL-27Ra (WSX-1, T-cell cytokine receptor) and gp130—a signal transducing chain that is shared by several cytokines.[103] IL-27 is believed to have inflammatory activity because it promotes early commitment of naive T cells to the T_H1-cell lineage.[104] Interestingly, it directly antagonizes the development of T_H17-cell responses and limits induction of inflammation by cells that produce IL-17 in the central nervous system.[105] IL-27 also limits induction of uveitis and scleritis by cells that produce IL-17,

induces FoxP3 expression by Treg cells,[106] and might contribute to immune privilege.[107]

IL-35

IL-35 is a heterodimeric hematopoietin that consists of EBI3 and the p35 subunit of IL-12 (Fig 1).[108] EBI3 is specifically expressed in mouse FOXP3^{+} Treg cells[109]; the EBI3/p35 heterodimer is constitutively secreted by these cells.[109,110] Increased expression of EBI3 and IL-12a (p35) in mouse FOXP3^{+} Treg cells, compared with effector T cells, and transcription analyses indicated that EBI3 expression is regulated by FOXP3.[110] Covalent linkage between mouse or human forms of EBI3 and a p35 creates the heterodimeric IL-35 protein.[111] IL-35 stimulation of mouse CD4^{+}CD25^{+} Treg cells induced proliferation and IL-10 production but did not affect expression of FOXP3. On the contrary, stimulation of mouse CD4^{+}CD25^{−} effector T cells with IL-35 and anti-CD3 and anti-CD28 antibodies induced proliferation of these cells, increased IFN-γ production, and increased expression of T-box expressed in T cells (Tbet).[111] CD4^{+}CD25^{+} T cells expanded in the presence of IL-35 were able to suppress proliferation of CD4^{+}CD25^{−} T cells. IL-35, but not EBI3 alone, inhibited differentiation of mouse CD4^{+} T cells into T_H17 cells that produce IL-17. Furthermore, in mice with collagen-induced arthritis, IL-35 reduced the incidence of arthritis, numbers of arthritic paws, and pathologic features of the disorder; IL-35 also increased serum levels of IL-10 and IFN-γ and reduced induction of IL-17.[111]

T_H2-LIKE CYTOKINES

Cytokines produced during the induction and function of T_H2 response include IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, and IL-33; these mediate immunity against helminth infections, IgE production, and eosinophilia (Fig 2).

IL-5

IL-5 was initially described as an eosinophil and B-cell growth factor[112]; it is mainly produced by CD4^{+} T_H2 cells, activated eosinophils, mast cells, CD8^{+}Tc2 cells, γδ T cells, NK cells, NKT cells, and CD4^{−}ckit^{−}CD3ε^{−}IL-2Rα^{+} cells in Peyer patches. Its receptor shares the β-chain (CD131) with IL-3 and GM-CSF (Fig 1). IL-5 promotes proliferation, activation, differentiation, survival, and adhesion of eosinophils. T_H2 cells that secrete IL-5 recruit eosinophils and contribute to the induction of airway hyperreactivity in patients with asthma.[113] Levels of IL-5, T_H2 cells, and eosinophils are increased in cases of bronchoalveolar lavage and correlate with asthma severity. IL-5–deficient mice develop normally but are resistant to induction of experimental asthma, reduce expulsion of *Nippostrongylus brasiliensis*, and have fewer IgA^{+} cells in the lamina propria compared with control mice.[114] Clinical trials targeting IL-5 have produced mixed results, but patients with refractory eosinophilic asthma were reported to have reduced numbers of exacerbations and eosinophils in sputum and blood and increased the quality of life.[115]

IL-13

IL-13 is a 4-helix bundle protein expressed by activated T_H2 cells, mast cells, basophils, eosinophils, and NKT cells.[116] Its

receptors are IL-13Rα1 and IL-13Rα2, and signaling occurs via the IL-4R complex type II, which consists of IL-4Rα and IL-13Rα1 (Fig 1).[117] IL-13Rα2 inhibits IL-13 and has been linked to fibrosis.[118] IL-13 activates the same signal transduction pathways as IL-4 and induces IgE production. It also activates and recruits mast cells and eosinophils and promotes their survival. A combination of polymorphisms in factors in the IL-4 and IL-13 pathways increases risk of asthma by 16.8-fold; polymorphisms in only *IL13* increase the incidence of asthma exacerbations in children and increase total IgE and eosinophils in blood samples.[119,120] IL-13 knockout mice produce less IL-4, IL-5, IL-10, and IgE and fail to develop goblet cell hyperplasia (Table II).[121] They are unable to expel *N brasiliensis*, indicating the role of IL-13 in parasite defense. IL-13Rα1 knockout mice lack features of asthma and airway remodeling.

IL-25

Because of homology with IL-17 family members, IL-25 has also been named IL-17E. It is produced by T_H2 polarized T cells,[122] mast cells, eosinophils, and basophils from atopic individuals. IL-25 induces production of T_H2-associated cytokines. IL-25 knockout mice fail to expel *N brasiliensis* efficiently[123] because of subtle changes induction of T_H2 cytokine responses and are very susceptible to experimental autoimmune encephalomyelitis. An IL-4, IL-5, and IL-13–producing, non–T-cell, non–B-cell population that is ckit^{pos} FcεR1^{neg} precedes the increase in T_H2 CD4$^+$ cells and has been proposed to produce IL-25.[123] Transgenic expression of IL-25 leads to blood eosinophilia and increased levels of IgE, IgG$_1$, IL-13, and IL-5. IL-25 might be involved in pathogenesis of asthma because it is expressed at high levels in lungs of sensitized mice after allergen challenge. Transgenic mice that express IL-25 only in lungs have increased numbers of eosinophils and CD4$^+$ T cells on allergen-specific stimulation.

IL-31

IL-31 is expressed by activated CD4$^+$ T cells (mostly by T_H2 cells) and, at lower levels, by CD8$^+$ T cells.[124] IL-31 signals through a heterodimeric receptor complex that consists of the IL-31RA and oncostatin-M receptor β; this receptor is expressed mainly by keratinocytes but also by epithelial cells, dorsal root ganglia, eosinophils, basophils, and monocytes. IL-31 expression is increased in individuals with atopic dermatitis, contact dermatitis,[125] and prurigo nodularis.[126] Transgenic overexpression of IL-31 in mice results in a phenotype that resembles nonatopic dermatitis.[5] IL-31 might also be involved in pathogenesis of IBD. In mouse models of airway inflammation, IL31 mRNA is upregulated in lungs after antigen challenge.[5]

ILs WITH CHEMOKINE ACTIVITY
IL-8

IL-8 was identified as a neutrophil-specific chemotactic factor and later classified as a member of the CXC chemokine family.[127] IL-8 is produced by a variety of cells, such as monocytes and macrophages, neutrophils, lymphocytes, and endothelial and epithelial cells after stimulation with IL-1-α, IL-1-β, IL-17, TNF-α, or TLRs.[128] The receptors for IL-8 are CXCR1 (IL-8RA) and CXCR2 (IL-8RB).[129] The major effector functions of IL-8 are

activation and recruitment of neutrophils to the site of infection or injury.[130] In addition to neutrophils, IL-8 also attracts NK cells, T cells, basophils, and GM-CSF–primed or IL-3–primed eosinophils.[131] Increased concentrations of IL-8 were found in inflammatory sites in patients with diseases such as psoriasis, RA, respiratory syncytial virus infection, or chronic obstructive pulmonary diseases.[132,133]

IL-16

IL-16 was discovered as a T-cell–specific chemoattractant.[134] Pro–IL-16, its 80-kd precursor protein, is cleaved by caspases-3, resulting in a 60-kd N-terminal fragment and a 14-kd to 17-kd C-terminal fragment.[135] The N-terminal fragment regulates the cell cycle, whereas the C-terminal fragment forms homotetramers (56 kd) that mediate cytokine functions.[136] IL-16 mRNA and pro–IL-16 are constitutively expressed in T cells, eosinophils, and monocytes, whereas nonimmune cells such as epithelial cells and fibroblasts must be activated to transcribe IL-16 mRNA. IL-16 mediates its biological activity via CD4.[136] IL-16 inhibits T-cell proliferation,[137] promotes T_H1-mediated responses, and reduces T_H2-mediated inflammation by activating the release of TNF-α, IL-1-β, and IL-15 and concomitantly inhibiting the production of IL-4 and IL-5.[138]

IL-17 FAMILY

IL-17A, initially called IL-17, is the founding member of a structurally distinct cytokine family. It binds as a homodimer or as a heterodimer with IL-17F to its receptor, IL-17RA.[139] IL-17A is expressed by activated CD4$^+$ T_H17 cells (Fig 2),[11] but its expression has also been detected in CD8$^+$ T cells, γδ T cells, NK cells, and neutrophils.[139] During T_H17 differentiation, human naive T cells must be exposed to IL-1β, IL-6, IL-23, and TGF-β before they express maximum levels of IL-17.[10] IL-17RA is expressed by lung, spleen, kidney, and liver.[140] IL-17A is expressed by fibroblasts, epithelial cells, vascular endothelial cells, B and T cells, myelomonocytic cells, and bone marrow stromal cells.[141] Consistent with the broad expression pattern of its receptor, IL-17A acts on a variety of cells, which respond by upregulating expression of proinflammatory cytokines, chemokines, and metalloproteases. By inducing cells to produce chemokines, IL-17A attracts neutrophils to mediate defenses against different pathogens. IL-17A and T_H17 cells are involved in several inflammatory disorders, including pathogenesis of RA[142] and multiple sclerosis (MS).[143] Similarly, IL-17A is upregulated in mouse models of collagen-induced arthritis[144] and experimental autoimmune encephalitis.[145] Increased levels of IL-17A have also been found in patients with psoriasis, IBD, and allergic diseases like allergic asthma and atopic dermatitis.

In contrast with its homolog IL-17A, IL-17B and its receptor IL-17RB are not expressed in immune cells, but instead in spinal cord, testis, small intestine, pancreas, stomach, prostate, ovary, colon mucosa, and cartilage.[146] No specific receptors for IL-17C or IL-17D have been identified.[147] IL-17C induces production of proinflammatory cytokines and metalloproteases by certain cells[147] and has been associated with pathological conditions such as arthritic paws of mice with collagen-induced arthritis.[148] IL-17D is highly expressed in skeletal muscle, brain, adipose tissue, heart, lung, and pancreas.[149] Lower levels are also found in

bone marrow, fetal liver, kidney, lymph node, placenta, spleen, thymus, tonsils, resting CD4^{+} T cells, and resting B cells.

Among the IL-17 family members, IL-17A and IL-17F have the highest degree of homology—they are 50% identical at the protein level.[150] IL-17F binds to the same receptor as IL-17A (IL-17RA), although with lower affinity.[151] IL-17A and IL-17F form heterodimers, as expected from their structural similarities. There are 2 isoforms of IL-17F; each is expressed by activated T_H17 cells.[11] Like IL-17A, IL-17F acts on many cell types and induces similar proinflammatory cytokines and chemokines, as predicted on the basis of their structural homology and expression patterns.

OTHER ILs
IL-3

The human *IL-3* gene is on chromosome 5, close to *IL-5* and *GM-CSF*, indicating a common ancestral relationship. It is expressed by T cells, macrophages, stromal cells, NK cells, mast cells, and eosinophils. Because IL-3, IL-5, and GM-CSF share a common receptor subunit β-chain (CD131), their functions partially overlap (Fig 1). On binding IL-3, the β-chain forms a heterodimer with the cytokine-specific α-chain.[152] IL-3 is a multilineage hematopoietic growth factor during early stages of hematopoiesis, in synergy with other cytokines. In combination with erythropoietin or GM-CSF and granulocyte colony stimulation factor (G-CSF), IL-3 induces erythroid or granulocyte–macrophage lineages, respectively. IL-3 and TNF-α promote proliferation of CD34^{+} progenitor cells; IL-3 also increases the activation and release of mediators from eosinophils and basophils in response to IgE FcεR cross-linking.[153] Mice that do not produce β-chains lack IL-3, IL-5, or GM-CSF signaling; these hematopoietic cytokines mediate T_H2-mediated allergic airway inflammation by inducing eosinophil accumulation, airway hyperresponsiveness, mucus hypersecretion, and IgE production.[154,155]

IL-6

IL-6 is a member of the IL-6–type family of cytokines, which includes leukemia inhibitor factor, ciliary neurotrophic factor, and oncostatin-M. Its receptor consists of an IL-6–binding chain (IL-6Rα) and the signal-inducing component (gp130). IL-6R exists in membrane-bound and soluble forms.[156] IL-6 is a multifunctional, pleiotropic cytokine involved in regulation of immune responses, acute-phase responses, hematopoiesis, and inflammation. It is produced by endothelial cells, fibroblasts, monocytes, and macrophages in response to different stimuli (IL-1, IL-17, and TNF-α) during systemic inflammation. In innate immunity, IL-6 directs leukocyte trafficking and activation and induces production of acute-phase proteins by hepatocytes.[157] IL-6 promotes T-cell proliferation, B-cell differentiation and survival, and plasma-cell production of IgG, IgA, and IgM.[158]

IL-11

IL-11 is formed via cleavage of a 199–amino acid precursor, which results in a mature, 19-kd protein with 4 α-helices that are similar those of the IL-6 family.[159] IL-11 is expressed by stromal cells, including fibroblasts, epithelial cells, endothelial cells, osteoblasts, and several tumor cell lines. IL-11 binds a heterodimeric receptor, consisting of IL-11Rα and gp130.[160] IL-11Rα binds

IL-11 with high levels of specificity, whereas gp130 is shared by receptors for IL-11, IL-6, ciliary neurotrophic factor, leukemia inhibitory factor, oncostatin-M, and cardiotrophin-1. IL-11 stimulates hematopoiesis by supporting the proliferation of myeloid, erythroid, and megakaryocyte progenitor cells.[161] Recombinant IL-11 has been approved for treatment of thrombocytopenia—a major, dose-limiting, hematologic complication of chemotherapy for cancer.[162]

IL-14

IL-14 was first described as a high-molecular-weight, B-cell growth factor.[163] Two transcripts are produced from opposite strands of the *IL-14* gene, termed IL-14α and IL-14β.[164] IL-14 is produced by T cells and B-lineage and T-lineage lymphoma cell lines.[163,165] IL-14 binds and signals through a 90-kd receptor expressed on activated B cells[166] to promote B-cell proliferation. This receptor is expressed on especially germinal-center B cells and surface IgD[low] human tonsil B cells, including B1 cells and activated B2 cells.[163,167] Phenotypes of transgenic mice that overexpress IL-14α resemble features of SLE or Sjögren syndrome; older transgenic mice develop B-cell malignancies (CD5^{+} B-cell lymphoma) similar to these observed in patients with these disorders,[164] and the mice have hypergammaglobulinemia with IgG, IgA, and IgM autoantibodies.

IL-32

IL-32 was originally described as an mRNA that was called *NK cell transcript 4,* which encoded a protein with many characteristics of a cytokine.[168] The main sources of IL-32 are activated T cells and NK cells; epithelial cells express IL-32 on stimulation with TNF-α, IFN-γ, IL-1β, and IL-18.[169] Proteinase 3 cleaves IL-32α, resulting in the formation of 2 peptides that upregulate production of proinflammatory cytokines by mouse and human monocytes.[169] IL-32 is highly expressed in synovial tissue samples from patients with RA, and expression levels are associated with disease severity.[169] IL-32 also regulates keratinocyte apoptosis and contributes to eczema formation in atopic dermatitis.[170] Although IL-32 is not expressed by rodents, transgenic overexpression of IL-32 by endothelial and hematopoetic cells in mice intensified vascular inflammation and exacerbated sepsis.[171]

IL-34

IL-34 (also known as uncharacterized protein C16orf77) is secreted as a homodimer of 39-kd monomers. IL-34 is expressed in various tissues, including the heart, brain, liver, kidney, spleen, thymus, testes, ovary, small intestine, prostate, and colon, and is most abundant in the spleen.[172] The receptor for IL-34 is colony-stimulating factor (CSF)–1R. IL-34 stimulates monocyte proliferation. In human monocytes, IL-34, like CSF-1 (the other ligand for CSF-1R), stimulated phosphorylation of extracellular signal-regulated kinases 1 and 2. IL-34 also promoted development of colony-forming unit macrophage, a macrophage progenitor, in human bone marrow cultures.

IFN-γ

Cells from the innate (eg, NK cells, NKT cells, macrophages, myelomonocytic cells) and adaptive immune systems (eg, T_H1 cells, cytotoxic T lymphocytes, and B cells) produce IFN-γ.

A single IFN-γ molecule interacts with 2 ligand-binding IFNGR1 (or IFNGR α) chains and 2 signal-transducing IFNGR2 (or IFNGR β) chains. Each chain is a member of the class II cytokine receptor family.[173,174] High levels of IFN-γ are expressed by T_H1 cells, activating macrophages to kill microbes, promoting cytotoxic activities of other cells, and inducing apoptosis of epithelial cells in the skin and mucosa (Fig 2).[175,176] In addition to its role in the development of a T_H1 response and the B-cell isotype switching to IgG_{2a}, IFN-γ regulates MHC class I and II protein expression and antigen presentation. IFN-γ also inhibits cell growth and apoptosis yet controls the extension of the immune response by inducing activation-induced cell death of $CD4^+$ T cells.[9]

FUTURE DIRECTIONS

Several hundred secreted proteins regulate communication among immune system cells and between the immune system and cells of other tissues. Many new cytokines are likely to be categorized as ILs because of recent discoveries. The growing list of ILs requires a better classification strategy and improved understanding of their functions. Categorization according to sequence homogeneity, structure, and common receptor chains is useful, but most ILs do not fit into any particular structural category. It might be better to group them on the basis of functions of T-cell subsets that produce them. Bioinformatics data and information about their roles in the evolution of the immune system, as well as their nonimmune functions in mammals, should be taken into consideration before a secreted protein and transcellular communicator is designated as an IL. It is apparent that we are still in the initial stages of characterizing the functions of many novel ILs.

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FROM IL-1 TO IL-12

IL-1

Discovery and structure

IL-1 was first described as a protein inducing fever and was called *human leukocytic pyrogen*.[E1] After cloning of IL-1β cDNA, it was demonstrated that recombinant IL-1β produced fever in human beings.[E2] In the same year, 2 cDNAs for IL-1 were reported, and its cloning resulted in the expression of 2 related proteins, termed IL-1α and IL-1β.[E3] Now, 25 years later, 11 members of the IL-1 family exist. In this review, we concentrate on IL-1α and IL-1β and the IL-1Ra.

Genes for IL-1α, IL-1β, and IL-1Ra are closely associated in the region of 2q12-q21 of human chromosome 2. Human IL-1α and β share low sequence homology and are synthesized as 31 kd, variably glycosylated pro-cytokines that share 25% amino acid identity across their entire precursor structure and 22% amino acid identity over their mature segments.[E4] The mature forms of these 2 cytokines have a single β-trefoil domain that is shared with fibroblast growth factors.[E5]

Receptor and signaling

IL-1R belongs to the Toll–IL-1—receptor (TIR) superfamily, which is defined by an intracellular TIR domain that initiates the signaling cascade. TIR receptors can be divided into 2 subgroups regarding the extracellular domains. One group contains a leucine-rich repeat motif, and the other group is characterized by an immunoglobulin-like domain. TLRs belong to the group with the leucine-rich repeat motif, whereas the immunoglobulin domain subgroup includes the IL-1Rs. IL-1α and IL-1β exert their similar effects by binding to IL-1RI. They can also bind to IL-1RII, which is in contrast, acting as a decoy receptor and not involved in signal transduction.[E6] Two distinct IL-1R binding proteins plus a nonbinding signaling accessory protein have been identified.[E7,E8] Both IL-1Rs contain a ligand-binding domain, which is composed of 3 immunoglobulin-like domains. Moreover, each receptor has an N-terminal signal peptide and a single membrane-spanning region. The main difference between IL-1RI and IL-1RII is in the intracellular domain, which is extremely short (29 amino acids) compared with IL-1RI (213 amino acids). Thus, the IL-1RII is unable to complex with IL-1 accessory protein (IL-1R-AcP), which is necessary for signal transduction. The functional role of IL-1RII is to avoid the interaction between IL-1 and IL-1RI by binding IL-1. Therefore, IL-1RII is acting as a natural inhibitor of IL-1 activity, a function complementary to that of IL-1Ra, which is an endogenous inhibitor of IL-1α and β and binds competitively to the IL-1 receptor without activating it. The extracellular domain of IL-1RI consisting of 319 amino acids is responsible for ligand binding and interacts with similar affinity either with agonist proteins IL-1α and IL-1β or with the antagonist protein IL-1Ra.

In addition, pro–IL-1α binds with high affinity to IL-1RI, but there is no binding of pro–IL-1β. After binding of ligands to the IL-1R1 membrane receptor, the approximation of IL-1R1 and IL-1AcP is necessary for initiation of signaling, which involves recruitment of adaptor molecules such as MyD88 and activation of IL-1R–associated kinases (IRAKs), leading to activation of NF-κB and mitogen-activated protein kinase (MAPK)–regulated transcription factors such as c-jun n-terminal kinase (JNK) and p38.[E9]

Cellular sources and targets

IL-1 is expressed by many cells including macrophages, monocytes, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts, and synovial lining cells. IL-1RI is expressed on all cells responding to IL-1α and β, predominantly on T cells, fibroblasts, epithelial cells, and endothelial cells, and is often coexpressed with IL-1RII receptor. The translation of the precursors pro–IL-1α and pro–IL-1β starts after cell activation—for example, by stimulation of membrane-bound TLR by TLR agonists such as endotoxins or LPS. Although both proteins, IL-1α and β, are synthesized as leaderless secretory 31-kd precursors, there are fundamental differences in relation to localization, maturation, and secretion. Pro–IL-1α is already fully biologically active, in contrast with pro–IL-1β, which has no biological activity until it is processed by caspase-1.[E10] Calpain processes pro–IL-1α to mature IL-1α, which remains intracellular or is membrane-associated for the most part and is usually not secreted. Only a small part of pro–IL-1α is cleaved by calpain into the mature 17-kd IL-1α form and the 16-kd N-terminal cleavage product.[E11] IL-1α is only rarely found in the extracellular biological liquids or in the circulation.[E12] For the generation of the 17-kd mature form of IL-1β, a proteolytic step is necessary. For this intracellular processing step of IL-1β, the IL-1β–converting enzyme, also known as caspase-1, is needed. Although there are 11 caspases in human beings, the pro–IL-1β processing is mainly mediated by caspase-1, which is part of complex of intracellular proteins called inflammasome.[E13] In resting cells, pro–caspase-1 is bound to an inhibitor molecule, which prevents its activation. During initiation of IL-1β synthesis, caspase-1 is activated, which leads to processing of IL-1β precursor into a mature form ready for secretion. Caspase-8 also induces the processing of mature IL-1β in response to TLR3 and TLR4 stimulation.[E14] Mature IL-1β remains dispersed in the cytosol until a second stimulus drives processing and release of the active form. It was shown that agents that reduce intracellular levels of potassium like ATP induce IL-1β secretion. Secretory lysosomes start releasing the processed IL-1β on activation of the nucleotide P2X7 receptor, which is one of the ATP receptors and triggers the efflux of potassium ions out of the cell.[E15] Because of ion effluxes, the electrical potential of the membrane is transiently changed, which enables IL-1β secretion.

Role in immune regulation and cellular targets

IL-1 plays an important role of the innate immune system, which regulates functions of the adaptive immune system. IL-1α and β are both potent proinflammatory proteins and have diverse potentiating effects on proliferation, differentiation, and function of various nonadaptive as well as specific immunocompetent cells.[E16] Twenty years ago, it was reported that human IL-1 is one of the mediators responsible for the acute-phase protein response of the liver in inflammation.[E17] Intravenously administered recombinant IL-1 is acting as an endogenous pyrogen and induces a rise in body temperature in rabbits.[E18] The balance between IL-1 and IL-1Ra in local tissues influences the possible development of inflammatory diseases. In the presence of excess amounts of IL-1, inflammatory and autoimmune diseases may develop in many organs such as joints, lungs, central nervous system, gastrointestinal tract, or blood vessels.

IL-1β promotes the differentiation of human naive CD4+ T cells into T_H17 cells.[E19] In this context, it is described that

T$_H$17-cell differentiation is regulated via differential expression of IL-1RI, which is controlled by IL-7 and IL-15.[E20] The importance of IL-1β for the induction of IL-17 was also demonstrated on T cells, which produce IL-17 after stimulation with IL-1β in combination with IL-23.[E21] IL-17 is shown to play a key role in many autoimmune disorders, such as RA, MS, SLE, and IBD, as well as in allergy and asthma.[E22]

IL-1 also acts as a major inflammatory mediator. It has been implicated as a regulator of bone marrow hematopoietic stem cells and progenitor cells.[E23] It was shown that IL-1RI–deficient mouse embryos show an increased myeloid differentiation, suggesting that IL-1 is an important homeostatic regulator at the earliest time of hematopoietic stem cells.[E24]

IL-1β induces synthesis of chemokines, including IL-8, which is a potent neutrophil chemoattractant.[E25] Neutrophils can enhance the inflammation by inducing proinflammatory cytokines and release of neutrophil granule enzymes, which are involved in tissue damage.[E26]

Role in host defense or other immune-regulatory conditions

IL-1α and β, produced by activated macrophages and monocytes, are one of the key players in the innate immune response. They play an important role in coordination of local and systemic inflammation by causing inflammation and inducing the expression of other proinflammatory genes like COX type II, inducible nitric oxide synthase, and other cytokines or chemokines. Moreover, IL-1β activates local endothelium to induce vasodilation, which results in an increase of the permeability of blood vessels. Consequently, serum proteins and leukocytes can be recruited to the site of infection. In addition, IL-1β activates hepatocytes to produce acute-phase proteins, which are important to activate and opsonize pathogens for phagocytosis by macrophages and neutrophils. IL-1β is also a key inducer of antimicrobial proteins, for example β- defensin, which plays a role in mucosal defense in the lungs during first pathogen contact.[E27]

IL-1β plays a major role in a wide range of autoimmune and inflammatory diseases by initiating and potentiating inflammatory responses. IL-1 is implicated in RA, which is a chronic inflammatory disease characterized by inflammation, progressive joint destruction, and systemic manifestations. In this context, IL-1 was first described as a factor released from activated chondrocytes leading to proteoglycan degradation.[E28] Later, IL-1 could be measured in the local inflammatory environment and was correlated with RA disease activity.[E29] In experimental animal models of arthritis, injection of neutralizing antibodies to IL-1 suppressed cartilage proteoglycan synthesis and reversed synovial inflammation in mice, in contrast with injection of recombinant IL-1 into mouse knees, which stimulated proteoglycan synthesis and leukocyte infiltration.[E30,E31] However, IL-1α is also implicated in the pathogenesis of arthritis. IL-1α transgenic mice developed a severe polyarthritic phenotype characterized by accumulation of macrophages, hyperplasia of the synovial lining layer, and destruction of cartilage.[E32] Because of the wide range of experimental data supporting the role of IL-1 in RA, clinical trials with agents blocking IL-1 have been carried out (see section "IL-1Ra").

IL-1 is also important in the pathogenesis of the IBD, which covers a group of disorders in which the intestines become inflamed probably as a result of an autoimmune disorder. IBD is divided into 2 major disorders: ulcerative colitis and Crohn disease. In mucosal biopsies, higher IL-1 mRNA levels were present in active colitis samples than in samples with inactive colitis and noninflammatory controls.[E33] The correlation between tissue levels of IL-1 with the degree of mucosal inflammation suggests that IL-1 is one of the critical mediators of intestinal inflammation in IBD. In experimental animal models, blocking IL-1 in immune complex–induced colitis in rabbits markedly reduced inflammatory cell infiltration and necrosis in the colon, whereas neutralization of IL-1Ra led to prolonged intestinal inflammation and increased the mortality.[E34]

Inflammation plays an important role in the development and progression of atherosclerosis where the chronic inflammation mediated by IL-1 has a recognized role. It could be demonstrated that IL-1 knockout (KO) or IL-1Ra KO mice developed less atherosclerosis.[E35] In human beings, an association between IL-1Ra gene polymorphisms and the severity of coronary disease has also been identified.[E36] IL-1 also has important functions in many other diseases including osteoarthritis, chronic obstructive pulmonary disease, MS, and Alzheimer disease.

Role in allergic diseases

Although IL-1 has major functions in a wide range of autoimmune diseases, it is also implicated in the inflammatory process of allergic diseases. It is well known that patients with atopic dermatitis have defects in innate immune responses and therefore are predisposed for skin infections with *Staphylococcus aureus* resulting in disease aggravation. IL-1 pathways are implicated in the host response to *S aureus*. It has been shown that patients with atopic dermatitis have an increased ratio of IL-1R antagonist to IL-1α in the stratum corneum, which would have an inhibitory effect on IL-1–mediated actions.[E37] The importance of IL-1 for the *S aureus* defense is also demonstrated by a cutaneous infection model in IL-1R–deficient mice showing larger skin lesions, higher bacterial counts, and lower neutrophil numbers.[E38] IL-1β is required for the differentiations of T$_H$17 cells,[E39] which are increased in airways of patients with asthma.[E40] In addition, IL-1β induces airway neutrophilia and increases airways responsiveness selectively to bradykinin in the rat.[E41]

IL-1 in mice and human mutations

Mice deficient in IL-1α or IL-1β or doubly deficient in IL-1α and IL-1β show no different phenotype compared with the same strain of wild-type mice, indicating that IL-1 is not essential for normal embryonic development and postnatal growth. In contrast, when local or systemic inflammation is induced, IL-1 deficiency leads to reduced inflammatory response and increased susceptibility to infections, whereas IL-1β plays a greater role in inflammation than IL-1α. Fever development on injection with turpentine was suppressed in IL-1β as well as IL-1β–deficient mice, but not in IL-1β–deficient mice, indicating that IL-1β but not IL-1α is crucial in febrile responses.[E42]

IL-1Ra
Discovery, structure, receptor, and signaling

Another member of the IL-1 super family is the IL-1Ra, which was discovered in 1984. IL-1Ra is also synthesized and released in response to the same stimuli that drive IL-1 release. However, IL-1Ra lacks the IL-1R-AcP interacting domain. Thus, its binding to IL-1RI results in inhibition of the IL-1 signaling cascade. Consequently, IL-1Ra acts as a physiological inhibitor of IL-1 by silencing IL-1–dependent cell activation. IL-1Ra can also bind to IL-1RII,

suggesting that the inhibitory activity of IL-1Ra depends on the balance between IL-1RI and IL-1RII.[E43] There are at least 4 isoforms of IL-1Ra, of which 3 isoforms are intracellular located and 1 has a signal peptide and is generally secreted without requiring maturation in the endoplasmic reticulum-Golgi exocytic pathway. The intracellular isoforms could be detected in monocytes, fibroblasts, endothelial cells, keratinocytes, and other epithelial cells, whereas the originally described isoform of IL-1Ra is secreted from monocytes, macrophages, neutrophils, and other cells.[E44]

Role in immune regulation and cellular targets

IL-1Ra neutralizes the effects of IL-1. Complete inhibition of IL-1 requires 10-fold to 100-fold molar excess of IL-1Ra over IL-1. As a drug for therapeutic applications, a nonglycosylated recombinant form of human IL-1Ra called anakinra is available that competitively inhibits IL-1 by binding to IL-1RI. Anakinra binds IL-1 receptors with an affinity nearly equal to that of IL-1 and operates in the same manner as the endogenous IL-1Ra.[E45] In vitro, it has been demonstrated that anakinra antagonizes IL-1–induced prostaglandin E2 secretion, production of metalloproteinases, and proteoglycan degradation.[E46] In addition, IL-1–induced stimulation of hyaluronic acid was inhibited by anakinra in a dose-dependent manner in human synovial cells, and anakinra reversed the decrease in proteoglycan synthesis induced by IL-1.[E47] Intravenous injection of IL-1Ra into rabbits given an intra-articular injection of recombinant IL-1β inhibits leukocyte infiltration into the synovial lining and joint cavity and also blocks the ability of IL-1 to cause loss of proteoglycan from articular cartilage.[E48]

Role in host defense or other immune-regulatory conditions

The fact that IL-1Ra gene deficiency causes autoimmunity and joint-specific inflammation suggests that the balance between IL-1 and IL-1Ra is important in maintaining the normal physiology of the joints and homeostasis of the immune system.[E49] Polymorphisms of the IL-1Ra gene, which can lead to changes in the IL-1Ra and IL-1 balance, is associated with susceptibility and progress of a variety of diseases, such as ulcerative colitis, lupus erythematosus, osteoporosis, and viral infections.[E50]

Anakinra is administrated as a once-daily subcutaneous injection and is well tolerated by the patients. Studies demonstrate its efficacy as monotherapy for treatment of patients with RA.[E51] Ten years ago, results of the first clinical study in human beings evaluating the efficacy and safety of IL-1Ra antagonist in patients with RA showed a beneficial effect on the rate of joint erosion after treatment with anakinra (150 mg/d).[E51] In addition, anakinra treatment has been reported to be effective in some patients with systemic-onset juvenile idiopathic arthritis or adult-onset Still disease. Lequerre et al[E52] showed that therapy with anakinra was effective in most patients with adult-onset Still disease, but less than 50% of patients with systemic-onset juvenile idiopathic arthritis achieved a marked improvement.[E52]

Because of the strong connection between IL-1 and cardiovascular diseases, the anti–IL-1 therapy with anakinra was also applied to patients with cardiovascular disease. Recently, it was shown that IL-1 inhibition by administration of anakinra improves vascular and left ventricular function in patients with RA and is associated with reduction of nitro-oxidative stress and endothelin.[E53] An animal study with mice demonstrated that administration of anakinra within 24 hours of acute myocardial infarction significantly ameliorates the remodeling process by inhibiting cardiomyocyte apoptosis.[E54] These results may suggest that anakinra could be useful to prevent postischemic cardiac remodeling and heart failure.

Depletion of granulocytes and monocytes by selective apheresis is one treatment opportunity of ulcerative colitis. The mechanism of clinical efficacy associated with this therapy could be explained by the release of IL-1Ra and the increase of IL-1Ra in the Adacolumn (Otsuka Pharmaceuticals, Middlesex, UK) outflow during therapy.[E55] Moreover, it is well accepted that patients with IBD have a decreased ratio of IL-1Ra/IL-1β in their colonic mucosal tissue.[E56] In animal models, it has been suggested that exogenous administration of IL-1Ra has a therapeutic benefit in experimental colitis. Regarding the beneficial effects of anakinra in patients with RA, further investigations of this mode of therapy in IBD are warranted.

IL-1Ra in allergic diseases

Although IL-1Ra has its main functions in autoinflammatory diseases, there is some evidence that IL-1Ra could be involved in the pathogenesis of atopic dermatitis and asthma. As described, IL-1β is detected in the airways and contributes to the changes in the airways. Therefore, inhibition of IL-1β by IL-1Ra can reduce local inflammation and airway hyperresponsiveness. In this context, it was demonstrated that variants in the IL-1Ra gene are associated with asthma and contribute to the pathology of asthma.[E57] After treatment of antigen-sensitized guinea pigs with IL-1Ra, the bronchial hyperreactivity and the leukocyte influx into the BAL decreased.[E58]

IL-1Ra in mice models

Mice deficient in IL-1Ra have low litter numbers and exhibit growth retardation in adult life.[E59] Moreover, IL-1Ra KO mice spontaneously developed inflammation in constitutively stressed artery walls, suggesting that IL-1Ra is required to prevent the development of lethal arteritis.[E60] Furthermore, another study shows that IL-1Ra KO mice spontaneously developed chronic inflammatory polyarthropathy. The developed disease was similar to human RA, and in the joints, proinflammatory cytokines such as IL-1β, IL-6, and TNF-α were overexpressed.[E49]

IL-2
Discovery and structure

Morgan et al[E61] and Gillis and Smith[E62] demonstrated 30 years ago that cultured media of activated T cells contain mediators that induce the proliferation of antigen-activated T cells. In 1965, Kasakura and Lowenstein[E63] and Gordon and MacLean[E64] found a soluble mitogenic factor for lymphocytes in the culture media of mixed leukocytes. In the ensuing years, it had become clear that a single protein was responsible for this effect, and this T-cell growth factor has been called IL-2.

IL-2 is a monomer of 15.5 kd and consists of 133 amino acids. It is a member of the 4 α-helix bundle cytokine family. These family members (IL-2, IFN, and IL-10 subfamilies) are characterized by antiparallel juxtaposed helices A, C, B, D, and 2 long end-to-end loops, loops AB and CD, which are connected by a short β-sheet packed against helices B and D.[E65]

Receptor and signaling

The IL-2R consists of 3 subunits, the ligand-specific α-chain IL-2Rα (CD25, originally called Tac for T activation); the

β-chain IL-2Rβ (CD122), which is also part of the IL-15 receptor complex; and the common γc (CD132), which is shared by IL-4, IL-7, IL-9, IL-15, and IL-21. IL-2Rα consists of 2 sushi domains (see also IL-15Rα).[E66] IL-2Rα and IL-2Rβ are important for cytokine binding, whereas IL-2Rβ and γc are involved in signal transduction. All 3 subunits are required for the formation of the high-affinity IL-2R (kd $\sim 10^{-11}$ M/L). The IL-2Rβ/γc complex is expressed at low levels on resting T cells (and on NK cells). Binding of IL-2 to this complex (kd $\sim 10^{-9}$ M/L) induces cell growth. On T-cell activation, IL-2Rα is rapidly induced, thereby building the high-affinity quaternary complex, reducing the concentration of IL-2 needed for growth stimulation. IL-2Rα is found on subsets of developing pre-T and pre-B cells, but because these cells lack γc, they do not respond to IL-2. Also, the development of T and B cells in young IL-2Rα–deficient mice is normal before their accompanying severe autoimmunity disrupts lymphocyte development. In addition, IL-2Rα is prominently found on natural CD4+FOXP3+ Treg cells, the commonly known CD4+CD25+ Treg cells.[E67,E68]

Binding to IL-2Rα alone with low affinity (kd $\sim 10^{-8}$ M) does not lead to a detectable biologic response, but promotes association with IL-2Rβ and γ-chains. The quaternary complex (IL-2, IL-2Rα, IL-2Rβ, γc) induces IL-2 signaling that results in the activation of multiple signal transduction pathways, including the Janus kinase (Jak)/signal transducer and activator of transcription (STAT), Ras/MAPK, and phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathways. Chronic T-cell stimulation leads to a shedding of IL-2Rα, which is a marker for strong antigenic stimulation.

Although individual IL-2R subunits are widely distributed on many different cell types, only 2 major cell subsets readily coexpress all 3 subunits, which are required for the high affinity IL-2R, namely CD4+FOXP3+ Treg cells and activated conventional CD4+ and CD8+ T cells. Thus, Treg cells and antigen-activated T cells represent the main population of cells poised to respond to IL-2 *in vivo*.

Cellular sources and targets

IL-2 is mainly produced by CD4+ and CD8+ T cells after activation by antigens/T-cell receptor (TCR) and costimulation. IL-2 production is transient; a peak secretion occurs after 8 to 12 hours after stimulation. To a lesser extent, activated DCs and NK and NKT cells produce IL-2; however, the biological relevance of this is not known yet. Target cells of IL-2 include CD4+CD8+ T cells, NK cells, and B cells.

Role in immune regulation and cellular networks

IL- 2 is a central player for T-cell–dependent immune responses. Activation of T cells through TCR and costimulatory molecules such as CD28 induces production of IL-2 and expression of IL-2R. The binding of IL-2 to its receptor subsequently drives extensive clonal expansion and effector T-cell and B-cell development.

Role in host defense or other immune-regulatory conditions

IL-2 is an essential growth factor for T cells; however, repeated activation of CD4+ T cells with IL-2 makes these cells sensitive to Fas-induced apoptosis (activation-induced cell death [AICD]) and contributes thereby to the termination of a persistent immune response. IL-2 is also essential for the development of Treg cells, which provides another mechanism to abate the immune response.[E69] IL-2 promotes also the proliferation and differentiation of NK cells and enhances their cytolytic functions. Because NK cells express only the IL-2Rβ/γc complex (they do not express IL-2Rα), high amounts of IL-2 are necessary for their stimulation. Furthermore, IL-2 acts on B cells as a growth factor and as a stimulus for antibody synthesis.

Functions as demonstrated in IL-2–deleted mice, receptor-deficient mice, human mutations, and clinical use

IL-2–deficient mice are normal with regard to thymocyte and peripheral T-cell subset composition, but a dysregulation of the immune system is manifested by reduced polyclonal *in vitro* T-cell responses and by dramatic changes in the isotype levels of serum immunoglobulins.[E70] Nevertheless, the IL-2 deficiency model evaluating the costimulatory signals in T-cell induction showed that secondary antiviral T-cell responses were absent unless IL-2 was given *in vivo*. Primary and secondary cytotoxic T-cell responses against vaccinia and lymphocytic choriomeningitis virus were within normal ranges, B-cell reactivity to vesicular stomatitis virus was not impaired, T_H-cell responses were delayed, but biologically functional and NK-cell activity was markedly reduced.[E71]

IL-2R–α-chain—deficient mice have demonstrated that this receptor chain is essential for the regulation of both the size and content of the peripheral lymphoid compartment. Young mice that lack IL-2Rα had phenotypically normal development of T and B cells, but adults developed massive enlargement of peripheral lymphoid organs associated with polyclonal T-cell and B-cell expansion.[E72] Older IL-2Rα–deficient mice also develop autoimmune disorders, including hemolytic anemia and IBD, which was shown in IL-2–deficient mice.[E73,E74]

It was quite surprising that the resulting phenotype of mice deficient in IL-2 or in the α-chain or β-chain of its receptor was not immunodeficiency, as predicted, but rather a very serious lymphoproliferative and autoimmune disorder.[E70,E75,E76]

The unexpected observation that deficiency of IL-2 or of the α-chain or β-chain of IL-2R results not in immunodeficiency but in autoimmune disease can be explained by failure of AICD in T cells and by a defect in CD4+CD25+ FOXP3+ Treg-cell production.[E77] Even though IL-2 and IL-15 share 2 of 3 receptor units (IL-2Rβ and γc), IL-15–deficient and IL-15Rα–deficient mice have no autoimmune deficiency and contain a normal number of FOXP3+ Treg cells, which indicates that IL-2 is the critical cytokine for Treg cells.

Thymus-restricted transgenic expression of IL-2Rβ can restore functional CD4+CD25+ Treg cells, suggesting that IL-2 signaling in the thymus is critical for the development of Treg cells.[E78]

In an IL-2Rα–deficient patient, an immunodeficiency has been described that was characterized by a decreased number of peripheral T cells, abnormal proliferation but normal B-cell development, and extensive lymphocytic infiltration is accompanied by tissue atrophy and inflammation. Although mature T cells were present, the absence of CD25 affected the differentiation of thymocytes.[E79]

Human beings with a mutation in the common γc (as mentioned, this includes defect signaling of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) have X-linked severe combined immunodeficiency

(XSCID) 1, a disease characterized by the absence of T and NK cells and the presence of nonfunctional B cells.

Because IL-2Rα is continuously expressed by malignant T cells of patients with leukemia, autoimmunity, and organ transplant rejections, but not expressed by any resting T and B cells except Treg cells, it is an interesting target for therapeutic interventions.[E80]

Antagonistic IL-2Rα mAbs (anti-Tac/daclizumab, basiliximab) are effective in preventing rejections of organ transplants. The administration of these antibodies blocks the interaction of IL-2 with IL-2R and leads to cytokine deprivation and death in IL-2–dependent cells. In addition, administration of daclizumab alone has been shown to be useful for the treatment of T-cell–mediated autoimmune diseases associated with abnormalities of the IL-2/IL-2R system. In particular, daclizumab provided an effective therapy for patients with noninfectious uveitis.[E81] IL-2 itself (proleukin) is therapeutically used as an immune adjuvant in certain types of lymphoproliferative diseases and cancers, but severe dose-limiting toxicity has limited its effectiveness in the clinic (activation of the IL-2Rβ/γc complex on NK cells).

IL-3
Discovery and structure

Human IL-3 was first identified by screening a human cDNA library using gibbon IL-3 cDNA as a hybridization probe.[E82] The human IL-3 gene is encoded on the long arm of chromosome 5 in proximity to the IL-5 and GM-CSF gene, indicating a common ancestral relationship. IL-3 is a monomeric, N-glycosylated protein, consisting of 152 amino acids with a molecular weight of 15.1 kd. The crystal structure of IL-3 reveals 4 α-helices in an up-up-down-down antiparallel conformation with long overhand loops between each of the helices.[E83] This 4 α-helical bundle motif is highly similar to the structure of GM-CSF and to the IL-5 homodimer.

Receptor and signaling

Beside the functional structure, IL-3, IL-5, and GM-CSF also share the common receptor subunit β-chain (CD131), resulting in partially overlapping functions of these hematopoietic cytokines. The β-chain forms a heterodimer together with the cytokine-specific Rα on cytokine binding.[E84] IL-3Rα (CD123)[E85] exists as a transmembrane molecule. It binds the antiparallel first and third loop of IL-3 and initiates the signaling via its cytoplasmic domain. The β-chain interacts with a distinct domain of IL-3, which is centered around a conserved glutamate residue, and completes the signal transductions via its long cytoplasmic tail. Although the β-chain displays a potential N-glycosylation site at asparagine 328, recently N-glycans were shown not to be relevant for ligand binding and receptor activation.[E86]

On binding of IL-3 to its heterodimeric receptor, 3 principal signaling pathways are activated: the Jak/STAT pathway, the MAPK pathway, and the PI3K pathway.

The first event in the Jak/STAT pathway is the phosphorylation of the receptor-associated kinases Jak2 and Jak1. Activated Jak2 and Jak1 in turn phosphorylate the β-chain on 6 critical tyrosine residues that serve as binding sites for STAT1 and STAT5. The STAT family members bind to the receptor complex via their SH2 domains, become tyrosine-phosphorylated, and dimerize. STAT1 and STAT5 homodimers are able to translocate to the nucleus and bind to specific enhancer sequences in the promoter region of activated genes.

The MAPK pathway leads to the sequential activation of Ras, Raf-1, and MEK, resulting in ERK, JNK, and p38 signaling cascades. ERK eventually activates c-Fos and c-Jun, which form the heterodimeric transcription factor AP-1. Besides the induction of proliferation, the activation of the MAPK pathway inhibits apoptosis of target cells. The expression of antiapoptotic factors such as Pim1, cIAP2, Mcl-1, and Bcl-XL becomes upregulated in response to IL-3,[E87] whereas the activity of the proapoptotic factor BAD is inhibited.

The PI3K pathway is initiated by protein kinase A, which phosphorylates the β-chain, resulting in the recruitment and activation of PI3K. PI3K regulates multiple cellular processes such as proliferation, growth and cell size, rearrangement of the cytoskeleton, and apoptosis via the second messenger phosphatidylinositol 3,4,5-triphosphate.

Several negative feedback mechanisms have been described that downregulate the IL-3 signaling. Cytosolic tyrosine phosphatases such as SHP1 control the level of ligand-induced phosphorylated proteins. Members of the suppressor of cytokine signaling (SOCS) family are able to inactivate Jaks, block the binding of STATs to the IL-3R, or induce the ubiquitination and the subsequent proteosomal degradation of signaling molecules. Moreover, protein inhibitor of activated STAT 1 binds activated STAT1 and inhibits its binding to the DNA. Finally, endocytosis and degradation of the IL-3R terminates cytokine signaling. Degradation of the cytoplasmic domain of β-chain results in a truncated IL-3R complex that lacks all intracellular phosphorylation sites needed for signal transduction. Because IL-3, IL-5, and GM-CSF all signal via β-chain, this downregulation process prevents the cell from being further activated by other β-chain–engaging cytokines.

Cellular sources and targets

IL-3 is expressed by T cells, macrophages, stromal cells, NK cells, mast cells, and eosinophils, and its transcription is regulated by 2 nuclear factor of activated T cells-dependent enhancers that have distinct tissue-specific activity.[E88] Whereas the first enhancer, located 14 kb upstream of the IL-3 gene, functions only in a subset of T cells, the second element is induced in both T cells and mast cells.

IL-3Rα is expressed on bone marrow stem cells, megakaryocytes, monocytes, and granulocytes. Although the IL-3Rα transcript expression is low in unstimulated blood eosinophils, its expression is significantly increased after stimulation with IL-3, IL-5, or GM-CSF.[E89]

Role in immune regulation and cellular networks

IL-3 is a multilineage hematopoietic growth factor, acting on early stages of hematopoiesis rather than on late differentiation and maturation processes. In synergy with other cytokines, IL-3 plays an important role in the differentiation and growth of various cell lineages.

In combination with erythropoietin, IL-3 induces erythroid lineages, whereas it synergizes with GM-CSF or G-CSF to induce the granulocyte-macrophage lineage. This effect was recently shown to be inhibited by the presence of CD4$^+$CD25$^+$FOXP3$^+$ Treg cells. IL-3 together with TNF-α leads to short-term proliferation of CD34$^+$ progenitor cells and the differentiation of DCs and Langerhans cells. Moreover, it supports the effect of stem cell factor on the proliferation of mast cell precursors and enhances the

IL-2–induced proliferation and differentiation of B cells. Besides its function as a hematopoietic growth factor, IL-3 is responsible for the activation and the survival of different mature cell types, including basophils.

The effects of IL-3 are not limited to hematopoietic cells, because IL-3 plays a potential role in the pathogenesis of inflammatory diseases and neurodegeneration in the central nervous system. Microglial cells secrete and respond to IL-3. The expression of β-chain in the brain is restricted to microglial cells, suggesting that IL-3 acts in an autocrine manner. IL-3 stimulation of microglia *in vitro* leads to their proliferation and the generation of multinucleated giant cells. Moreover, IL-3 was detected in postmortem brains of patients with Alzheimer disease, indicating a clinical relevance of the effects observed *in vitro*.[E90]

Role in allergic disease and other pathologic conditions

IL-3 plays a role in allergic diseases by preventing the apoptosis of basophils via PI3K *in vitro* but has little effect on basophil survival *in vivo*.[E91] On stimulation with IL-3, basophils upregulate the activation markers CD69[E92] and CD203c[E93] and show enhanced mediator release in response to FcεR cross-linking. Further IL-3 stimulation of basophils leads to the expression of retinaldehyde dehydrogenase-II, which generates retinoic acid. This vitamin A metabolite regulates diverse functions of immune and resident cells; among other functions, it skews the differentiation of naive T cells toward a T$_H$2 or Treg phenotype. Notably, neither constitutive nor inducible retinaldehyde dehydrogenase-II expression has been detected in any other myeloid, lymphoid, or DC type.[E94] In eosinophils, IL-3 induces the expression of HLA-DR and the costimulatory molecule B7.2 (CD86) on their surface. Therefore, IL-3–treated eosinophils are able to present antigenic peptides and support antigen-specific T-cell proliferation in allergic and parasitic diseases.[E95] Furthermore, the expression of the eosinophilic activation molecule CD48 is enhanced by IL-3 and allergen challenge. Cross-linking of CD48 on the surface of eosinophils triggers the release of granule proteins and thereby promotes the allergic inflammation.[E96] Stimulation of monocytes with IL-3 and GM-CSF leads to increased expression of HLA-DR, CD14, IL-1α, and integrin CD18, which mediate cell adhesion. Interestingly, DCs, which differentiate in the presence of IL-3 and IL-4, show decreased IL-12 production and preferentially induce T$_H$2 responses.[E97] Thus, IL-3 is a potential target in the development of strategies to modify the balance of different T$_H$-cell subsets.

Several malignant tumors are shown to secrete hematopoietic cytokines, and increased concentrations of IL-3 were described in sera of patients with cancer. The IL-3Rα has been detected on several cancer cell lines, and IL-3 stimulation induced the proliferation of hematopoietic and nonhematopoietic cancer cells derived from colorectal adenocarcinomas, bladder, and lung cancers. Although under healthy conditions, B cells do not express IL-3Rα, it is found on the surface of B cells in 40% of patients with B-cell acute lymphocytic leukemia or acute myeloid leukemia. In these patients, the increased expression of IL-3Rα is accompanied by enhanced blast proliferation, increased cellularity, and poor prognosis.[E98] Because IL-3Rα is overexpressed on acute myeloid leukemia blasts compared with normal hematopoietic cells, it might serve as a target for therapy. Cytotoxic diphtheria toxin–IL-3 fusion proteins were shown to kill specifically acute myeloid leukemia cells in mice.[E99]

Functions as demonstrated in IL-3–deficient mice, receptor-deficient mice, and transgenic models

Mice deficient in the IL-3 gene or the IL-3Rα do not show altered basal hematopoiesis, growth, development, or longevity.[E100,E101] However, IL-3 KO mice have reduced numbers of mast cells and basophils and impaired immunity in response to parasites such as *Strongyloides venezuelensis*.[E102] These findings are supported by recent work showing that on infection of mice with the gastrointestinal parasite *N brasiliensis*, activated T cells secrete IL-3, which enhances basophil production.[E91]

Inhibition of IL-3, IL-5, and GM-CSF signaling in β-chain–deficient mice demonstrates an essential role for hematopoietic cytokines in the regulation of T$_H$2 immunity and allergic airway inflammation. In a mouse model of allergic airway inflammation, β-chain–deficient mice showed reduced expansion and accumulation of eosinophils in the lung, inhibition of airway hyperresponsiveness, mucus hypersecretion, and IgE production. T$_H$2 cells in the lung of allergen-challenged animals had diminished ability to proliferate, secrete cytokines, and migrate.[E103] A natural occurring mutation in the IL-3 gene (Ser27Pro) was shown to have protective effects on the development of asthma.[E104]

IL-4
Discovery and structure

IL-4 was discovered in 1982 and originally designated B-cell growth factor I (BCGF-I) or B-cell–stimulating factor (BSF)–I.[E105] It is a monomer of 15 kd and consists of 129 amino acids. It is a member of the 4 α-helix bundle cytokine family. These family members are characterized by antiparallel juxtaposed helices A, C, B, D, and 2 long end-to-end loops, loops AB and CD, which are connected by a short β-sheet packed against helices B and D.[E65,E106]

Receptor and signaling

There are 2 types of IL-4 binding receptors: the type I IL-4R, which predominates in hematopoietic cells and which is responsible for IL-4 signaling in T cells, and the type II IL-4R, which is expressed on both hematopoietic and nonhematopoietic cells but not on T cells.[E107] Both types have the IL-4Rα-chain in common. Type I IL-4R binds IL-4 exclusively and consists of IL-4Rα (CD124) and the common γc (CD132), which is also a receptor for IL-2, IL-7, IL-9, IL-15, and IL-21. Type II IL-4R binds IL-4 and also IL-13 and consists of the IL-4Rα chain and the IL-13Rα1 chain. Binding to these receptor complexes promotes activation of Jaks that are constitutively associated with IL-4Rα (Jak1), the γc (Jak3), and the IL-13Rα1 chain (Tyk2 or Jak2).[E106] Whereas the signals of the type II IL-4R are transduced by STAT3, the signals of the type I IL-4R are transduced by the transcription factor STAT6.

Cellular sources and targets

The main sources for IL-4 are T$_H$2 cells. However, IL-4 is in addition produced by basophils, eosinophils, mast cells, and a specialized subset of T cells that express NK1.1 and appear to be specific for CD-1 (NK T cells). Also, γ/δ T cells produce IL-4, and mice lacking these cells fail to develop IL-4–dependent airway hypersensitivity. The main target cells for IL-4 are T and B cells.

Role in immune regulation and cellular networks

IL-4 plays a central role in the differentiation of antigen-stimulated naive T cells into T$_H$2 cells.[E108,E109] IL-4 has a variety

of other effects in hematopoietic tissues. It increases the expression of class II MHC molecules in B cells, enhances expression of CD23, induces IgE class switch, upregulates the expression of the IL-4R, and, in association with LPS, allows B cells to express Thy 1. It also acts as a co-mitogen for B-cell growth. Although not a growth factor by itself for resting lymphocytes, it can substantially prolong the lives of T and B lymphocytes in culture. IL-4 has also an important role in tissue adhesion and inflammation. It acts with TNF-α to induce expression of vascular cell adhesion molecule-1 (VCAM-1) on vascular endothelial cells, and it downregulates the expression of E-selectin. IL-4 plays a role in *in vitro* differentiation of myeloid DCs in combination with GM-CSF.[E105,E110-E114]

Role in host defense or other immune-regulatory conditions and allergy

IL-4 has a central role in the regulation of allergic conditions. It is the major stimulus for T_H2 development and suppresses T_H1 development. Furthermore, IL-4 is important in the control of immunoglobulin class switching. It determines that human B cells switch to IgE and IgG_4 and mouse B cells to IgE and IgG_1. IL-4 plays a major role in the development of protective immune responses to helminths and other extracellular parasites.[E115]

Functions as demonstrated in IL-4–deleted mice, receptor-deficient mice, human mutations, and clinical use

IL-4 and IL-4Rα KO mice have severely compromised T_H2 differentiation, and even though the T-cell and B-cell development is normal, the serum levels of IgG_1 and IgE are strongly reduced.[E116] The IgG_1 dominance in a T-cell–dependent immune response was lost, and IgE was not detectable on nematode infection.[E116,E117]

In a quadruple IL-4/5/9/13 KO model, complete inhibition of allergic airway inflammation and remodeling has been shown.[E118]

Human beings with a mutation in the common γc (as mentioned, this includes defect signaling of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) have XSCID1, a disease characterized by the absence of T and NK cells but the presence of nonfunctional B cells.

Clinical use. IL-4 inhibits the production of inflammatory cytokines (IL-1, IL-6, TNF-α) and is therefore interesting for the treatment of inflammatory and autoimmune diseases such as allergy/asthma and insulin-dependent diabetes mellitus.[E106,E119] There is also some evidence that IL-4 might be useful in the treatment of certain tumors. IL-4 can have negative or positive effects on the control of tumor growth, depending on the type of effector cell mediating the tumor clearance and the type of tumor cell model analyzed.[E120] Furthermore, IL-4 may play an important role in the pathogenesis of chronic lymphocytic leukemia disease by preventing death and proliferation of the malignant B cells.[E121]

IL-5
Discovery and structure

IL-5 was described for the first time as an eosinophil and B-cell growth factor in 1987. It is a hematopoietic cytokine that is encoded on chromosome 5q23.3-q31.1. Like IL-3 and GM-CSF, it belongs to a group of short chain 4 α-helical bundle proteins that shares the β-receptor chain for signaling.[E122] The structure is characterized by 4 helices with antiparallel conformation. In contrast with IL-3 and GM-CSF, IL-5 consists of a pair of identical 4 α-helical bundles that share the fourth helix of 1 chain.[E123]

Receptor and signaling

IL-5 binds to a heterodimeric receptor that was defined by Tavernier et al[E122] in 1991. It consists of the specific receptor α unit and the β-chain it shares with IL-3 and GM-CSF.[E122] On binding to the α receptor unit, recruitment of the β-chain takes place. IL-5Rα is encoded on chromosome 3 and characterized by an extracellular domain with a proximal Trp-Jer-x-Trp-Ser motif (WSXWS motif) and a homology module containing 2 fibronectin type III domains with paired cysteine residues the distal part of the membrane.[E124] Both motifs are highly conserved. The β-chain R shows a similar structure but is generally larger with a longer extracellular and intracellular tails. The extracellular part of the β-chain unit consists of 2 homology modules containing 2 fibronectin type III domains with paired cysteine residues the distal part of the membrane. The membrane proximal cytoplasmatic proline rich sequence motif is vital, both for IL-5αR signal and ßc signal transduction, whereas the carboxyterminal region of the IL5Rα is involved in IL-5–induced IgH class switch recombination.[E125]

IL-5 signaling takes place via the Jak/STAT,[E126] MAP-K,[E126,E127] and PI3K pathways.[E128] Jak/STAT phosphorylation of Jak1 and Jak2 after heterodimerization of the receptor results in STAT1 and STAT5 activation and is considered to play an important part in IL-5–induced proliferation and differentiation. With regard to the MAPK pathway, actions are induced via ERK and TCF, ultimately increasing cytokine-induced proliferation and preventing apoptosis of eosinophils by upregulation of genes encoding for bcl-2 and bcl-x.[E129,E130] In addition, the JNK pathway has been reported to be affected by IL-5. PI3K-mediated signaling via Akt/PKB has been linked to inhibition of apoptosis via IL-5. Recently, Oct-2 has been shown to facilitate differentiation of B cells to plasma cells by upregulation of the IL-5R.[E131]

Several negative regulators are considered to play an important role: SHP-1 downregulates βc activation, and cytokine inducible negatively influences STAT5. In addition, SOCS1 is considered to be involved in negative feedback via a reduction of Jak1 activity.[E131]

Cellular sources and targets

Major target cells of IL-5 are eosinophils (highest IL-5Rα density) and, to a lesser extent, basophils and mast cells. The cytokine is mainly produced by T_H2 cells, activated eosinophils, and mast cells, but also by Tc2 cells, γδ T cells, NK cells,[E132] NKT cells,[E133] and CD4⁻ckit⁻CD3ε⁻IL-2Rα⁺ in Peyer patches.[E134] In mice, IL-5Rα is constitutively expressed on B1 cells and upregulated on B2 cells on stimulation. IL-5 may increase the likelihood of B2 B cells to differentiate into antigen-producing plasma cells and synergizes with IL-4.

Role in immune regulation and cellular networks

IL-5 secretion is mainly controlled via the transcription factor GATA-3 that also acts as a transcription factor for IL-4 and IL-13. IL-3, GM-CSF and IL-5 synergize for differentiation and function of myeloid cells. In general, IL-5 leads to growth, activation, mobilization, differentiation, and survival of eosinophils.[E129,E130,E135] Moreover, IL-5 displays eosinophil chemotactic activity, increases eosinophil adhesion to endothelial cells, and thereby enhances effector functions of eosinophils. However,

the later effects are less pronounced. Eotoxin-2 seems to be crucial for IL-5–induced IL-13 production and airway hyperresponsiveness (AHR).[E136]

Recently, interaction of eosinophils with fibroblasts has been described, leading to proliferation and matrix production of fibroblasts.[E137] This suggests a role of IL-5 in remodeling and wound healing. Furthermore, there is some evidence that IL-5 links innate and adaptive immunity not only in terms of wound healing but also in terms of IgM-mediated suppression of atherosclerotic plaque formation.[E138]

Role in allergic disease

IL-5 plays a central role in allergic asthma. T_H2 cells, which secrete IL-5, recruit eosinophils and contribute to the induction of airway hyperreactivity. Recruitment of eosinophils in the lung is a key feature of asthma.[E139] IL-5 levels, T_H2 cells, and eosinophils are increased in BAL and in biopsies of patients with asthma. Moreover, IL-5 levels correlate with severity of the disease.[E140] The IL-5Rα is already expressed in $CD34^+$ cells. This particular subset increases on allergen challenge and ultimately increases the number of mature eosinophils in the periphery.[E141]

In experimental models, anti–IL-5 treatment was suggested to be effective. The treatment of asthma with anti–IL-5 antibodies (mepolizumab, reslizumab) reduced blood eosinophilia and sputum eosinophils, but little or no effect on asthma symptoms was observed in the initial clinical trials.[E142-E144] However, recent studies reported significant reductions in exacerbation rates in refractory eosinophilic asthma[E145] and steroid-dependent asthma with sputum eosinophilia.[E146]

Anti–IL-5 treatment also showed some promising effects in a subgroup of patients with hypereosinophilic syndrome. Mainly patients with the lymphocytic variant are considered to profit from anti–IL-5 therapy. In this subtype of hypereosinophilic syndrome, expansion of T-cell subsets with aberrant surface marker expression ($CD3^+CD4^-CD8^-$, $CD3^-CD4^+$) secrete eosinophilopoietic cytokines, including IL-5. A corticosteroid-sparing effect was observed over a period of 36 weeks in patients receiving 750 mg mepolizumab every fourth week.[E147]

Functions as demonstrated in IL-5–deleted mice, receptor-deficient mice

IL-5–deficient mice do not show abnormal development but are resistant to induction of experimental asthma and display difficulties expelling *N brasiliensis*. These mice were almost devoid of eosinophils in the airways and had no blood eosinophilia. Furthermore, there was AHR or eosinophil invasion observed on allergen challenge.[E148] The same effects were observed on treatment with αIL-5 antibodies.[E149] In accordance with these findings, topical overexpression of IL-5 resulted in AHR and increased eosinophil counts in the lung.[E150] Leitch et al[E151] recently reported that IL-5 overexpression leads to prolonged wound healing, most likely because of increased eosinophilic invasion into the wound areas. IL-5Rα$^{-/-}$ mice displayed reduced numbers of B1 cells and consequently low IgM and IgG$_3$ serum concentrations. In addition, *Angylostrongylus cantonesis* survived longer in IL-5Rα$^{-/-}$ mice. As expected, there was no eosinophilia in response to IL-5.

IL-6

Alternative names are IFN-β2 (IFNB2), B-cell differentiation factor, BSF2, hepatocyte stimulatory factor, and hybridoma growth factor.

Discovery and structure

IL-6 was originally discovered as a B-cell differentiation factor[E152] with IFNβ2 activity. Further investigations revealed that IL-6 does not show any IFN activity, but this factor has been demonstrated to be a multifunctional pleiotropic cytokine that regulates immune response, acute-phase response, hematopoiesis, and inflammation. The human gene of IL-6 maps to locus 7p2[E153]; the murine IL-6 is located on chromosome 5.[E154] Human and murine IL-6 contains 5 exons and 4 introns.

IL-6 is a member of the IL-6–type cytokine family, including, among others, leukemia inhibitory factor (LIF), ciliary neurotrophic factor, and oncostatin-M (OSM). IL-6 mRNA spanning a length of 1.3 kb is translated into a 212–amino acid precursor protein. After removal of a 28–amino acid signal peptide, IL-6 with 2 possible N-glycosylation sites (position 73 and 172) is secreted in different molecular masses of 19 to 26 kd.[E155] As a member of the IL-6 cytokines, IL-6 has a helix bundle structure consisting of 4 long α-helices.

Receptors and signaling

IL-6 signals through a cell-surface signaling complex composed of IL-6, IL-6a-receptor, and the signal-inducing component gp130. IL-6R is a member of a cytokine receptor family characterized by 4 conserved cysteine residues in the N-termini and a tryptophan-serine-X-tryptophan-serine motif located above the transmembrane domain. In a first step, IL-6 binds to its low-affinity a-receptor unit, an 80-kd glycoprotein. Two forms of the 80-kd receptor are known: the transmembrane form and a soluble form. When IL-6 binds to the transmembrane form containing a short intracytoplasmic region, the signaling receptor unit gp130 is recruited. IL-6R is also secreted as a soluble form (sIL-6R).[E156] On binding to IL-6, sIL-6R associates with gp130 to trigger several cellular steps termed "IL-6 *trans*-signaling." It has been shown that sIL-6R plays a key role in the regulation of IL-6 responses. Besides IL-6, other cytokines of the IL-6 family such as LIF and ciliary neurotrophic factor use signaling through gp130. This explains why these cytokines share many biological activities, although the factors themselves are not related to each other.

gp130 is expressed ubiquitously in tissues,[E157] whereas the expression of the IL-6a-receptor subunit is limited and predominantly confined to hepatocyte and leukocyte subpopulations. The interaction of IL-6 with its receptor leads to a complex consisting of 2 IL-6 molecules (homodimer), 2 IL-6R proteins, and 2 gp130 signaling units. On dimerization of gp130, intracytoplasmic Jak tyrosine kinases induce tyrosine phosphorylation and the recruitment of STAT3.[E158] The following dimerization and translocation of STAT3 to the nucleus induces gene expression —for example, for acute-phase protein synthesis in hepatocytes. The negative feedback mechanism of this signaling pathway is regulated by the SOCS proteins 1 and 3 and the protein inhibitors of activated STATs.

Cellular sources and targets

IL-6 is produced after stimulation by many different cells: T cells, B cells, granulocytes, smooth muscle cells, eosinophils, chondrocytes, osteoblasts, mast cells, glia cells, and keratinocytes. Endothelial cells, fibroblasts, and monocytes/macrophages triggered by various stimuli during systemic inflammation are the main source of this cytokine. Monocytes/ macrophages are driven

by bacterial LPS, IL-1α, TNF-α, IFN-γ, and GM-CSF to produce IL-6, whose release is inhibited by glucocorticoids. Human fibroblasts secrete IL-6 on stimulation with IL-1α, bacteria/yeast, TNF-α, and IFN-α. The main cellular targets are hepatocytes, leukocytes, T cells, B cells, and hemopoietic cells.

Role in immune regulation and cellular networks

IL-6 is involved in a broad spectrum of biological activities, in humoral as well as in cellular defense, and acts on various target cells. IL-6 directs leukocyte trafficking and activation. Although it has been shown in studies with IL-6–deficient mice that neutrophil accumulation at sites of infection or inflammation is inhibited by IL-6,[E159] neutrophil clearance and the transition from neutrophil to mononuclear cell recruitment is driven by soluble IL-6R and the following IL-6 trans-signaling.[E160] *In vitro* studies demonstrated that IL-6 trans-signaling suppresses the TNF-α or IL-1β–induced control of CXCL1, CXCL8, and CXCL1 and increases chemokine secretion of CXCL5, CXCL6, CCL2, and CCL8.[E160,E161] Besides the recruitment of neutrophils and mononuclear cells, it is evident that IL-6 regulates T-cell infiltration by influencing chemokine secretion (CXCL10, CCL4, CCL5, CCL11, and CCL17) and chemokine receptor (CCR3, CCR4, CCR5, and CXCR3) expression on CD3+ infiltrate. In addition, CD62 ligand, adhesion, and the expression of intercellular adhesion molecule 1 (ICAM-1) and VCAM-1 are regulated by IL-6. IL-6 activation of STAT3 promotes T-cell apoptosis.[E162] Through the gp130 signaling of IL-6, human monocytes are driven to differentiate into a more macrophage phenotype, which is eventually attributed to induction of the macrophage colony stimulating factor receptor on monocytes.[E163] The discovery of IL-6 stresses as IFN-β2 and BSF-2 stresses the function of IL-6 in the regulation of T-cell proliferation and differentiation[E164] as well as in the induction of B cells to produce IgM, IgG, and IgA.[E165-E167] Moreover, IL-6 plays an important role in the differentiation of stimulated B cells into plasma cells.[E166] It has also been demonstrated that IL-6 induces cytotoxic T-cell differentiation by increasing the IL-2R expression and IL-2 production.[E168,E169] IL-6 induces proliferation of thymocytes and is probably involved in the development of thymic T cells. TGF-β stimulates in the presence of IL-6 the differentiation of naive T lymphocytes into proinflammatory TH17 cells, leading to autoimmunity and inflammation.[E170] Moreover, IL-6 can convert natural occurring Treg cells to TH17 cells.[E171] Recently it has been shown that IL-6 promotes NK-cell expression of RORgt and IL-17 during toxoplasmosis.[E172] IL-6 can synergize with IL-15 or IL-7 to stimulate TCR-independent proliferation and effector functions of CD8+ T lymphocytes.[E173] As a costimulant together with IL-3, IL-6 initiates the proliferation of multipotential hemopoietic cells. It has been reported that IL-6 shortens the G0 period of hemopoietic stem cells. Macrophage differentiation and megakaryocyte maturation are driven by IL-6. The cytokine acts efficiently on bone, where it affects mainly osteoclastogenesis and bone resorption. It is also involved in the recruitment of mesenchymal vascular cells, neoangionesis *in vivo*, synovial fibroblast proliferation, and cartilage degradation.[E174] IL-6 is responsible for the initiation of the acute-phase response in human hepatocytes.[E175] Studies with recombinant IL-6 show an increase in protein synthesis of β-fibrinogen, α-1-antichymotrypsin, ceruloplasmin, haptoglobin, α1-acid glycoprotein, α1-antitrypsin, C-reactive protein, and complement factor B. IL-6 also has a negative inotropic effect on the heart. In neuronal cells, IL-6 induces the differentiation of pheochramocytoma 12 cells, supports the survival of cholinergic neurons, and leads to the induction of adrenocorticotropic hormone synthesis.

Role in host defense and autoimmunity

Because IL-6 has an important role in the regulation of the immune response, a deregulated production of IL-6 affects the pathogenesis of several autoimmune and inflammatory diseases. The first suggestion that IL-6 contributes to autoimmunity was observed in patients with cardiac myxoma. Cardiac myxoma cells produce IL-6, and the patients exhibit autoimmune symptoms.[E176] Further studies indicate the involvement of IL-6 in autoimmune diseases, chronic inflammatory proliferative disease, and B-cell malignancy, and SLE,[E177] Castleman disease, and plasmacytoma/multiple myeloma.[E178] IL-6 is required for experimentally induced autoimmune diseases such as type II collagen-induced arthritis[E179] and antigen-induced arthritis,[E180] myelin oligodendrocyte protein-induced experimental autoimmune encephalomyelitis,[E181] and pristine-induced autoantibody production in mouse models.[E182] There is some evidence that IL-6 could play a role in diabetes derived from an animal model for insulin-dependent diabetes mellitus. In psoriasis, it has been demonstrated that IL-17F is able to induce IL-6 production in human epidermal keratinocytes and in mouse skin, and thus the IL-17F/IL-6 axis may enhance inflammation of lesional skin in psoriasis.[E183]

Role in allergic disease

IL-6 plays a role in the development of allergic diseases by increasing the number of the effector cells via the sIL-6R on the one hand and by suppressing Treg cells and the initial stages of TH2-cell development via gp130 signals mediated by the membrane-bound IL-6R on the other hand. It was demonstrated that patients with allergy have increased levels of sIL-6R in airways compared with control subjects.[E184]

Functions in IL-6–deleted mice and receptor-deficient mice

In general, IL-6-/- deficient mice of both sexes are viable and fertile and do not present any evident phenotype abnormality. In more detail, IL-6-/-–deficient mice remain resistant to the induction of a number of experimental autoimmune conditions. They are not able to regulate T-cell trafficking, which results in an impaired local chemokine secretion and reduced chemokine receptor expression. Mice homozygous for a targeted disruption of IL-6 show a normal development, whereas the number of thymocytes and peripheral T cells is reduced compared with the wild-type. In IL-6–deficient mice, abnormalities in acute-phase reaction during tissue damage and infection are observed. gp130–deficient mice embryos die between 12.5 days postcoitum and term. Hypoplastic ventricular myocardium is observed 16.5 days postcoitum and later. The mutant embryos show a decreased number of pluripotential and committed hematopoietic progenitors in the liver and differentiated lineages such as T cells in the thymus.[E185] IL-6R–deficient mice are viable and fertile and have one third fewer T cells than wild-type mice, and the production of serum amyloid A is significantly decreased. IL-6–overexpressing transgenic BALB/c mice develop a massive increase of IgG1 and monoclonal transplantable plasmacytoma.[E175]

IL-7

Discovery and structure

IL-7, also known as pre–B-cell growth factor and lymphopoietin-1, was originally derived from bone marrow stromal cells and described as a mediator that alone could support the growth of B-cell progenitors.[E186] It is a monomer of 25 kd and consists of 152 amino acids. It is a member of the 4 α-helix bundle cytokine family. These family members are characterized by antiparallel juxtaposed helices A, C, B, D, and 2 long end-to-end loops, loops AB and CD, which are connected by a short β-sheet packed against helices B and D.[E65]

Receptor and signaling

The IL-7R is present on most T cells, progenitors of B cells, and bone marrow macrophages. It is downregulated by its own ligand. Also, soluble IL-7 receptor has been described.[E187-E191] IL-7R consists of 2 receptor chains, the IL-7Rα (CD127) and the common γc (CD132). Neither of these subunits/signaling elements is unique to IL-7. Whereas γc is also a receptor for IL-4, IL-7, IL-9, IL-15, and IL-21, IL-7Rα is shared with TSLP. Because γc is ubiquitously expressed on lymphocytes, IL-7 responsiveness is mainly controlled by IL-7Rα expression regulation.

Binding of IL-7 to IL-7Rα leads to dimerization of IL-7Rα and γc. Jak3 associated with the γc phosphorylates IL-7Rα after dimerization.[E192] The phosphorylated IL-7Rα serves as the site for recruiting other signaling molecules to the complex to be phosphorylated and activated, including STAT5, src kinases, PI3K, proline-rich tyrosine kinase 2 (Pyk2), and Bcl2 proteins. Some targets of IL-7 signaling contribute to cellular survival, including Bcl2 and Pyk2.[E193] Other targets contribute to cellular proliferation, including PI3K, src family kinases (lck and fyn), and STAT5.[E194] The transcription factor STAT5 contributes to activation of multiple different downstream genes in B and T cells and may contribute to VDJ recombination through alteration of chromatin structure.

Cellular sources and targets

IL-7 is a tissue-derived cytokine. It is produced by multiple stromal tissues, including epithelial cells in thymus and bone marrow. Additional sites of IL-7 production include intestinal epithelium, keratinocytes, fetal liver, adult liver, DCs, follicular DCs, B cells, and monocytes/macrophages.[E195] However, it has to be mentioned that the primary sources of IL-7 are nonmarrow-derived stromal and epithelial cells. Target cells of IL-7 are developing B and T lymphocytes, mature T cells, and NK cells.

Role in immune regulation and cellular networks

IL-7 stimulates the proliferation of pre-B and pro-B cells in mice (inhibited by TGF-β) without affecting their differentiation and with no effect on mature B cells. It promotes VDJ recombinations and selectively supports the maturation of megakaryocytes. Furthermore, IL-7 is required for the survival of naive T-cell populations and contributes to homeostatic cycling of naive and memory cells. It stimulates the proliferation of thymocytes and is therefore an important differentiation factor for functionally different subpopulations of T cells. In addition, IL-7 induces the synthesis of inflammatory mediators in monocytes.[E195]

Role in host defense or other immune-regulatory conditions

IL-7 and its receptor are linked to the development of MS and other autoimmune diseases,[E196,E197] and its expression is increased in the skin of psoriatic plaques and after *Schistosoma mansoni* infection.[E198] IL-7 is capable *in vivo* of causing CD4+ T-cell–dependent destruction of tumor cells and shows a potential contribution to allergen-induced eosinophilic airway inflammation in asthma.[E199]

Functions as demonstrated in IL-7–deleted mice, receptor-deficient mice, human mutations, and clinical use

Knockout/transgenic mice. There are several IL-7 and IL-7Rα KO models.[E200-E204] Phenotypic differences between these models may be attributed to TSLP because this cytokine also binds to IL-7Rα. However, both IL-7 and IL-7Rα KO mice showed that IL-7 is important for proper T-cell and B-cell development.[E201,E203]

IL-7–deficient mice were the first example of single cytokine–deficient mice that exhibited severe lymphoid abnormalities. IL-7–deficient mice were highly lymphopenic in the peripheral blood and lymphoid organs. Bone marrow B lymphopoiesis was blocked at the transition from pro-B to pre-B cells. Splenic B cells were also reduced in number like thymic and splenic T cellularity and showed an abnormal population of immature B cells in adult animals. The remaining splenic populations of lymphocytes showed normal responsiveness to mitogenic stimuli.[E201]

IL-7Rα KO mice displayed a profound reduction in thymic and peripheral lymphoid cellularity, and analyses of lymphoid progenitors revealed a critical role of IL-7R during early lymphoid development. This study indicated that the phase of thymocyte expansion occurring before the onset of TCR gene rearrangement is critically dependent on and mediated by the high-affinity receptor for IL-7.[E202,E203]

Transgenic overexpression of IL-7 results in T-cell expansion,[E205] which is not based only on increased survival, because transgenic expression of Bcl-2 (which is induced by IL-7) does not compensate for IL-7.[E206]

It also must be mentioned here that transgenic expression or injection of IL-7 augments the expansion of early B cells *in vivo*,[E207-E210] and phenotypes from transgenic mice expressing IL-7 under different promoters show a range from a benign increase in T and B cells to lymphoproliferative disorders, particularly in the skin.[E211-E213] In another transgenic mice model, chronic colitis developed.[E214]

Human mutations. Humans with a mutation in the common γc (as mentioned, this includes defect signaling of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) have XSCID1, a disease characterized by the absence of T and NK cells but the presence of nonfunctional B cells.

Also, patients with severe combined immunodeficiency (SCID) and defective IL-7Rα expression have been identified. They showed a T(-)B(+)NK(-) form of SCID, which underlines the nonredundant role of human IL-7Rα for T-cell but not B-cell development.[E215]

Clinical use. IL-7 has a potential for adoptive immunotherapy (a form of immunotherapy used in the treatment of cancer in which an individual's own white blood cells are coupled with a naturally produced growth factor to enhance their cancer-fighting capacity) because IL-7 is capable *in vivo* of causing CD4+ T-cell–dependent destruction of tumor cells. Furthermore, similar to IL-2, it has the potential to induce cytotoxic T cells in lung metastases of murine sarcomas. In addition, it has been shown to induce

lymphokine-activated killer cell activity obtained from patients early after bone marrow transplantation.[E216]

IL-8
Discovery and structure

In 1987, a neutrophil-specific chemotactic factor was purified from the medium of LPS-stimulated monocytes[E217] and was later identified as a member of the CXC chemokine family and termed CXCL8 or IL-8. The gene encoding IL-8 consists of 4 exons and 3 introns and is located together with 10 other members of the CXC chemokine family in a gene cluster on the long arm of chromosome 4.[E218] The IL-8 promoter contains binding sites for the transcription factors NF-κB (-80 to-71) and AP-1 (-123 to -12).

IL-8 is generated as a nonglycosylated precursor protein of 99 amino acids and secreted after cleavage of a 22–amino acid leader sequence. Enzymatic processing at the N-terminus results in multiple isoforms: monocytes mainly produce a 72–amino acid isoform with a molecular weight of 8.3 kd and only small amounts of the 77–amino acid, 70–amino acid, and 69–amino acid isoforms. In contrast, the 77–amino acid isoform is the major product of endothelial cells. IL-8 forms a homodimer in solution, and the crystal structure reveals 2 antiparallel helices situated on top of a 6-stranded antiparallel β-sheet formed by both monomer units.[E219,E220] Two disulfide bridges between cysteines 7 and 34 and between cysteines 9 and 50 are essential for the biological activity of IL-8. The conserved cysteines 7 and 9 define the family of CXC chemokines. The NH2 terminus of IL-8 and of the majority of the other CXC chemokines contains the 3 amino acid residues Glu-Leu-Arg (ELR-motif), which are indispensable for receptor binding. IL-8 is a basic protein with an isoelectric point of 8.3. It was found to be resistant to plasma peptidases, heat, extreme pH, and other denaturing conditions, but is rapidly inactivated on reduction of the disulfide bonds. IL-8 does not show any homology with other ILs; however, it shares considerable similarity with other CXC chemokines such as platelet basic protein (CXCL7), IFN-γ–inducible protein-10 (CXCL10), or platelet factor 4 (CXCL4).[E221]

Receptor and signaling

IL-8 acts via 2 related receptors, IL-8RA (CXCR1, CDw128a) and IL-8RB (CXCR2, CDw128b), which are both expressed on neutrophils, monocytes, lymphocytes, NK cells, and mast cells.[E222,E223] Both receptors belong to the same superfamily of CXC chemokine receptors, characterized by 7 transmembrane domains and signal transduction through G-protein–activated pathways. CXCR1 and CXCR2 are able to form homodimers and heterodimers during protein synthesis and maturation in the endoplasmic reticulum before cell surface delivery. The presence of IL-8 does not influence receptor dimerization, and the affinities of CXCR1 and CXCR2 dimers for IL-8 are similar to those of the corresponding homomeric interactions.[E224] On contact of neutrophils with bacterial LPS, *S aureus*, or *Helicobacter pylori*, CXCR1 and CXCR2 are rapidly downregulated by receptor internalization and degradation, indicating a mechanism of invading pathogens to modulate the host's immune response.[E225-E227]

Receptor-binding of IL-8 leads to activation of the coupled G-protein by replacing bound GDP by GTP. Subsequently, the trimeric G-protein dissociates into α and β-γ subunits, both of which activate signal transduction pathways.

First, activated PI3K generates phosphatidylinositol (3,4,5) triphosphate, which leads to the activation of phospholipase D.

Hydrolysis of phosphatidyl choline by phospholipase D results in the accumulation of phosphatidic acid, actin reorganization, and finally cell movement. Second, binding of IL-8 to CXCR1 or CXCR2 activates phospholipase C,[E228] which cleaves phosphatidylinositol (4,5) bisphosphate to inositol (1,4,5) trisphosphate and diacylglycerol. Inositol (1,4,5) trisphosphate increases cytosolic Ca^{2+}, while diacylglycerol together with Ca^{2+} leads to the activation of protein kinase C and the transcription factor NF-κB. Third, CXCR1 and CXCR2 ligands were found to activate p38 MAPK.[E229] Subsequently, p38 was able to translocate into the nucleus and to induce the transcription factor AP-1.

Cellular sources and targets

A wide variety of different cells such as monocytes and macrophages, neutrophils, lymphocytes, endothelial and epithelial cells, fibroblasts, keratinocytes, synovial cells, chondrocytes, hepatocytes, and smooth muscle and skeletal muscle cells as well as several tumor cell types produce IL-8.[E230-E234] IL-8 synthesis is usually induced on stimulation with IL-1α, IL-1β, TNF-α, or bacterial LPS, but also retinoic acid, zinc, nitric oxide, or irradiation. Viral, gram-negative, or positive bacterial infections were also found to activate the expression. Compared with other cytokines, IL-8 transcription is a rapid process; IL-8 mRNA can be detected by Northern blot within 1 hour after stimulation of the cells, and maximum expression is reached after 6 hours and persists for 6 hours.

Role in immune regulation and cellular networks

The regulation of IL-8 transcription seems to depend on the stimulus, its receptor, and the cell type. In a human monocytes and bronchial epithelial cells, TNF-α and LPS activate the MAP kinases JNK, ERK, and p38. JNK in turn activates the transcription factor NF-κB, which induces IL-8 promoter activity. ERK was found to enhance IL-8 transcription via the transcription factor AP-1, whereas p38 regulates the IL-8 synthesis on a posttranscriptional level by stabilizing the IL-8 transcript.[E235,E236] In addition, stimulation of bronchial and colonic epithelial cells with lysophosphatidic acid activated protein kinase C and protein kinase δ2, leading to the induction of NF-κB and IL-8 transcription.[E237,E238]

The major effector function of IL-8 is the recruitment of neutrophils to the site of infection or injury.[E221] The neutrophil accumulation is rapid and reaches a maximum after 30 minutes, continues up to 6 hours, and remains detectable up to at least 8 hours.[E239] Moreover, IL-8 activates neutrophils to generate respiratory burst responses by the formation of toxic oxygen-derived production, to degranulate and release lysosomal enzymes and antimicrobial peptides, and to express adhesion molecules such as leukocyte functioning antigen-1 and CD11b.

Besides neutrophils, IL-8 attracts NK cells, T cells, basophils, and GM-CSF or IL-3–primed eosinophils.[E240] In the presence of IL-3, IL-8 activates basophils to release leukotrienes and histamine. Thus, IL-8 plays an important role in the innate immunity, providing a first line of defense against invading pathogens.

In addition to its chemokine function, IL-8 stimulates the release of hematopoietic progenitor cells from the bone marrow into the peripheral blood.[E241] Activated neutrophils rapidly secrete prestored metalloproteinases from granules, leading to the cleavage of extracellular matrix molecules to which hematopoietic stem cells are attached.[E242]

CXC chemokines containing the ELR-motif, like IL-8, are potent promoters of angiogenesis under physiologic and pathophysiologic conditions. In contrast, members of the CXC chemokine family that lack the ELR-motif and that are inducible by IFN-γ, like platelet factor 4, inhibit angiogenesis and bind to CXCR3 on the epithelium.[E243] IL-8 was found to be highly expressed by endothelial cells on stimulation with vascular endothelial cell growth factor (VEGF), and by cancer cells and infiltrating macrophages. It is supposed to mediate its angiogenic activity in an autocrine and paracrine manner via binding and activating CXCR2 on endothelial cells.[E244] Enhanced survival and proliferation of endothelial cells lead to growth of new blood vessels. In cancer cells, IL-8 induces the production of metalloproteinases, serine and cysteine proteinases, which degrade the extracellular matrix and basement membrane, leading to reduced cellular adherence, migration of tumor cells, and entry into the circulation. The levels of IL-8 mRNA were found to correlate directly with intratumor microvessel counts, with the metastatic potential, and inversely with patient survival.[E245,E246]

Role in allergic diseases and other pathologic conditions

There is no direct importance of IL-8 described in T_H2-mediated allergic diseases. However, repeated injections of IL-8 lead to neutrophil accumulation in the lung and joints, resulting in pulmonary inflammation and cartilage damage. In line with these studies in rabbits, elevated IL-8 concentrations were detected in various inflammatory sites in human diseases, such as psoriatic lesions, synovial fluids of patients with RA, or BAL of patients with acute respiratory distress syndrome, respiratory syncytial virus infection, chronic obstructive pulmonary disease, or cystic fibrosis.[E247] In contrast with other chemoattractants, like C5a or leukotriene B4, which act transiently and are rapidly inactivated by oxidation or hydrolysis, IL-8 shows resistance to inactivation and slow clearance, leading to excessive accumulation of immune cells and negative effects on the outcome of the disease. For instance, in patients with RA, IL-8 is released by synovial cells and chondrocytes in elevated concentrations compared with healthy controls. Accumulated neutrophils are considered to be the major source of cartilage-degrading enzymes in this disease. During *H pylori* infection, the expression of IL-8 is enhanced in the gastric mucosa and correlates with bacteria load, chronic inflammation, and disease activity.[E248] The IL-8 promoter polymorphism -251A/A is associated with a higher expression of IL-8, severe neutrophil infiltrations, and an increased risk of atrophic gastritis and gastric cancer.[E249] Thus, anti–IL-8 mAbs are suggested as a therapeutic intervention for distinct inflammatory diseases.

Functions as demonstrated in IL-8R–deficient mice

IL-8R KO mice show a dysfunctional neutrophil response. Although neutrophils from IL-8R–deficient mice demonstrate normal rolling and arrest, their migration across the epithelial barrier is reduced, leading to neutrophil accumulation in the tissue and impaired bacterial clearance.

IL-9
Discovery and structure

IL-9 was first described in mice as a potent, antigen-independent T-cell growth factor.[E250] Subsequently, more activities on various cell types such as mast cells, B cells, eosinophils, neutrophils, and airway epithelial cells have been demonstrated.[E251] IL-9 is a monomer of 14 kd and consists of 125 amino acids. It is a member of the 4 α-helix bundle cytokine family. These family members are characterized by antiparallel juxtaposed helices A, C, B, D, and 2 long end-to-end loops, loops AB and CD, which are connected by a short β-sheet packed against helices B and D.[E65] Whereas the murine IL-9 is active on human cells, the human IL-9 has not been shown to be active on mouse cells.[E252]

Receptor and signaling

The IL-9R consists of 2 receptor chains, the ligand-specific α-chain IL-9Rα and the common γc (CD132), which is also present in the receptor complexes for IL-2, IL-4, IL-7, IL-15, and IL-21. The IL-9–specific α-chain is sufficient to bind IL-9 with high affinity, but it is not able to mediate any signal alone; γc is necessary for signal transduction. IL-9R activation results in phosphorylation of Jak1 and Jak3, which subsequently leads to the activation of STAT1, STAT3, STAT5, insulin receptor substrate-PI3K, and MAPK pathways. IL-9 also seems to regulate NF-κB activity through B-cell chronic lymphocytic leukemia/lymphoma 3 gene induction, which encodes a protein with close homology to inhibitor of κB proteins.[E253-E256]

Cellular sources and targets

The main sources of IL-9 are T_H2 cells and the recently discovered T_H9 cells.[E257,E258] To a lesser extent, mast cells (mainly within the airways of patients with asthma) and eosinophils have been shown to secrete IL-9. Target cells for IL-9 include B, T, and mast cells.[E259] For the induction of IL-9, a cascade of cytokines is involved. IL-2 is required for IL-4 production, IL-2 and IL-4 are required for IL-10 production, and IL-4 and IL-10 are required for IL-9 induction. It was shown that TGF-β can govern effector T-cell differentiation along a new pathway.[E257,E258] TGF-β in the presence of IL-4 reprograms T_H2-cell differentiation and leads to the development of a new population of T_H9 cells that produce IL-9 and IL-10.[E258] In other words, IL-4 blocks the generation of TGF-β–induced FOXP3$^+$ Treg cells and instead induces T_H9 cells.[E257,E260]

Role in immune regulation and cellular networks

IL-9 is a multifunctional cytokine. It is a potent growth factor for T cells and mast cells, promotes proliferation of CD8$^+$ T cells, and inhibits cytokine production of T_H1 cells.[E251,E261] IL-9 is involved in T_H2 inflammatory reactions, promotes the production of IL-4–induced IgE, induces chemokine and mucus secretion by bronchial epithelial cells, and leads to mast cell proliferation.[E262,E263]

Role in host defense or other immune-regulatory conditions

IL-9 is important in the protection against helminth infections. Furthermore, in Hodgkin lymphoma tumors, IL-9 is believed to stimulate and activate the infiltrating T_H2 cells, and it has been identified as an autocrine growth factor for Hodgkin and Reed-Sternberg cells.[E264,E265]

Role in allergic disease

IL-9 is important for the inflammatory responses in asthma and allergy. It plays a key role in the development of the asthmatic

phenotype, including eosinophilic inflammation, bronchial hyperresponsiveness, elevated IgE levels, and increased mucus secretion.[E266,E267] IL-9 has been shown to act on many cell types involved in asthma, including T cells, B cells, mast cells, eosinophils, neutrophils, and epithelial cells, and thus might be important in the pathophysiology of allergic asthma.[E268-E270] Furthermore, IL-9 has been suggested to play a role in food allergy.[E271]

Functions as demonstrated in IL-9–deleted mice, receptor-deficient mice, human mutations, and clinical use

Knockout/transgenic mice. In IL-9 KO mice, the lymphoid compartment develops normally, but these mice exhibit excessive mucus production and mast cell proliferation.[E272] In a quadruple IL-4/5/9/13 KO model, complete inhibition of allergic airway inflammation and remodeling has been shown.[E118]

Seven percent of transgenic mice overexpressing IL-9 developed thymic lymphomas in a model published by Renauld et al[E273] in 1994. In another transgenic model, where IL-9 was selectively overexpressed in the lung, it could been shown that IL-9 is an important cytokine in asthma because these mice developed many features that resembled human asthma, including eosinophilic and lymphocytic infiltration of the lung, mucus hypersecretion, subepithelial fibrosis, mast cell hyperplasia, and bronchial hyperresponsiveness.[E266,E267]

Human mutations. Human beings with a mutation in the common γc (as mentioned, this includes defect signaling of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) have XSCID1, a disease characterized by the absence of T and NK cells but the presence of nonfunctional B cells.

Clinical use. IL-9 is expressed on Reed-Sternberg cells and Hodgkin lymphoma cells and some large aplastic lymphoma cells, whereas non-Hodgkin lymphomas and peripheral T-cell lymphomas do not express IL-9. It has also been shown to be an autocrine growth modulator for Hodgkin cell lines. Therefore, the use of anti–IL-9 may play a role in the future in the treatment of Hodgkin disease and large-cell anaplastic lymphomas.

IL-10
Discovery and structure

IL-10 was first described in 1989 as cytokine synthesis inhibitory factor, a T_H2-derived factor inhibiting the production of IFN-γ and other cytokines in murine T_H1 cells.[E274] However, in the human system, IL-10 production is not a typical feature of T_H2 cells, because both T_H1 and T_H2 cells are capable of producing IL-10, whereas the main source of T-cell–derived IL-10 is Treg cells.

The *IL-10* gene maps to chromosome 1 both in the human (1q31-32) and murine genomes.[E275] Its structure is highly conserved and consists of 5 exons and 4 introns, a trait that is shared by most *IL-10* homologs. Human IL-10 has an MW of 18 kd and is secreted as a homodimer consisting of 2 subunits of 178 amino acids long.[E276,E277] The IL-10 protein contains 4 conserved cysteine residues in its mature protein sequence and forms 6 α-helices (A-F) in its tertiary structure.[E277] The first exon encodes the signal sequence and the A helix, the second exon encodes the AB loop and B helix, the third exon encodes the C and D helices, the fourth exon encodes the DE loop and E helix, and the fifth exon 5 encodes the F helix, the COOH tail, and an untranslated sequence that plays a role in mRNA stability.[E278]

Receptor and signaling

IL-10 binds to a tetrameric receptor complex belonging to the IFN receptor family and is composed of 2 IL-10R1 chains and 2 IL-10R2 chains.[E279] The IL-10R1 chain is expressed on T cells, B cells, NK cells, monocytes, mast cells, and DCs, whereas the IL-10R2 chain is ubiquitously expressed.[E280] IL-10 can bind to the IL-10R1 chain with high affinity (K_d 50-200 pM/L), whereas it does not directly interact with the IL-10R2 chain.[E281] Murine IL-10 binds both human and murine IL-10R1, whereas human IL-10 binds only to the human IL-10R1. Despite the fact that the IL-10R2 chain does not directly bind IL-10 and does not provide STAT3 docking sites, it is essential for IL-10–mediated signal transduction, as was demonstrated using an *il-10r2*$^{-/-}$ mouse model. These animals developed a phenotype similar to IL-10$^{-/-}$ mice and *stat3*$^{-/-}$ mice, which is mainly characterized by the development of chronic colitis.[E282]

The IL-10R1 chain is associated with Jak1, whereas the IL-10R2 chain is associated with Tyk2. The IL-10R complex signals via activation of Jak1 and Tyk2 followed by phosphorylation of STAT1, STAT3, and STAT5.[E283,E284] Binding of IL-10 to the extracellular domain of IL-10R1 initiates the activation of Jak1 and Tyk2, which in turn phosphorylate the tyrosine residues Y427 and Y477 or Y446 and Y496 in the murine and human IL-10R1 intracellular domains, respectively.[E285] These phosphorylated tyrosine residues and their flanking peptide sequences provide docking sites for STAT3 but not STAT1 and STAT5 (these STATs may be activated by IL-10 binding in a different manner). STAT3 docks to the IL-10R1 chain through its SH2 domain and is subsequently phosphorylated and released, after which STAT3 either homodimerizes or forms heterodimers with STAT1 or STAT5.[E285] These STAT dimers translocate to the nucleus, where they bind to STAT-binding elements in the promoter regions of IL-10–responsive genes and initiate gene transcription. STAT3 was shown to be essential for all known aspects of the anti-inflammatory effects of IL-10, as was demonstrated by a mouse model with a targeted deletion of *stat3* in neutrophils and macrophages. In these animals, the suppressive effects of IL-10 on the production of inflammatory cytokines were completely abolished. They were highly susceptible to endotoxic shock and developed chronic enterocolitis.[E286]

The IL-10R–associated tyrosine kinase Tyk-2 acts as a constitutive reservoir for SHP-1 in resting T cells, and then tyrosine phosphorylates SHP-1 on IL-10 binding.[E287] SHP-1 rapidly binds to CD28 and inducible T-cell costimulator (ICOS) costimulatory receptors and dephosphorylates them within minutes. In consequence, the binding of PI3K to either costimulatory receptor no longer occurs, and downstream signaling is inhibited. Accordingly, spleen cells from SHP-1–deficient mice showed increased proliferation with CD28 and ICOS stimulation in comparison with wild-type mice, which was not suppressed by IL-10. Generation of dominant-negative SHP-1–overexpressing T cells or silencing of the SHP-1 gene by small inhibitory RNA both altered SHP-1 functions and abolished the T-cell–suppressive effect of IL-10. The rapid inhibition of the CD28 or ICOS costimulatory pathways by SHP-1 represents a novel mechanism for direct T-cell suppression by IL-10.[E287]

Cellular sources and targets

In human beings, IL-10 is mainly produced by monocytes, T cells (mainly Treg cells), B cells, macrophages, and DCs.[E280]

Recently it was described that mast cells also produce IL-10 and thereby limit the rate of leukocyte infiltration, inflammation, and skin pathology in the context of contact dermatitis or chronic UV-B irradiation.[E288] *IL-10* gene expression is controlled by the ubiquitously expressed transcription factors Sp1 and Sp3.[E289,E290] However, another level of regulation of IL-10 expression results from the presence of multiple copies of mRNA destabilizing motifs present in the 3' untranslated region of the IL-10 mRNA.[E290] These findings suggest that in many cells the *IL-10* gene are ubiquitously transcribed, whereas the actual production and secretion of the IL-10 protein also depends on posttranscriptional signals. IL-27 was recently described as a potent inducer of IL-10 expression in T cells, a process that was dependent on STAT1 and STAT3. This was demonstrated in *IL-27r1*^{-/-} mice, which were unable to generate T_H1 cells producing both IFN-γ and IL-10.[E291] Another regulator of IL-10 expression in APCs was recently identified. The histone deacetylase 11 protein was shown to bind to the distal *IL-10* promoter region, thereby inhibiting gene transcription. The mechanism for the inhibition of *IL-10* expression was explained by the formation of more compact chromatin as a result of histone deacetylase 11–mediated deacetylation leading to impaired accessibility of this region for *IL-10*–inducing transcription factors such as STAT3 and Sp1.[E292]

Besides the cellular IL-10, several viral IL-10 (vIL-10) homologs have been found in the genomes of herpesviruses, poxviruses, and cytomegaloviruses, most of which show a high degree of amino acid sequence conservation compared with human IL-10. These vIL-10 homologs bind the same receptor complex (often with much lower affinity)[E293] as human IL-10 and induce similar responses. Therefore, viruses expressing homologs of human IL-10 are likely more successful in immune evasion through suppression of the host antiviral response. However, there is no detailed knowledge on the exact role of vIL-10 in these processes.

Role in immune regulation and cellular networks

IL-10 is a key regulator of the inflammatory response. Its immunosuppressive effects protect the host from exaggerated inflammatory responses to microbial infections as well as autoimmune diseases. Its primary function is to limit the production of TLR agonist (mainly LPS)–induced cytokines and chemokines in macrophages and DCs. IL-10 directly affects macrophage/monocyte functions by downregulating surface expression of class II MHC molecules and costimulatory molecules CD80/CD86 on these cells.[E294] Furthermore, IL-10 inhibits the expression of many cytokines including IL-1α, IL-1β, Il-6, IL-10, IL-12, IL-18, GM-CSF, G-CSF, and TNF-α; chemokines including monocyte chemoattractant protein (MCP)–1, MCP5, macrophage inflammatory protein (MIP)–1α, MIP1β, RANTES, IL-8, and IFN-γ–inducible protein 10 (IP-10); and chemokine receptors.[E294,E295] IL-10 inhibits cytokine production and proliferation of CD4^{+} T cells mainly indirectly through its effects on APCs.[E294,E295] However, IL-10 was also shown to directly affect T-cell cytokine production through suppression of CD28 and ICOS.[E287] Contrary to its inhibitory effects on many cell types, IL-10 enhances the expression of MHC class II molecules and stimulates the differentiation of murine B cells into antibody-secreting cells. Despite this, immunoglobulin levels are normal in *il-10*^{-/-} mice.[E296] IL-10 enhances the survival of human B cells as well as their proliferation, differentiation, and isotype switching.[E297]

It has been suggested that IL-10 exerts its immune suppressive effects through interference with the NF-κB activation pathway through inhibition of IκB activation as well as inhibition of NF-κB DNA binding activity.[E298] However, this direct inhibitory effect of IL-10 on NF-κB activation was later shown to be negligible.[E299] On the other hand, an indirect inhibitory effect of IL-10 signaling on the NF-κB pathway was recently demonstrated. The transcriptional repressor ETV3 and the corepressor strawberry notch homolog 2 were found to be specifically upregulated in mouse and human macrophages by IL-10 but not IL-6 signaling. These factors repressed NF-κB–activated transcriptional reporters, suggesting that they contribute to the downstream anti-inflammatory effects of IL-10.[E300]

It appears that the primary mechanism of IL-10–induced anti-inflammatory effects is mediated by the activation of STAT3, which acts indirectly by selectively inhibiting the transcription of specific LPS-induced genes in a manner that requires the synthesis of new proteins. This was demonstrated by using a mouse model in which the *Tnf-α 3' UTR* was replaced by the more stable *Gapdh 3' UTR.* Using this system, it was shown that IL-10–induced reduction of Tnf-α (one of the genes that is selectively inhibited by IL-10) expression was the result of transcription inhibition rather than mRNA degradation or other posttranscriptional modifications.[E299]

Why IL-10 induces such a broad range of anti-inflammatory effects in a STAT3-dependent manner whereas other cytokines such as IL-6 that also signal through STAT3 do not remains largely unknown. However, a clue is provided by the fact that IL-10 induces the expression of SOCS1 and SOCS3 in monocytes.[E301] SOCS3 inhibits IL-6R signaling both *in vitro* and *in vivo* by binding to the gp130 subunit of this receptor, whereas is does not inhibit IL-10–induced signaling.[E302,E303] When the SOCS binding site on the IL-6 receptor is mutated, IL-6R signaling can induce an anti-inflammatory response similar to IL-10.

Role in autoimmunity

IL-10 appears to have a protective role in several autoimmune diseases such as SLE, RA, and diabetes mellitus. A correlation between IL-10 serum levels and the severity of SLE as well as autoantibody levels has been observed, and treatment of patients with SLE with monoclonal anti–IL-10 antibodies showed an improvement of the disease outcome.[E304] Moreover, elevated expression of IL-10 has been associated with several cancers including melanomas and lymphomas.

Role in allergic disease

IL-10 has a protective role in allergic disease. It is constitutively expressed by APCs in the respiratory tract of healthy individuals, but its expression is reduced in patients with asthma and allergic rhinitis. Furthermore, T-cell tolerance induced during specific immunotherapy is the result of increased IL-10 production.[E305] Especially IL-10–producing Tr1 cells play key role in allergen tolerance and can be induced by allergen-SIT in human beings.[E305-E308]

Tr1 cells are the dominant type of T-cell subset in healthy individuals. Studies clearly show that allergen-specific Tr1 cells are predominant in healthy individuals to prevent unwanted immune responses to nonpathogenic environmental antigens such as house dust mite, birch pollen, bee venom, and food antigens (hazelnut, pear), which lead to allergy.[E309,E310] Healthy

individuals and those with allergy display 3 different allergen-specific T-cell subtypes—T_H1, T_H2, and Tr1—in different ratios.[E310] The imbalance between T_H2 and Tr1 cells and depending the dominant subset may induce allergy development or recovery. Tolerance to venom allergen is an appropriate model for high dose tolerance to allergens in human beings. During beekeeping season, repeated exposure of healthy beekeepers without allergy to bee venom antigens is an estimable model to apprehend mechanisms of immune tolerance to bee venom allergens.[E311] During the exposure to venom allergen, venom-specific IL-10–secreting Tr1 cells are clonally differentiated from allergen-specific T_H1 and T_H2 cells. This leads to suppression of the allergen-specific unwilling immune response by T_H1 and T_H2 cells. This immunomodulator response persists as long as venom exposure and returns to previous levels within 2 to 3 months after the end of beekeeping season. Interestingly, histamine receptor 2 also upregulated on specific T_H2 cells suppresses allergen-stimulated T cells and enhances IL-10 production related to tolerance mechanism. Beekeepers without allergy have an approximately 1000 times higher allergen-specific IgG_4 versus allergen-specific IgE ratio compared with individuals with bee venom allergy.[E312] Another tolerance model with cat allergen also showed elevated levels of allergen-specific IgG_4 levels after exposure to high-dose cat allergen.[E313] This also represents a tolerance to the T_H2 immune response to specific allergens. Together these outcomes may mean that animals in the house induce tolerance and can decrease the risk of asthma.

IL-10–secreting Tr1 cells not only suppress T_H2 immune response. Peripheral tolerance is achieved with multiple mechanism to overcome and suppress allergic inflammation. The other roles of Treg cells are suppression DCs, thereby enhancing the generation of effector or induction of DCs that support the generation of Treg cells[E314-E316]; suppression of T_H1 and T_H2 cells[E317]; suppression of allergen-specific IgE and induction of IgG_4 and/or IgA[E318]; suppression of mast cells, basophils, and eosinophils[E319]; and interaction with resident cells and remodeling.[E320,E321]

Functions as demonstrated in IL-10–deficient mice, receptor-deficient mice, and human mutations

Several animal models have provided insight into the mechanisms of action of IL-10. Mice overexpressing IL-10 under the control of an MHC class II promoter show a defect in $\alpha\beta$–T-cell maturation characterized by a rapid thymic aplasia starting directly after birth, demonstrating that IL-10 regulates T-cell maturation.[E322] Transgenic overexpression of IL-10 under control of a macrophage-specific promoter results in suppression of systemic cytokine responses in response to LPS challenge as well as impaired clearance of *Mycobacterium bovis* infection compared with normal animals, whereas no differences in T-cell and B-cell responses were observed.[E323] This suggests that macrophage-derived IL-10 mainly acts in an autocrine or paracrine manner. IL-10 KO mice show normal lymphocyte development and antibody responses while they grow slower, are anemic, and develop chronic colitis.[E296] This demonstrates that IL-10 is essential for the control of normal intestinal immune responses against enteric antigens. Interestingly, a frameshift insertion at nucleotide 3020 (3020insC) in the gene encoding Nod2 is strongly associated with Crohn disease and impaired IL-10 production. Recently it was shown that this mutant Nod2 protein actively inhibited IL-10 transcription by blocking phosphorylation of heterogeneous nuclear ribonucleoprotein A1 via p38.[E324]

T-cell–specific IL-10–deficient mice develop a phenotype that largely resembles that of the complete IL-10–deficient model with the difference that T-cell–specific IL-10 KOs are less sensitive to endotoxic shock and irritant responses of the skin. This suggests that, in these situations, IL-10 derived from sources other than T cells is more important.[E325]

Many polymorphisms, including single nucleotide polymorphisms (SNPs) and microsatellites, have been identified in the promoter region of the human IL-10 gene that are associated with altered expression levels of IL-10.[E326,E327] Altered IL-10 expression levels as a result of such genetic variations have been linked with several diseases including cancer, tuberculosis, allergies, and a number of autoimmune disorders.

The IL-10 cytokine family

The family of IL-10–related cytokines consists of IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29. The genes encoding IL-22 and IL-26 map to chromosome 12q15 together with IFN-γ. Because they have been frequently classified as part of the typical T_H17 cytokine profile, these 2 cytokines are discussed in the context of T_H17-related cytokines. The genes encoding IL-10, IL-19, IL-20, and IL-24 co-localize on chromosome 1q31-32, whereas the genes encoding IL-28A, IL-28B, and IL-29 map to chromosome 19q13.

The members of the IL-10 cytokine family are mainly linked through their similar intron-exon structure. At the amino acid level, these proteins are not very similar. However, their secondary structure is highly conserved and contains 6 to 7 α-helices that form either monomeric or dimeric proteins. All IL-10 family members exert their effects through binding to a transmembrane receptor complex composed of R1 and R2 chains belonging to the class II cytokine receptors, and their main signal transduction pathway acts through Jak/STAT phosphorylation. IL-19, IL-20, and IL-24 can bind more than 1 receptor complex, and some of the heterodimeric receptor complexes can be activated by different members of the IL-10 family of cytokines.

Despite their many similarities, the members of this cytokine family play roles in different physiological processes including immune suppression (IL-10), skin biology (IL-19 and IL-20), tumor suppression (IL-24), and antiviral responses (IL-28 and IL-29).

IL-11
Discovery and structure

Human IL-11 is a pleiotropic and redundant cytokine that interacts with a variety of hemopoietic and nonhemopoietic cell types. It was first isolated from bone marrow–derived stromal cells in 1990.[E328] The human IL-11 gene is located on the long arm of chromosome 19 (19q13.3-13.4) and consists of 5 exons and 4 introns. It encodes a precursor protein consisting of 199 amino acids. After cleavage of a 21–amino acid hydrophobic signal sequence, the mature protein has a molecular weight of 19 kd and lacks any cysteines or N-glycosylation sites. It is proline-rich and has a high basic charge (pI=11.3). Although it shows little sequence homology with other cytokines, its 3-dimensional structure is supposed to be similar to that of members of the IL-6 family. The high helicity of IL-11 together with computer predictions of secondary structure indicate that the molecule has a 4 α-helical bundle structure.

Receptor and signaling

IL-11 binds to a heterodimeric receptor, consisting of the specific IL-11Rα and the signal-transducing subunit gp130.[E329] IL-11Rα is a 150-kd protein consisting of an extracellular region, a transmembrane, and a cytoplasmic domain. The extracellular part of the protein contains 3 domains similar to those of the IL-6 receptor: an N-terminal immunoglobulin-like domain and 2 fibronectin type III–like domains that contain the cytokine receptor-homology region defined by 4 conserved cysteine residues and a characteristic WSXWS sequence motif. Mutational analysis of the IL-11Rα demonstrated that the third extracellular domain is responsible for ligand binding; the affinity of this domain for IL-11 was found to be as high as that for the whole receptor.[E330] Experiments using a soluble form of IL-11Rα that lacks the cytoplasmic domain showed that this domain is not required for the biological effects of IL-11, but the gp130 subunit mediates the signaling.[E331] gp130 belongs to the family of class I cytokine receptors and is the common signal-transducing subunit shared by IL-11, IL-6, ciliary neurotrophic factor, LIF, OSM, and cardiotrophin-1.

On binding of IL-11 to its receptor, a hexameric complex is formed consisting of 2 molecules each of IL-11, IL-11Rα, and gp130.[E332] The dimerization of gp130 initiates several signal transduction pathways in parallel: the Jak/STAT pathway gets triggered, and MAPKs, ribosomal S6 protein kinases, and Src-family kinases such as p60 src and p62 yes are activated.[E333]

Cellular sources and targets

IL-11 is produced by a variety of stromal cells including fibroblast, epithelial cells, endothelial cells, vascular smooth muscle cells, synoviocytes, osteoblasts, and several tumor cell lines.[E334-E337] Its expression is induced after stimulation with the cytokines IL-1α, TGF-β, or TNF-α[E335,E338] as well as IL-13 during T$_H$2-dominated inflammatory disorders.[E339] Although each cytokine is sufficient to stimulate IL-11 expression, IL-1α and TGF-β synergistically augment the production of IL-11. Moreover, several tissue-specific stimuli of IL-11 synthesis have been described. For instance, parathyroid hormone,[E340] hepatocyte growth factor,[E341] or viral infections[E342,E343] are shown to induce the production of IL-11 in osteoblasts and airway smooth muscle cells, respectively. Histamine and eosinophil major basic protein further enhance IL-11 expression, whereas IL-6, IL-4, heparin, and steroids inhibit IL-11 synthesis.[E340,E344]

IL-11 acts widely in hematopoietic and nonhematopoietic cell types, including hematopoietic progenitor cells, platelets, T cells, B cells, monocytes, and hepatocytes.

Role in immune regulation and cellular networks

In synergy with IL-3, it shortens the G0 period of early hematopoietic progenitor cells and thereby stimulates hematopoiesis by supporting the growth of myeloid, erythroid, and megakaryocyte progenitor cells as well as plasmacytoma cells.[E345]

IL-11 increases peripheral platelet counts and was shown to enhance T-cell–dependent secretion of immunoglobulins by B cells. Recent work demonstrates the expression of IL-11Rα and gp130 on CD4+ and CD8+ lymphocytes, indicating a direct effect of IL-11 on T cells. *In vitro* IL-11 modulates the cytokine production from activated murine CD4+ T cells in such a way that IL-4 and IL-10 secretion is enhanced, but the production of IFN-γ and of the T-cell growth factor IL-2 is inhibited. However, no effect of IL-11 on T-cell proliferation was observed.[E346]

Moreover, IL-11 regulates monocyte and macrophage proliferation as well as activity by inhibiting the synthesis of inflammatory cytokines such as TNF-α, IL-1, IL-12, IFN-γ, and nitric oxide after LPS stimulation. The decreased cytokine production is associated with inhibited nuclear translocation of NF-κB and enhanced production of NF-κB inhibitors IκB and IκB-β.

During the acute-phase response, IL-11 stimulates the production of acute-phase proteins such as ferritin, haptoglobin, C-reactive protein, and fibrinogen in hepatocytes.[E345]

IL-11 promotes neuronal development and plays a role in adipogenesis by potently inhibiting the lipoprotein lipase activity and the differentiation of adipocytes.[E347]

In addition, IL-11 is involved in bone remodeling because it stimulates osteoclast development, inhibits their apoptosis, and suppresses the activity of osteoblasts, which leads to decreased bone formation.[E337]

IL-11 was shown to have intriguing protective effects on epithelial cells and connective tissue after cell damage induced by irradiation or chemicals.[E348] It downregulates proinflammatory mediators, inhibits epithelial cell proliferation and apoptosis, and induces the secretion of tissue inhibitor of metalloproteinases 1 from chondrocytes, synoviocytes, and hepatocytes. Tissue inhibitor of metalloproteinases 1 is a potent inhibitor of matrix metalloproteinases, a group of peptidases involved in the degradation of the extracellular matrix that promote cell proliferation while inhibiting apoptosis in a wide range of cell types. Most prominent are the protective effects of IL-11 in the gastrointestinal tract, where IL-11 protects small-intestinal cells after combined radiation and chemotherapy and ameliorates tissue injury in animal models of IBD. Additional protective effects of IL-11 were observed in different models of inflammatory skin disease, RA, and infection-endotoxemia syndromes or patients with Crohn disease, MS, and psoriasis.[E349-E351]

Role in allergic diseases

IL-11 is supposed to be a regulator of inflammation and tissue remodeling in the asthmatic airway. During asthmatic inflammation, IL-13 together with respiratory viruses induces the expression of IL-11 in eosinophils and in a variety of structural cells in the lung. Overexpression of IL-11 in transgenic mice showed that IL-11 causes airway hyperresponsiveness and airway remodeling, which is characterized by subepithelial fibrosis and airway obstruction, whereas asthmalike inflammations are inhibited.[E352] IL-11 can be found in nasal secretions of children with upper respiratory tract infections, and patients with moderate or severe asthma show increased IL-11-expression in eosinophils and lung epithelial cells compared with healthy controls. In individuals with asthma, the levels of IL-11 even correlate directly with disease severity and inversely with FEV$_1$.[E352]

These natural protective effects of IL-11 are exploited by using recombinant IL-11 for the treatment of different diseases. Recombinantly expressed IL-11 has been approved for the treatment of thrombocytopenia induced by chemotherapy. Thrombocytopenia is frequently the major dose-limiting hematologic toxicity during chemotherapeutic treatment of cancers and can be significantly reduced by the ability of IL-11 to accelerate platelet recovery and stimulate peripheral platelet counts *in vivo*.[E353]

The anti-inflammatory and mucosal protective effects of IL-11 are of use to accelerate healing and improve T_H1-mediated inflammatory diseases. In a phase I clinical trial, treatment of patients with psoriasis resulted in amelioration of the disease, as shown by reduced keratinocyte proliferation and cutaneous inflammation. Levels of proinflammatory cytokines such as IFN-γ, IL-8, IL-12, TNF-α, and IL-1 decreased, whereas the expression of endogenous IL-11 increased.[E349] Moreover, recombinant IL-11 was found to protect from acute gastrointestinal mucosal damage and to induce remission in patients with mild to moderate Crohn disease.[E350,E351] Animal models of RA as well as a phase I clinical study in patients with RA indicate a positive effect of IL-11 treatment on the outcome of the disease by inhibiting macrophage activity and modulating T-cell responses.[E354]

Functions as demonstrated in IL-11–deficient mice and receptor-deficient mice

Although IL-11 effectively acts as a multilineage growth factor in the hematopoietic compartment, IL-11Rα–deficient mice show no obvious hematologic abnormalities.[E355] The numbers of different hematopoietic cells in the bone marrow, spleen, or peripheral blood did not differ between wild-type and KO animals, indicating that IL-11 is dispensable for hematopoiesis because of growth factor redundancy in the hematopoietic compartment. In addition, the activities of IL-11 are similar to those of IL-6 with regard to the promotion of antibody secretion by B cells, the downregulatory effects on monocytes and macrophages, and the induction of acute-phase proteins. Thus, the effects of IL-11 can at least in part be accomplished by other cytokines, mainly those that signal via the common receptor subunit gp130. However, in contrast with normal hematopoiesis, IL-11Rα$^{-/-}$ mice have increased trabecular bone volume, associated with low bone resorption and formation, and decreased osteoclast numbers. Female IL-11Rα$^{-/-}$ mice are infertile because of abnormal development of the placenta. During normal pregnancy, IL-11 is expressed by endometrial stromal cells and activates the expression of α2-macroglobulin via the transcription factor STAT3. α2-Macroglobulin is a protease inhibitor essential for the development of the placenta; downregulation of α2-macroglobulin results in degeneration of the decidua and uncontrolled trophoblast invasion.[E356] This finding points out a critical action for IL-11 in nonhematopoietic organs.

IL-12
Discovery and structure

IL-12 was first described as natural killer stimulating factor in 1989. The heterodimeric cytokine consists of a 35-kd light chain (p35 or IL-12a) and 40-kd heavy chain (p40 or IL-12b).[E357] The gene encoding p35 is located on chromosome 3 in human beings and on chromosome 6 in mice. The p35 protein contains 197 amino acids and has homology to other single-chain cytokines (eg, IL-6 and G-CSF). The IL-12 p40 gene is on the human chromosome 5 in the same area as IL-3, IL-5, and GM-CSF, and the mice gene is on chromosome 11. p40 has homology to the extracellular domain of members of hematopoietic cytokine-receptor family (eg, IL-6Rα).[E358] Because of their localization on different chromosomes, protein expression of the 2 subunits is independently regulated, and when they are coexpressed in the same cell, they form the biologically active IL-12 p70 heterodimer.[E359] Both subunits are covalently linked by a disulfide bond between Cys74 of p35 and Cys177 of p40 to form the active IL-12 p70.

IL-12p40 can be produced as a free monomer or homodimer (p40$_2$) in large excess over the IL-12p70 heterodimer *in vitro* and *in vivo*. The p40 homodimers have been suggested to antagonize IL-12p70 signaling in mice but not in human beings. That IL-12p40 acts as a macrophage chemoattractant has also been proposed. Unlike p40, p35 is not secreted in monomeric form.

Receptor and signaling

The heterodimeric IL-12R is composed of IL-12Rβ1, which is structurally related to the type I cytokine receptor superfamily, and of IL-12Rβ2, which is homologous to the gp130 subunit. The genes for the β1 and β2 chains reside on chromosomes 19p13.1 and 1p31.2, respectively. The affinity of IL-12 for either β1 or β2 alone is low, and coexpression of both β1 and β2 subunits is required for the generation of human high-affinity IL-12 binding sites.[E360] The receptorlike subunit, IL-12p40, interacts with the β1 subunit, and IL-12p35 interacts with the β2 subunit. The β2 subunit is the signal transducing chain of the receptor. In contrast, IL-12Rβ1 has no intracellular tyrosine residues and presumably cannot signal. IL-12Rβ1 is more important for ligand binding.[E361] IL-12R is expressed on T cells, NK cells, and DCs. However, naive CD4$^+$ T cells express low levels of IL-12Rb2 at the resting state and require TCR, CD28, IL-27, or IFN-γ stimulation to increase their IL-12 responsiveness.[E362] The specific T_H1-cell transcription factor Tbet, induced by IL-27, upregulates IL-12Rb2, whereas IFN regulation factor (IRF)–1, induced by IFN-γ, directly regulates IL-12Rb1.[E363] This enables the formation of the IL-12R complex. Like many cytokine receptors, IL-12R lacks intrinsic enzymatic activity and instead transduces signals through the action of the Jaks. Tyk2 and Jak2 are involved in IL-12 signaling; Tyk2 associates with the β1 subunit, and Jak2 associates with IL-12Rβ2.[E364,E365] On ligand binding, receptor-associated Jaks are activated by transphosphorylation and later STAT4 activation. The phosphorylated STATs then homodimerize or heterodimerize, translocate into the nucleus, bind specific DNA sequences, and modulate gene expression.[E366]

Cellular sources and targets

Produced by activated inflammatory cells (eg, monocytes, macrophages, neutrophils, microglia, and DCs), and to a lesser extent B cells. Whereas p35 is expressed ubiquitously and constitutively at low levels, p40 expression is limited to phagocytic cells that produce IL-12p70.[E367-E369]

A variety of different pathogenic organisms induce high levels of IL-12p40 and IL-12p70 production, including gram-positive and gram-negative bacteria, parasites, viruses, and fungi. Microbial products such as LPS, lipoteichoic acid, peptidoglycan, and bacterial (CpG) DNA induce T-cell–independent production of IL-12 by cells of the innate immune system via TLR signaling.[E370-E372] Intact gram-positive bacteria preferentially stimulate IL-12.[E373] The p40 gene is regulated at the level of transcription and is highly inducible by microbial products. Numerous transcription factors, including NF-κB family members (p50, p65, and c-Rel), IRF-1, IFN consensus binding protein, and Ets-family members, can bind and regulate the p40 promoter.[E374-E378] IL-12 is also produced in a T-cell–dependent manner through the engagement of CD40 on APCs with its receptor CD40 ligand on T cells.[E379] IL-12 production is positively regulated by IFN-γ, which is induced by IL-12 itself. IL-12 participates in a positive feedback loop by promoting IFN-γ secretion that, in

turn, potently primes monocytes and PMNs for further IL-12 production.[E376,E380] Conversely, IL-12 production is inhibited by IL-10, IL-11, IL-13, and type I IFNs. G-protein coupled receptors including the receptors for MCP1, prostaglandin E2, histamine, and FcR cross-linking also inhibit IL-12 production, although some G-protein coupled receptors like CCR5 positively regulate production. Cholera toxin and measles virus also downregulate IL-12 production.[E381-E385]

Role in immune regulation and cellular networks

IL-12–activated cells expressed increased levels of transcripts for many genes involved in host defense, including IFN-γ, granzyme, TRAIL, FasL, and CCL5. Thus, the IL-12/IFN-γ pathway predominantly induces cytotoxic factors important for the direct killing of microbes or infected cells. By inducing IFN-γ production from NK cells and T cells, IL-12 indirectly activates the antimicrobial, antiparasitic, and antitumor activity of phagocytotic cells and promotes cytolytic activity of NK cells and lymphokine-activated killer cells.[E386-E391] IL-12 also acts on DCs to induce IL-12 production further, and by increasing the expression of CD2, CD11a, CD45, CD56, CD69, CD71, and HLA-DR, IL-12 supports the maturation of DCs and is of great importance for the differentiation and proliferation of T cells.[E360,E392] IL-12 is a major player in the development and maintenance of T_H1 cells. Activation of the IL-12R complex further stimulates IFN-γ production and induces expression of IL-18Ra, thereby conferring IL-18's responsiveness to mature T_H1 cells. IL-18 serves as a cofactor for IL-12–induced T_H1 development and enhances IFN-γ production from effector T_H1 cells. In contrast, IL-4 inhibits IL-12Rβ2 expression.[E362,E393] Therefore, the opposing effects of IFN-γ and IL-4 on IL-12R expression may contribute to T_H1/T_H2 differentiation. Conversely, IL-12 and IFN-γ antagonize T_H2 differentiation and the production of IL-4, IL-5, and IL-13.

Functions as demonstrated in IL-12–deleted mice and receptor-deficient mice

Mice deficient in IL-12p35, IL-12p40, or IL-12Rβ1 display similar phenotypes and show no obvious developmental abnormalities.[E394-E397] Their IFN-γ secretion, T_H1 differentiation, and NK cytolytic activity are greatly impaired, and decrease of IL-12 production results in higher susceptibility to intracellular pathogens. Mice lacking the IL-12p40 subunit are more immunocompromised than p35$^{-/-}$ mice in terms of their ability to generate allospecific CD8$^+$ T cells.[E398] However, the generation of T_H1 lymphocytes in p35-null mice is totally abrogated, and these mice and are highly susceptible to experimental autoimmune encephalomyelitis (EAE), whereas p40-deficient mice are resistant.

Patients with IL-12p40 deficiency show increased susceptibility to poorly pathogenic mycobacterial and salmonella infection. This condition seems to be more severe than IL-12Rβ1 deficiency, with a mortality of 38%.[E399,E400] A number of mutations in IL-12RB1 have been identified and result in the complete absence of responsiveness to IL-12 and IL-23. Antigenic stimulation (eg, BCG or *M avium*) of patient peripheral blood lymphocytes resulted in markedly reduced IFN-γ production. Activated T-cell lines derived from these patients did not respond to IL-12 by the nuclear translocation of phosphorylated STAT4 protein as detectable by electrophoretic mobility shift.[E401] Atopic patients with heterozygous IL-12Rβ2 chain mutations show decreased STAT4 phosphorylation and IFN-γ production in response to IL-12 stimulation.[E402,E403]

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FROM IL-13 TO IL-24

IL-13

Discovery and structure

IL-13 was first described in 1989 as P600, a protein expressed by activated mouse T_H2 cells,[E1] and was cloned in 1993.[E2-E4] It has a molecular weight of 10 kd and is encoded in a cytokine gene cluster on chromosome 5 (5q31) that includes genes encoding for IL-3, IL-4, IL-5, IL-9, and GM-CSF. The structure of IL-13 consists of a 4-helix bundle with a characteristic up-up-down-down topology that includes a β-sheet formed between residues in the AB-loop and CD-loop.[E5,E6] It shows considerable similarity to IL-4 and is highly conserved with little species-specificity.[E3]

Receptor and signaling

IL-13 has 2 known receptors: IL-13R1α1 and IL-13R1α2.[E7] It signals, together with IL-4, through the IL-4R complex type II that consists of the IL-4Rα and IL-13Rα1. IL-13 binds with its helical faces to the elbow-shaped cytokine-binding homology region. Recently, LaPorte et al[E8] defined the structural basis of type I and type II ternary signaling complexes and the subtle differences that results from IL-4 and IL-13 receptor interactions leading to type II complex formation. IL-13Rα1 bears an evolutionary relationship to γc, but it contains an extra N-terminal immunoglobulin-like domain (D1) not found in other receptors of the γc subfamily that is required for IL-13 but not for IL-4 signaling. For its binding specificity, the IL-13R1D1 domain has been defined as the crucial part type II complex formation that results in IL-13 signaling. IL-4–mediated signaling via this complex is not affected by mutations of this domain. IL-4 binds to IL-4Rα with high affinity, whereas the recruitment of either γc or IL-13Rα1 contributes little affinity. On the contrary, binding of IL-13 by IL-13Rα1 occurs with moderate affinity, but its affinity is significantly enhanced by the presence of its ligand, IL-4Rα. Consequently, the expression patterns of the receptors are decisive to define the signaling efficiency of IL-4 and IL-13. In general, IL-4Rα is limited, however, for example, in cells in which IL-13Rα1 is limiting the higher affinity for its trigger the receptor may lead to a more potent IL-13 signaling.[E8] Another important factor is the presence of the γc that allows IL-4 to signal via the type I complex. Mainly macrophages and hematopoetic cells express both the γc and IL-13R1α. Consequently, γc expression results in a 10-fold to 100-fold higher sensitivity of bone marrow–derived macrophages and monocytes to IL-4 than to IL-13.[E9]

After binding of IL-13 to IL13Rα1, the IL-13 type II receptor complex is formed and leads to Jak-mediated phosphorylation of STAT6.[E10] This is considered to be the major mode of action. However, recently IL-13 was demonstrated to act via the MAPK pathway. The activation of ERK 1/2 in mouse model with transgenic IL-13 expression in the lung was demonstrated.[E11] Inhibition of the ERK 1/2 MAPK pathway decreased the expression of several chemokines—MIP-1α/CCL-3, MIP-1β/CCL-4, RANTES/CCL-5, matrix metalloproteases (MMP)–2, MMP-9, MMP-12, and MMP-14, and cathepsin B—and led to the upregulation of α1-antrypsin. MIP-2/CXCL-1 expression was exclusively ERK 1/2–dependent. Moreover, remodeling and recruitment of eosinophils were also affected by IL-13–dependent activation of ERK 1/2. IL-13–induced eotaxin/CCL-11, MIP-1/CCL-2 and C10/CCL-6 mRNA production, IL-13R regulation,15-lipoxygenase regulation (*in vitro* experiments), and mucus cell metaplasia (*in vivo*) in an ERK 1/2–independent manner.[E11] In addition to ERK1/2, JNK-dependent effects have been suggested to have an effect on AHR by affecting Ca^{++} influx in airway smooth muscle cells.[E12]

The second receptor, IL-13Rα2, is assumed to act as a decoy receptor. It binds IL-13 with a higher affinity than IL-13Rα1 and is considered to serve as potent inhibitor of IL-13–induced actions.[E13] In a double-KO asthma model (IL10$^{-/-}$IL13Rα2$^{-/-}$), an additive inhibitory effect of IL-13Rα2 on IL-13–induced airway hyperreactivity, mucus production, inflammation, and fibrosis with IL-10 was observed.[E14] Furthermore, a role of IL-13Rα2 in IL-13–induced fibrosis by TGF-ß1 in the presence of TNF-α has been demonstrated in mouse models for oxazolone-induced or trinitrobenzene sulfonic acid-induced colitis and bleomycin-induced lung fibrosis. After an initial step of upregulation of IL-13Rα2 by IL-13 (via the IL-13Rα1), TNF-α mediates fibrosis, which is induced via IL-13Rα2 in an STAT6–independent fashion via AP-1.[E15,E16] There is some evidence that the N-linked glycosylation of IL-13Rα2[E17] plays a decisive role for IL-13Rα2–mediated inhibition.

Cellular sources and targets

IL-13 is produced by T cells, mast cells, basophils, eosinophils, and NKT cells. Major target cells are B cells, mast cells, epithelial cells, eosinophils, smooth muscle cells, and macrophages.[E18]

Role in immune regulation and cellular networks

IL-13 is antagonized via the T_H1-type cytokines IFN-γ, IL-12, IL-18, and TNF-α and the regulatory cytokine IL-10. IL-13 can induce class-switching to IgG_4 and IgE in combination with CD40 stimulation.[E19] The expression of CD23 and MHC II are upregulated on B cells in the presence of IL-13. In addition, the induction of the adhesion molecules CD11b, CD11c, CD18, CD29, CD23, and MHC II on monocytes takes place. Moreover, IL-13 activates eosinophils and mast cells, recruits eosinophils, and prolongs their survival.[E20]

Role in allergic disease

Ovalbumin-transgenic T_H2-type cells from IL-13–deficient mice fail to induce AHR in B-cell and T-cell–deficient mice in the presence of airway eosinophilic infiltrates, IL-4, and IL-5.[E21] Thus, IL-13 itself is sufficient to induce AHR. IL-13–dependent AHR and mucus secretion was induced independently of IL-5 or eosinophilic cationic protein. However, the presence of IL-5 and ECP seems to be crucial for maintenance of IL-13 production of T_H2 cells. Chiba et al[E22] reported an IL-13–induced upregulation of a monomeric GTP-binding protein called RhoA, which is supposed to be involved in increasing the sensitivity of myofilaments to Ca^{++}. Interestingly, both an IL-4Rα and a Stat6-independent pathway through which IL-13 induces AHR and mucus secretion have been suggested.[E23,E24]

The role of IL-13 on asthma is supported by epidemiologic data demonstrating that a combination of polymorphisms of the IL-4/IL-13 pathway increased the risk of developing asthma 16.8-fold.[E25] Polymorphisms restricted to IL-13 itself lead to a higher frequency of asthma exacerbations in childhood and elevated total IgE and blood eosinophilia.[E26] IL-13 also contributes to allergic rhinitis late-phase responses, whereas its impact on the acute response appears to be limited *in vivo*.[E27]

In addition, IL-13 plays an important role in tissue remodeling and fibrosis.[E28,E29] In an *S mansoni* infection model, IL-4R^{-/-} and Stat6^{-/-} mice had a significantly reduced granuloma size and reduced fibrosis, whereas ablation of IL-4 had no effect, thus suggesting a key role of IL-13 in this process. Moreover, IL-13 is a potent inducer of collagen production in fibroblasts. Furthermore, it is able to induce arginase 1 in macrophages that are termed alternatively activated. This arginase uses L-arginine as a substrate to make L-ornithine and is converted to proline and polyamines. Proline is known to be necessary for the development of fibrosis. Increased polyamine production in the presence of IL-13 leads to rat aortic smooth muscle cell proliferation that can be inhibited via dexamethasone treatment.[E30]

Role in host defense or other immune-regulatory conditions

IL-13 plays a unique role in parasite defense. IL-13–deficient mice are unable to expel *N brasiliensis*. Importantly, this defect is more pronounced in IL-13^{-/-} mice than in IL-4–deficient mice, with IL-5 levels comparable to those of wild-type mice.[E31,E32]

Antiproliferative effects (human breast cancer cells, renal cell carcinoma, B-All) as well as promotion of proliferation by inhibition of T_H1-type tumor rejection via the STAT6 pathway were reported for IL-13. Thus, blocking or antagonizing IL-13 or targeting of IL-13Rα1–expressing cells may serve as a promising anticancer immunotherapy.[E33,E34] However, a detailed understanding of IL-13 in case of malignancies is needed.

Functions as demonstrated in IL-13–deficient mice, receptor-deficient mice, and transgenic models

IL-13–deficient mice produce reduced levels of IL-4, IL-5, IL-10, and IgE. They are unable to expel *N brasiliensis*. Moreover, IL-13^{-/-} mice fail to mount a profound goblet cell hyperplasia, although IL-4–producing and IL-5–producing cells are present. Mast cell cytokine production is unaffected in KO mice on stimulation with PMA and ionomycin.[E31,E32] Interestingly, IgE levels do not change in IL-13–deficient mice.

Recently, IL-13Rα1–deficient mice were generated.[E35,E36] Mice were healthy and showed no fundamental changes in the lymphocyte compartment. IL-13Rα1^{-/-} mice do not develop airway hyperreactivity and mucus hypersecretion, whereas soluble IL-13Rα2 and IL-13 were upregulated.[E35] Surprisingly, the percentage of CD4^{+} T_H2 cells was reported to be significantly higher on *S mansoni* infection in IL-13Rα1^{-/-} mice.[E36] In addition, significantly less hepatic fibrosis and a modestly increased frequency of eosinophils in granuloma related to a higher IL-5 production were reported.

TGF-β has been linked to IL-13–related fibrosis. TGF-ß1 and MMP-9 were increased in IL-13Rα1^{-/-} mice when challenged with *Schistosoma* antigen.[E36] Thus, IL-4R complex II seems to be involved in the activation of fibroblasts and epithelial cells. Moreover, IL-13Rα1 KO mice had lower[E36] or nondetectable[E35] serum IgE levels without any changes of other immunoglobulin titers.

Specific overexpression of IL-13 in the lung leads to typical features of asthma including pulmonary eosinophilia, airway epithelial hyperplasia, mucous cell metaplasia, subepithelial fibrosis, Charcot-Leyden–like crystals, airway obstruction, and nonspecific airway hyperresponsiveness to cholinergic stimulation.[E37]

IL-14

The alternative name is high-molecular-weight BCGF.

Discovery and structure

Several years ago, IL-14 was originally discovered as a high-molecular-weight BCGF with a molecular size of 60 kd,[E38] which differs from the human low-molecular-weight BCGF. Human IL-14 is a member of BCGF family including IL-2, IL-4, IFN-α, IFN-β, IFN-γ, TNF-α, and low-molecular-weight BCGF. There is evidence that IL-14 is eventually a precursor for the low-molecular-weight BCGF, which has a molecular weight of 12 to 14 kd.[E39] The human IL-14 gene maps on chromosome 1p34-6; the murine IL-14 gene is located on chromosome 4. Two transcripts are produced from opposite strands of the IL-14 gene, termed IL-14a and IL-14b.[E40]

Cloning of IL-14 cDNA revealed a 53-kd protein composed of 498 amino acids including a signal peptide of 15 amino acids and 3 potential N-linked glycosylation sites. The sequence is rich in cysteines.[E41] Concerning the sequence, no homology to other ILs and cytokines has been observed, and its 3-dimensional structure has not been solved.

Receptor and signaling

IL-14 binds to a 90-kd receptor, identified by using a mAb (BA5). This mAb recognizes a binding site for IL-14 on solubilized membranes of activated B cells. A high correlation between the expression of the receptor and capacity of the cells to react on stimulation was seen. The expression of IL-14R is very low on resting normal tonsillary or peripheral blood B lymphocytes (50-350 IL-14R/cell), hence these cells do not respond efficiently to IL-14, whereas activated normal tonsillary or peripheral blood B lymphocytes express much more IL-14R ($1\text{-}5 \times 10^4$ IL-14R/cell) and proliferate in the presence of IL-14.[E42] However, it is still unknown in which stage of human B-cell ontogeny the B-cell lineage cells express the receptor and are able to respond to IL-14 stimuli.

Cellular sources and targets

IL-14 has been identified in normal T cells, T-cell clones, and B-lineage and T-lineage lymphoma cell lines.[E39,E43-E45]

Role in immune regulation and cellular network

It was found that IL-14 inhibits the immunoglobulin secretion of activated B cells, but the mechanism is still poorly understood.[E46] Furthermore, IL-14 stimulates B-cell precursor acute lymphoblastic leukemia cells, hairy cell leukemia cells, prolymphocytic leukemia cells, and chronic lymphocytic leukemia cells.[E38,E43,E47] The complement component, factor B, related antigenically to IL-14, is also a mitogenic factor for B lymphocytes and competes with IL-14 for binding to the B-cell membrane.[E48] A recent study showed production of IL-14 by aggressive intermediate lymphomas of B-cell–type non-Hodgkin lymphoma in human beings. These cells express IL-14mRNA, secrete IL-14, and proliferate in response to IL-14. Because exogenous IL-14 causes proliferation of B-cell–type non-Hodgkin lymphoma cells *in vitro* as well, it is suggested that IL-14 acts in an autocrine and a paracrine manner.[E47]

Functions as demonstrated in IL-14 transgenic mice

Data from a recent study with IL-14a transgenic mice stress a role for IL-14a in the development of autoimmunity and lymphoma genesis. Two distinct transcripts are produced from opposite strands of the IL-14 gene, designated IL-14a and IL-14b.

Increased expression of IL-14a in transgenic mice results in a phenotype that is very similar to this from SLE and Sjögren syndrome. The changes in the transgenic mice include hypergammaglobulinemia where IgG, IgA, and IgM autoantibodies are detectable. Immunoglobulins were also found in the kidney, and an increased number of lymphocytes was observed in the salivary glands of these mice. The peritoneal cavities of the transgenic mice are more infiltrated with B1 cells. Mice vaccinated with T-dependent and T-independent antigens show a stronger immune response than wild-type mice. B-cell malignancies (CD5+ B-cell lymphoma) similar to those observed in patients with SLE and Sjögren syndrome appear in aged IL-14a transgenic mice.[E40,E49] Further, in peripheral blood of patients with primary and secondary Sjögren syndrome, high levels of IL-14a are expressed.[E49]

IL-15
Discovery and structure
IL-15 was discovered by its ability to mimic IL-2–mediated T-cell proliferation.[E50,E51] Many of the biological actions attributed to IL-2 can also be induced by IL-15. However, there are important *in vivo* differences in the actions of these 2 cytokines. IL-15 is a monomer of 14 to 15 kd and consists of 114 amino acids. It is a member of the 4 α-helix bundle cytokine family. These family members are characterized by antiparallel juxtaposed helices A, C, B, D, and 2 long end-to-end loops, loops AB and CD, which are connected by a short **β**-sheet packed against helices B and D.[E52]

Receptor and signaling
The IL-15R consists of 3 subunits, IL-15Rα chain, IL-2Rβ chain (CD122), and the common γc (CD132).[E51,E53] Only the IL-15Rα subunit is unique to IL-15. IL-2Rβ is also a receptor for IL-2, and the common γc is shared by IL-2, IL-4, IL-7, IL-9, and IL-21. The IL-2Rα consists of 2 sushi domains, whereas the IL-15Rα contains only 1. These domains are structurally different from other cytokine receptors. Both IL-2Rα and IL-15Rα use their sushi domains for ligand binding. The biological activities of IL-15 are mediated through Jak-STAT signal transduction pathways and are remarkably similar to those of IL-2.

Cellular sources and targets
IL-15 is produced by nonimmune cells (keratinocytes, skeletal muscle cells) and immune cells (monocytes and activated CD4+ T cells) in response to viral infections, LPS, and other signals that trigger innate immunity. Target cells include T, NK, and NKT cells.

Role in immune regulation and cellular networks
Although IL-15 shares some functions with IL-2, such as T-cell activation, stimulation of NK cell proliferation, and induction of NK cytolytic activity, differences in their biological function have been clearly identified. IL-15 is important for CD8+ memory cell, NK-cell, and NKT-cell homeostasis and is necessary for the development/differentiation of γ/δ T cells.[E54-E56] Furthermore, IL-15 suppresses IL-2–induced AICD of T cells.[E57]

Role in host defense or other immune-regulatory conditions (autoimmunity)
IL-15 plays a role in the defense against microorganisms and tumors. Because IL-15 is produced in response to viral infection, its stimulation of NK proliferation occurs in the first few days after infection. IL-15 is believed to be equivalent of IL-2 in the early innate immune response.

Increased levels of IL-15 have been reported in various autoimmune diseases, such as RA, IBDs, inflammatory synovitis, psoriasis, diabetes mellitus, asthma bronchiale, IBD, autoimmune vasculitis, and SLE.[E58]

Role in allergic disease
IL-15 enhances the differentiation into T_H2 cells. Furthermore, it has been shown recently that endogenous IL-15 plays an important role in the suppression of allergic rhinitis at the effector phase.[E59]

Functions as demonstrated in IL-15–deleted mice, receptor-deficient mice, human mutations, and clinical use
KO/transgenic mice. IL-15 and IL-15Rα KO mice show a reduced number of NK cells, NKT cells, and CD8+ T cells and almost a total lack of memory phenotype CD8+ T cells, showing that IL-15 is important in the development and homeostasis for NK cells and naive and memory CD8+ T cells.[E55,E56] In vesicular stomatitis virus and lymphocytic choriomeningitis virus infection models, IL-15 has been shown to be critical in the generation and expansion of virus-specific effector CD8+ T-cell clones.[E60,E61]

Transgenic expression of IL-15 increased CD8+ T-cell numbers, IL-2–induced AICD was inhibited,[E57] and overexpression of a modified stable form of IL-15 mRNA caused CD8+ T-cell lymphomas.[E62] The overexpression of IL-15 in a mouse model of asthma inhibited allergic inflammation. It also increased antigen-driven memory CD8+ T cells after microbe exposure.[E63,E64] Furthermore, using IL-15 transgenic mice showed the importance of IL-15 in the elimination of colon carcinoma cells. Whereas wild-type mice were found to die with pulmonary metastases by 40 days after intravenous infusion of the carcinoma cells, IL-15 transgenic mice with large quantities of IL-15 did not develop such metastases and survived.[E65]

Human mutations. Human beings with a mutation in the common γc (as mentioned, this includes defect signaling of IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) have XSCID1, a disease characterized by the absence of T and NK cells but the presence of nonfunctional B cells.

Clinical use. In several studies, it has been shown that aberrant expression of IL-15 is associated with the pathogenesis of various autoimmune diseases; therefore, the use of IL-15 antibody may play a role in the future in the treatment of these diseases.[E66,E67]

IL-16
Discovery and structure
IL-16 was discovered in 1982 as a T-cell–specific chemoattractant secreted from PBMCs and was therefore named *lymphocyte chemoattractant factor*.[E68] The gene for IL-16 is localized on chromosome 15q26.1-3, and Northern blot analysis identified 2 transcripts of IL-16 mRNA which are deriving from alternative splicing. The IL-16 promoter is TATA-less but contains 2 CAAT boxlike motifs and 3 GA protein transcription factor binding sites. After translation, the 80-kd precursor protein pro–IL-16 is cleaved by caspase 3 at Ser511,[E69] resulting in an N-terminal and a C-terminal domain.[E70] The 60-kd N-terminal domain is made up of 2 PDZ domains that mediate protein-protein

interactions by binding to other PDZ domains or to the C-terminus of a certain target protein in a sequence-specific fashion. A dual phosphorylation-regulated nuclear translocation sequence drives the protein to the nucleus, where it is able to regulate the cell cycle. The shorter C-terminal fragment has a molecular weight of 14 to 17 kd. It consists of 6 β-sheets and a PDZ domain for the formation of homotetramers (56 kd), thought to form biologically active IL-16 molecules that mediate cytokine function.[E71] IL-16 is an atypical IL because it lacks the classic structural motifs present in either ILs or chemokines.

Cellular sources and targets

IL-16 is mainly produced by lymphatic tissues including T cells, eosinophils, mast cells, monocytes, and DCs, but also by fibroblasts, epithelial cells, or synoviocytes under pathological conditions. IL-16 mRNA and pro–IL-16 are constitutively expressed in immune cells, whereas nonimmune cells such as epithelial cells have to be induced to transcribe IL-16 mRNA. The generation of mature IL-16 is regulated by the activity of caspase 3. Only CD8^{+} T cells constitutively express active caspase 3, and cleaved IL-16 homotetramers are stored in cytoplasmic lipid bodies. On stimulation of the CD8^{+} T cells with antigen, histamine, serotonin, or GM-CSF, a preformed protein is rapidly released within 1 to 4 hours. In contrast, CD4^{+} T cells, eosinophils, mast cells, and DCs depend on stimulation with antigen, IL-4, GM-CSF, IL-1β, or TGF-β to activate caspase 3 and generate bioactive IL-16, taking up to 24 hours until IL-16 is released.[E72,E73] Like IL-1, IL-16 does not display a signal peptide mediating secretion, and ongoing work is investigating the secretory pathway. The targets of IL-16 include all CD4-expressing cell types.

Receptor and signaling

IL-16 was shown to mediate its biological activity via CD4.[E71] First, recombinant IL-16 binds to recombinant soluble CD4 in solution and can be purified by affinity chromatography using immobilized CD4. Second, monomeric Fab of anti-CD4 antibody (anti-OKT4 mAb) specifically inhibits IL-16–induced functions. The binding site for IL-16 was found to be distant from the MHC class II and HIV-1 gp120 binding regions. Third, the chemoattractant activity of IL-16 for CD4^{+} monocytes directly correlates with the amount of cell surface–expressed CD4. Moreover, transfection of human CD4 into IL-16–nonresponsive mouse T-cell hybridoma cells leads to the activation of signaling cascades and migration on IL-16 stimulation.

CD4 is constitutively expressed on CD4^{+} T cells, on CD8^{+} T cells after anti-CD3 and anti-CD28 stimulation, and on monocytes, macrophages, DCs, eosinophils, and mast cells. Binding of tetrameric IL-16 leads to cross-linking of CD4 and the activation of src-related kinase p56lck, which is associated with the intracellular domain of CD4.[E74] However, the kinase activity of p65lck is not required for CD4-mediated motile response, but p65lck is supposed to recruit further signaling molecules via its SH2 and SH3 domains. The activation of protein kinase C[E75] and its translocation from the cytosol to the cell membrane, together with the activation of PI3K, increased intracellular Ca2^{+}, and inositol(1,4,5)-triphosphate and provide the link to the cytoskeleton for the motile response.

KO experiments indicate that another molecule may substitute for CD4 in transmitting IL-16–induced signaling. The chemokine receptor CCR5 is constitutively linked with CD4 in plasma cell membranes, and soluble CCR and CD4 associate *in vitro*.[E76] Studies using T cells from CCR5-deficient mice demonstrate that the presence of CCR5 significantly increases binding of IL-16 to the cell surface and migration of T cells.[E77] Signaling of IL-16 via CD4 leads to reciprocal desensitization of CCR5 and loss of MIP-1β/CCR5–induced chemotaxis,[E78] suggesting that the functions of the chemokine receptor CCR5 and CD4 are intimately connected. However, the precise physiological role of CCR5 in IL-16–induced signaling remains unknown.

In mast cells lacking CD4, the IL-16–mediated effects were shown to depend on the tetraspannin CD9 because CD9-specific antisense oligonucleotides or anti-CD9 mAbs block the binding of IL-16 to the cell, Ca2^{+} mobilization, and their chemotactic response.[E79]

Role in immune regulation and cellular networks

IL-16 serves as a chemoattractant for CD4^{+} T cells mainly, but also for CD8^{+} T cells, monocytes, mast cells, and eosinophils.[E68] Among the CD4^{+} T cells, IL-16 preferentially induces migration of T_H1 cells[E77] and FOXP3^{+} Treg cells.[E80] Moreover, it facilitates *de novo* production of FOXP3^{+} Treg cells *in vitro*.

IL-16–induced chemotaxis is accompanied by the expression of HLA-DR on monocytes, by increased adhesion of eosinophils to the extracellular matrix, and by the expression of the IL-2Rα subunit (CD25), leading to proliferation in the presence of IL-2. Although IL-16 does not induce the synthesis of IL-2, the proinflammatory cytokines TNF-α, IL-1β, and IL-15 are released from T cells on IL-16 stimulation. At the same time, the synthesis of the T_H2-specific cytokines IL-4 and IL-5 is inhibited without affecting the release of IFN-γ or IL-10.[E81] Thus, IL-16 contributes to T_H1-mediated responses and dampens T_H2-mediated inflammation.

In addition, it was shown that binding of IL-16 to CD4 inhibits T-cell proliferation induced by antigen, anti-CD3 antibodies, or mixed lymphocyte reactions.[E82] This means that IL-16 renders T cells refractory to antigen-specific activation, but favors the recruitment of nonclonotypic T cells and antigen-independent inflammation. It remains to be elucidated whether this transient inhibition of responsiveness via the CD3/TCR complex is a result of a negative signal delivered by CD4 or whether IL-16 binding sterically inhibits the association of CD4 and the CD3/TCR complex.

Pro–IL-16, the precursor of secreted IL-16, was found to have a nuclear function independent of its role as a cytokine precursor. In resting T cells, pro–IL-16 translocates into the nucleus and recruits histone deacetylase 3 to block gene transcription, resulting in G0/G1 cell cycle arrest. On activation of the cells, the levels of pro–IL-16 decline and the transcription repressor complex dissociates, leading to cell cycle progression and proliferation.[E83,E84]

Role in allergic disease and other pathologic conditions

IL-16 is associated with exacerbations of various immune-mediated, autoimmune, and infectious inflammatory disorders. For instance, patients with allergic asthma show increased secretion of IL-16 from mast cells, epithelial cells, or T cells on antigen challenge.[E85] Although the levels of IL-16 in the airways were found to correlate with the infiltration of CD4^{+} T cells, several studies indicate that IL-16 does not play a negative role in

asthma but rather downregulates the allergic response by altering the ratio of T_H1/T_H2 cells. In a murine model of allergic asthma, the administration of exogenous IL-16 during allergen challenge decreases histologic and physiological markers of allergic airway inflammation. Airway hyperreactivity was inhibited, accompanied by reduced numbers of eosinophils in BAL. Lymph node cells from IL-16–treated mice produced near baseline levels of IL-4 and IL-5 on *ex vivo* antigen stimulation.[E81] In human beings with asthma, IL-16 is secreted by airway epithelial cells and subepithelial T cells and can be detected in the BAL after allergen or histamine bronchoprovocation. In line with the murine model of allergic asthma, PBMCs from individuals with ragweed allergy released less IL-5 in the presence of IL-16, whereas the level of IFN-γ increased after antigen stimulation.[E86,E87] Moreover, IL-16 reduces the expression of the Cε transcript and the secretion of IgE in stimulated PBMCs from atopic individuals.[E88] Thus IL-16 is supposed to be a natural modulator of allergic inflammation in the lung, providing opportunities for further investigations and for the potential use of IL-16 or IL-16–derived compounds in the treatment of allergic asthma.

Patients with atopic dermatitis, Crohn disease, SLE, or RA have elevated levels of IL-16 in skin, colonic biopsies, sera, or synovial fluids, leading to influx of immune cells into the skin, the colonic mucosa, or the synovial membranes and articular structures of multiple joints.[E89-E92] The observed levels of IL-16 were found to correlate directly with the numbers of infiltrating $CD4^+$ cells.

Moreover, the TT genotype of a described SNP in the IL-16 promoter region (-295 T-to-C) is frequently observed in patients with Crohn disease and is supposed to be responsible for increased IL-16 levels in these patients relative to healthy controls.[E93] Because IL-16 is supposed to exacerbate the mucosal inflammation in Crohn disease by promoting the infiltration of $CD4^+$ T cells, treatment of mice with anti–IL-16 mAb substantially attenuates colonic injury and inflammation induced in a mouse model of colitis.[E90]

Interestingly, IL-16 is also detectable in the central nervous system and markedly increased in MS lesions compared with the healthy tissue.[E94] During experimental autoimmune encephalomyelitis in mice, which resembles the immunopathology of MS, the levels of IL-16 in the central nervous system correlate with the extent of $CD4^+$ T-cell infiltrations and disease severity.[E95] Treatment of paralyzed mice with neutralizing anti–IL-16 mAb ameliorated the relapsing disease, diminished the $CD4^+$ T-cell infiltrations, and reduced axon demyelination.

During HIV infections, IL-16 was shown to suppress viral replication.[E96] Although HIV-1 envelope glycoprotein gp120 and IL-16 share the CD4 receptor, no steric inhibition of viral binding was observed. In contrast, binding of CD4 by IL-16 induces a repressor of HIV promoter activity, resulting in inhibition of Tat and PMA-induced HIV transcription.

Functions as demonstrated in IL-16–deleted mice, receptor-deficient mice

Cells from CD4-deficient mice are as responsive to IL-16 as cells from wild-type animals, indicating that CD4 is not necessarily required for IL-16 function, and another molecule may substitute for CD4 in transmitting IL-16–induced signaling[E97]:

CCR5 is supposed to substitute for CD4 in transmitting IL-16–induced signaling because studies using T cells from CCR5-deficient mice show reduced binding of IL-16 to the cell surface and diminished T-cell migration.

IL-17A
Discovery and structure

The cDNA encoding IL-17A, initially named *cytotoxic T-lymphocyte–associated 8*, was first identified by screening a cDNA library from murine cytotoxic T-lymphocyte (CTL) hybridomas.[E98] It exhibited 57% identity to a predicted open-reading frame, herpes simplex virus13, in the T-lymphotropic herpesvirus *Herpesvirus samiri*.[E99] The gene was cloned and used to search for a receptor binding to cytotoxic T-lymphocyte–associated 8. Thereafter, viral and mammalian homologs were renamed IL-17, and the receptor was termed IL-17R. Subsequently, 5 homologous cytokines have been identified, and IL-17, as the founding member of this new cytokine family, has been designated IL-17A. Structurally, the IL-17 family represents a distinct cytokine family with no sequence similarity to any other known cytokines or proteins. The C-termini of all IL-17 family members are conserved and contain 4 cysteines that account for a characteristic structure, called the *cysteine knot*.[E100] IL-17A is a glycoprotein consisting of 155 amino acids and acts as a disulfide-linked homodimer with a molecular weight of 35 kd.[E99] Heterodimers of IL-17A and IL-17F also exist.[E101] Human IL-17A shares significant structural homology as well as glycosylation sites with both mouse and rat IL-17A.[E102]

Receptor and signaling

Similar to the cytokines, the IL-17 receptors form a unique family,[E99] suggesting that IL-17 cytokines and receptors represent a distinct signaling system. In addition to the initially identified IL-17R, also named IL-17AR, 4 members have been found on the basis of their sequence homology and have been termed IL-17RB, IL-17RC, IL-17RD, and IL-17RE. Although they share only limited sequence similarity, they are all predicted to be type I transmembrane proteins with long intracellular tails. Interestingly, alternative splicing of the receptors IL-17RB and IL-17RC introduces stop codons leading to secreted soluble proteins.[E103,E104] IL-17RA consists of a 293–amino acid long extracellular domain, a 21–amino acid long transmembrane domain, and a 525–amino acid long cytoplasmic tail.[E99] It binds to IL-17A and to IL-17F, although with a 10-fold lower affinity to the latter.[E100] As described for all other known cytokine receptors, IL-17RA is apparently expressed as a preformed multimeric complex before ligand binding.[E105] Binding of IL-17A or IL-17F to this complex leads to a conformational change followed by the dissociation of the intracellular domains. It has also been suggested that another member of the receptor family, IL-17RC, contributes to effective binding of IL-17A.[E106] The signaling cascade downstream from the receptors involves MAPKs[E107] as well as NF-κB and PI3K-Akt pathways.[E108] NF-κB activator 1 binds to the cytoplasmic tail of IL-17RA and thereby acts as a critical adaptor for IL-17RA signaling.[E109,E110]

Cellular sources and targets

IL-17 cytokine family members appear to come from very distinct cellular sources. IL-17A was originally found to be expressed by activated memory $CD4^+$ T cells.[E99] Analysis of various T-cell clones revealed that IL-17–producing T cells cannot be classified into T_H1 or T_H2 subsets but rather represent a distinct

cell population.[E111] Some years later, further evidence for a distinct IL-17 secreting effector cell lineage has been provided, and this new subset has been named T$_H$17.[E112,E113] However, expression of IL-17A has also been detected in CD8$^+$ T cells, γδ T cells, NK cells, and neutrophils.[E114-E116]

mRNA encoding the IL-17RA can be found in various tissues like lungs, spleen, kidney, and liver.[E99] On a cellular level, it is detected in fibroblasts, epithelial cells, vascular endothelial cells, B and T lymphocytes, myelomonocytic cells, and marrow stromal cells.[E102,E117] Expression of the IL-17RC, which is apparently also involved in IL-17A binding, is found in human prostate, cartilage, kidney, liver, heart, and muscle.[E104]

Role in immune regulation and cellular networks

Given the broad expression pattern of its receptor, it is not surprising that IL-17A acts on a large variety of cells. IL-17A was initially found to induce IL-6 and IL-8 (CXCL8) potently in fibroblasts.[E99,E118] Subsequently, the induction of further CXC-chemokines like CXCL1 (Gro-α), CXCL6, CXCL10, and CINC by IL-17A in different cells has been reported.[E119-E122] Tissue fibroblasts and bronchial epithelial cells release IL-6 and IL-11 on stimulation by IL-17A,[E123] whereas certain monocytes respond by secreting TNF-α and IL-1β.[E124] Furthermore, IL-17A has been shown to induce colony-stimulating factors like GM-CSF and G-CSF, the MCP1, and metalloproteases.[E122,E125-E127] In accordance with induction of these factors, IL-17A has a high potential in the recruitment and activation of neutrophils.[E128]

Role in host defense or other immune-regulatory conditions

IL-17A's role in neutrophil recruitment is crucial for host protection against various extracellular pathogens, as shown in several *in vivo* infection studies. IL-17A signaling plays an important role in the defense of certain bacteria like *Klebsiella pneumoniae*,[E129] *Toxoplasma gondii*,[E130] and *Porphyromonas gingivalis*,[E131] but also in infections by *Candida albicans*.[E132] Furthermore, it plays an important role in neutrophil attraction and abscess formation on *Bacteroides fragilis* infection.[E133]

Besides these important roles in host defense, IL-17A is involved in several inflammatory disorders. Psoriasis, a chronic inflammatory disease of the skin, was initially suggested to be a T$_H$1-dominated disease because of the high expression of IFN-γ, IL-2, IL-18, and the p40 subunit of IL-12. However, levels of IL-17A and other T$_H$17 cytokines are also increased in serum and skin of patients with psoriasis.[E134] Consistently, IL-23, which induces IL-17A and shares the p40 subunit with IL-12, seems to play a role in the pathogenesis of psoriasis,[E135] suggesting a contribution of T$_H$17 cells to the disease. However, although it is known that IL-17A induces antimicrobial peptides and matrix metalloproteases that are commonly found in psoriatic skin,[E136,E137] the exact role of IL-17A in psoriasis awaits further elucidation.

Clearer is the situation in RA, an autoimmune disease characterized by chronic inflammation of synovial tissue in several joints, accompanied by destruction of bone and cartilage. Similar to psoriasis, RA and collagen-induced arthritis (CIA), a mouse model for RA, were thought to be T$_H$1-dominated, because mice deficient in the IL-12 subunit p40 were resistant to CIA. It then became clear that IL-23, which also consists of the p40 subunit, is responsible for the disease, rather than IL-12. Increased levels of IL-17A have been found in sera, synovial fluid, and in the T-cell–rich area of the synovium in patients with RA,[E138,E139] and these levels are predictive of a more severe joint damage progression.[E140] Furthermore, IL-17RA is required for full progression of destructive synovitis.[E141] Therefore, besides the enhancement of inflammation commonly observed in arthritis, IL-17A also mediates bone and cartilage destruction.

Although elevated levels of IL-17A mRNA have been found in blood and cerebrospinal fluid of patients with MS,[E142] very few studies have investigated the role of IL-17A in this disease. Evidence for a function of IL-17A in MS comes from studies using the mouse model EAE. Although previously it was considered to be a T$_H$1 disease, it became apparent that IL-17A–producing cells are sufficient to induce EAE on adoptive transfer into susceptible mice.[E143] In the human disease MS, recent data suggest that IL-17A disrupt the blood-brain barrier, thereby promoting inflammation of the central nervous system.[E144] Apparently, more work is needed to characterize all effects of IL-17A in this disease.

An involvement of IL-17A becomes apparent in IBD, specifically in Crohn disease and ulcerative colitis, because biopsies from inflamed colonic tissue of patients with IBD showed increased levels of IL-17A.[E145] Because IL-17A stimulates production of MMPs and the release of proinflammatory cytokines in colonic subepithelial myofibroblasts,[E146] it strongly contributes to the chronic inflammation characteristic for this disease. In addition, IL-17A inhibits the proliferation of intestinal epithelial cells (IECs),[E147] suggesting that it might interfere with the repair mechanism important for the maintenance of the tissue integrity.

Role in allergic disease

Increased levels of IL-17A have also been found in patients with asthma.[E123,E148] This increase may explain the high numbers of neutrophilic granulocytes in allergic airways.[E120,E149] IL-17A has also been described to induce expression of 2 mucin genes, MUC5AC and MUC5B, contributing to mucus hypersecretion.[E150] IL-17A might have a role in airway remodeling, a feature commonly observed in severe asthma, because it was shown to induce the profibrotic cytokines IL-6 and IL-11.[E151] Therefore, evidence suggests an involvement of IL-17A in chronic inflammation and irreversible changes in asthmatic airways, although further investigations are needed in this area.

In addition, IL-17A production is commonly observed in skin inflammation. Nickel-specific IL-17A–secreting T cells have been described in human keratinocytes,[E152] and neutralization of IL-17A ameliorated contact hypersensitivity in a mouse model.[E153] Furthermore, emerging evidence suggest that IL-17A is involved in the pathogenesis of atopic dermatitis, where IL-17A is expressed preferentially in acute lesions.[E154]

Functions as demonstrated in IL-17A–deleted mice and receptor-deficient mice

Initial studies investigating IL-17A KO mice suggest an important role for IL-17A in allergen-specific T-cell–mediated immune responses, because airway hypersensitivity responses as well as T-cell–dependent antibody production were significantly reduced in these mice.[E155] More recent studies showed that, in line with IL-17A's role in host defense, IL-17RA–deficient mice have a markedly reduced survival after pulmonary *K pneumoniae* infection, accompanied by a reduced number of neutrophils in the lung.[E129] These mice were also more susceptible to *T gondii*,[E130] *C albicans*,[E132] and *P gingivalis*[E131] infections.

IL-17A KO mice develop significantly less arthritis,[E156] and IL-17RA is required for full progression of destructive synovitis,[E141] indicating a function of IL-17A in RA. Similarly, IL-17A plays a role in EAE, because adoptive transfer of T_H1 lines into IL-17A–deficient mice lead to reduced EAE clinical outcomes.[E157]

Another study suggests a role for IL-17A signaling in hematopoiesis after radiation, because hemopoietic toxicity is significantly more pronounced in IL-17RA KO mice when challenged with γ-irradiation.[E158] However, it should be kept in mind that IL-17RA also binds to IL-17F. Effects observed in IL-17RA–deficient mice can therefore be a result of defective signaling of IL-17A or IL-17F or even both.

IL-17B
Discovery and structure

IL-17B has been identified on the basis of its sequence homology to IL-17A.[E159,E160] With 29% homology, it is less related to IL-17A than IL-17F, but more than the other family members. Human IL-17B shares 88% homology with mouse IL-17B, and it is localized to the human chromosome 5q32-34. IL-17B is a glycoprotein of 180 amino acids in length, giving rise to a molecular weight of 41 kd. Like the other IL-17 family members, it bears 4 cysteines in its C-terminus that account for a characteristic structure called the cysteine knot.[E100] This cysteine knot is a common structural motif found in many growth factors such as bone morphogenetic proteins, TGF-β, or nerve growth factor. However, the knot in these proteins is formed by 6 cysteines compared with 4 cysteines found in IL-17 family members. Interestingly, whereas the subunits of IL-17A, IL-17C, IL-17D, IL-17E, and IL-17F are covalently linked by a disulfide bond in the dimeric structure, IL-17B dimers are noncovalently linked.

Receptor and signaling

The receptor for IL-17B, IL-17RB (also named IL-17RH1, evi27, or IL-25R), has been identified by sequence homology to the IL-17RA.[E159] IL-17RB is 426 amino acids in length and, surprisingly, lacks the long cytoplasmic tail observed in its homolog IL-17RA. Receptor binding revealed that IL-17B binds with relatively high affinity to IL-17RB, whereas no binding to IL-17RA was observed.[E159,E160]

Interestingly, alternative splicing of IL-17RB introduces stop codons, leading to the production of secreted soluble proteins that might act as decoy receptors.[E103,E104] It has not been demonstrated yet whether this happens *in vivo.* Later, IL-17RB was found to bind IL-17E (also termed IL-25), another IL-17 family member.[E161] The affinity of IL-17RB for this cytokine was even higher than that observed for IL-17B. Although the intracellular parts of IL-17RA and IL-17RB differ dramatically in size, they share some elements, suggesting that these receptors engage similar signaling pathways. This is supported by the finding that signaling by IL-17E through IL-17RB induces activation of NF-κB, a transcription factor also involved in IL-17RA signaling. Further studies need to be done to elucidate the exact mechanism of the signaling downstream IL-17RB.

Cellular sources and targets

In contrast with its homolog IL-17A, IL-17B does not seem to be expressed in immune cells. Instead, IL-17B was detected in spinal cord, testis, small intestines, pancreas, stomach, prostate, ovary, and colon mucosal lining.[E159,E160] Another study confirmed the high expression in spinal cord.[E162] In an analysis of human spinal cord, dorsal root ganglia, cerebral cortex, cerebellum, and hippocampus, IL-17B protein was shown to be primarily localized to the neuronal cell bodies and axons.

Other reports describe the expression of IL-17B in chondrocytes and mouse limb buds, suggesting a role for IL-17B in chondrogenesis and osteogenesis.[E102,E163] Similarly, the receptor IL-17RB is expressed in kidney, liver, pancreas, testis, colon, and small intestines, but not in lymphocytes.[E159,E161] The expression pattern of IL-17B and its receptor together with the fact that IL-17B stimulates the release of TNF-α and IL-1β from a cell line[E160] suggest IL-17B to be involved in inflammatory responses like its family member IL-17A.

Role in immune regulation and cellular networks

Compared with IL-17A and IL-17F, relatively little is known about the physiological function of IL-17B. One study describes IL-17B to be expressed in calf articular cartilage but not in adult cow cartilage, suggesting a role in cartilage development.[E163] Consistently, IL-17B mRNA was maximally expressed in the limb buds of 14.5 days postcoitus mouse embryos and declined to a low level at 19.5 days postcoitus. IL-17B expression was high in cells of the bone collar in the primary ossification center, whereas chondrocytes in the resting and proliferative zones expressed moderate levels of IL-17B. In accordance with these findings, another report identifies IL-17B expression during fracture healing, where IL-17B was localized in prehypertrophic chondrocytes of both the growth plate and the fracture callus.[E164] Therefore, IL-17B appears to be involved in embryonic chondrogenesis as well as tissue regeneration.

Role in host defense or other immune-regulatory conditions

One study addressing the mechanism of BCG treatment found that, among many other cytokines, IL-17B was induced on intravesical BCG application.[E165] Although acute BCG instillation upregulated IL-17A, IL-17B, and IL-17RA, chronic BCG also induced IL-17RB. In another report, intraperitoneal injection of IL-17B into normal mice was found to cause marked neutrophil migration in a dose-dependent manner.[E159] These findings suggest a role for IL-17B in host defense, especially in tissues in which IL-17A and IL-17F are not expressed.

The role of IL-17B in disease is not well studied yet. Given the clear involvement of IL-17A in RA together with the finding that IL-17B and IL-17RB are expressed in cartilage, it can be suspected that IL-17B is implicated in RA as well. A few studies addressed the expression of IL-17B and its receptor in patients with RA. One of them found that synovial fluid mononuclear cells (SFMCs) expressed IL-17RB.[E138] However, the expression has not been compared with levels in SFMCs from healthy individuals. Another study detects IL-17B expression in 17 of 19 nodules of patients with RA, whereas IL-17A gene expression was present in only 1 of 19 nodules.[E166] Stronger evidence for a role of IL-17B in RA comes from a report using CIA, a mouse model of RA.[E167] In this study, elevated levels of IL-17B could be observed in the arthritic paws of CIA mice. *In vitro*, IL-17B induced TNF-α production in mouse peritoneal exudate cells, whereas adoptive transfer of IL-17B transduced CD4^{+} T cells evidently exacerbated arthritis. Furthermore, IL-17B bone marrow chimeric mice exhibited elevated serum TNF-α concentration and a high arthritis

score on CIA induction, whereas neutralization of IL-17B significantly suppressed the progression of arthritis and bone destruction in CIA mice.

Because IL-17B is expressed in prostate and ovary, its role in cancer affecting these tissues has been studied. In one study, an association between the expression ratio of homeobox 13 to IL-17RB and increased relapse and death was found in patients with tamoxifen-treated breast cancer.[E168] Taken together, although evidence strongly suggests a role of IL-17B in RA, its involvement in cancer and other diseases is less clear. Further studies need to be done to elucidate the functions of IL-17B and to analyze which of these functions overlap with IL-17A and which of them are distinct.

Role in allergic disease

So far, no role for IL-17B in asthma or allergy has been described. One study found an association of IL-17RB gene polymorphism with asthma.[E169] However, given IL-17B's expression pattern, it is more likely that these effects are a result of signaling by IL-17E, a T_H2 cytokine also using IL-17RB as a receptor.

IL-17C
Discovery and structure

IL-17C has been identified on the basis of a sequence similarity search of an expressed sequence tag (EST) database, and a full-length cDNA was isolated from a human fetal kidney library.[E160] IL-17C shares 23% homology with the founding family member IL-17A and 83% homology with its murine homolog. Consisting of 197 amino acids, it is the second longest family member and has a molecular weight of 40 kd. Like the other IL-17 family members, its structure is characterized by 4 cysteines in the C-terminus that account for the so-called cysteine knot.[E100] This cysteine knot is a common structural motif found in many growth factors such as bone morphogenetic proteins, TGF-β, or nerve growth factor. However, the knot in these proteins is formed by 6 cysteines compared with 4 cysteines found in IL-17 family members. IL-17C is likely to act as a homodimer with the 2 monomers covalently linked by a disulfide bond. It has been mapped to chromosome 16q24 in human and 8E1 in mice.[E160]

Receptor and signaling

IL-17C, like IL-17B, does not bind to the IL-17RA, as shown in an immunoprecipitation experiment,[E160] and so far, no receptor for IL-17C has been identified.

Cellular sources and targets

In contrast with IL-17B, which is expressed in many tissues like spinal cord, testis, small intestines, pancreas, stomach, prostate, ovary, and colon mucosal lining, IL-17C has not been detected in these tissues.[E160] Furthermore, under these conditions, IL-17C is not detected in CD4^{+} T cells, which are a major source of IL-17A and IL-17F. However, it has been found as a rare EST in an adult prostate and fetal kidney libraries. Later reports describe expression of IL-17C under certain pathological conditions. For example, one study finds IL-17C to be expressed in arthritic paws of CIA mice.[E167] More specifically, IL-17C was expressed in CD4^{+} T cells, CD11b^{+} MHC class II^{+} macrophages, and CD11c^{+} MHC class II^{+} DCs. Consistently, expression of IL-17C has been found in SFMCs of patients with RA, but also in

PBMCs.[E138] Furthermore, IL-17C expression was found in lung tissue of mice infected with *Mycoplasma pneumoniae*.[E170] Given these discrepancies, further investigations need to be done to clarify by which cells and especially under which conditions IL-17D is expressed.

Because no receptor has been identified for IL-17C so far, the target cells on which it might act are not well known. However, IL-17C was found to bind to the surface of the monocytic cell line THP-1 and to induce IL-1β and TNF-α production in these cells, suggesting that it acts on cells of this cell line.[E160] Interestingly, although IL-17A is known to induce IL-6 production in fibroblasts, no influence of IL-17C has been observed on these cells. In a second study, IL-17C was shown to induce IL-6, IL-8, LIF, and MMP-3 secretion in human subepithelial myofibroblasts, although the effects of IL-17A and IL-17F were more pronounced.[E146] Taken together, few reports investigate cellular sources and targets, and further studies are required to elucidate this area.

Role in immune regulation and cellular networks

To date, relatively little is known about the function of IL-17C. Because IL-17C was shown to act on cells in a way similar to its better known family members, namely to induce proinflammatory cytokines like IL-1β, TNF-α, and IL-6, it can be supposed that IL-17C has functions similar to IL-17A. In particular, IL-17C might take over functions of IL-17A in tissues in which IL-17A is not expressed, or it might act on cells that do not express IL-17RA. Interestingly, IL-17C seems not to depend on IL-23 for its induction but instead induces IL-23.[E167,E170] Therefore, one could imagine a mechanism in which IL-17C upregulates IL-17A through the induction of IL-23, thereby representing a potent inducer of a proinflammatory cascade. Further investigations are needed to elucidate these complex but interesting and important events.

Role in host defense or other immune-regulatory conditions

A report showing an upregulation of IL-17C in mice infected with *M pneumoniae* suggests a role for IL-17C in host defense.[E170] IL-17C was increased not only in BAL fluid but also in lung tissue of infected mice compared with the control. Interestingly, IL-23, a strong regulator of IL-17A and IL-17F, did not have any influence on IL-17C expression, suggesting a distinct upstream regulatory pathway. It remains to be determined whether IL-17C can substitute for other family members in host defense—for example, by attracting granulocytes—and whether it has distinct functions.

Although only a few studies addressed the role of IL-17C in disease, there is some evidence for involvement of this cytokine in RA. Given IL-17C's potential to induce proinflammatory cytokines and metalloproteases, this is not surprising. One study finds expression of IL-17C in SFMCs of patients with RA, but also in PBMCs.[E138] Interestingly, although IL-15 decreased the levels of IL-17C in normal PBMCs, IL-17C was clearly upregulated by IL-15 in SFMCs and PBMCs of patients with RA. Similarly, a study investigating nodules of patients with RA found IL-17C expression in 18 of 19 nodules, whereas IL-17A was present in only 1 nodule.[E166] Because tissue destruction in the nodules was also observed in the absence of IL-17A, and because IL-17C is known to induce MMP-3 secretion in certain cells, it might be that IL-17C accounts for the destruction of the nodule tissue. However,

further experiments need to be performed to confirm this hypothesis.

The role of IL-17C has also been addressed by using CIA, a mouse model of RA. IL-17C expression was found to be elevated in the arthritic paws of CIA mice, specifically in CD4^{+} T cells, CD11b^{+} MHC class II^{+} macrophages, and CD11c^{+} MHC class II^{+} DCs.[E167] In this study, IL-17C induced IL-1β in the fibroblast cell line *3T3* and IL-1β and IL-23 expression in peritoneal exudate cells. Although these results are a hint for an involvement of IL-17C in RA, stronger evidence comes from an experiment in which IL-17C–transduced CD4^{+} T cells were adoptively transferred before the onset of arthritis. In the recipients, an exacerbation of arthritis was observed, strongly suggesting a role for IL-17C in the disease. Moreover, bone marrow chimeric mice of IL-17C exhibited elevated serum TNF-α concentration and a high arthritis score on CIA induction. In addition, higher levels of IL-23 and IL-6 could be found in the spleen of these mice. In summary, these reports suggest a role of IL-17C in RA, as is observed for the better known family member IL-17A.

Role in allergic disease

IL-17A and IL-17F seem to contribute to allergic disease by attracting neutrophils to the inflamed airways. One study addressed the question of whether a similar role could be attributed to IL-17C. Indeed, adenoviral administration of IL-17C induced neutrophilia in the BAL of treated mice.[E171] Because IL-17C expression was found in lung tissue of mice infected with *M pneumoniae*,[E170] it might contribute to the attraction of neutrophils in asthma as well. It remains to be elucidated whether IL-17C is also found in human lungs and, if so, under which conditions.

Taken together, although relatively few reports investigated the role of IL-17C in disease, there is a strong potential for this cytokine in several disorders.

IL-17D
Discovery and structure

IL-17D was identified and cloned on the basis of its homology to the other IL-17 family members.[E172] With a length of 202 amino acids and a molecular weight of 52 kd, it is the largest IL-17 family member. IL-17D shares 25% homology with the founding family member IL-17A, and with 27% identity, it is most homologous to IL-17B. Seventy-eight percent homology is found between human and mouse IL-17D. As is commonly observed for IL-17 family members, IL-17D has 4 cysteine residues that may participate in interchain disulfide linkages. It probably exists as a homodimer with the 2 monomers covalently linked by a disulfide bridge. Unlike other members of the IL-17 family, IL-17D shows an extended C-terminal domain, which may mediate a unique receptor interaction. IL-17D was mapped to chromosome 13p11, a region that has been linked to translocations found in Hodgkin lymphoma.

IL-17D is the most evolutionary conserved member because 4 divergent fish species share significant sequence identity and synteny with mouse and human IL-17D genes. In lamprey (*Lethenteron japonicum*), for example, a single IL-17 gene (*LampIL-17*) has been found.[E173] This gene was most homologous to IL-17D of other species. Similarly, the IL-17 protein from pacific oyster, *Crassostrea gigas* (*CgIL-17*), was compared with other sequences, and it was found to be most similar to the

IL-17D member of other species.[E174] IL-17D genes have been identified also in rainbow trout, sea urchin, zebrafish, and pufferfish as well as in chicken and opossum.[E175,E176] Because IL-17 family members can be regulated by TGF-β and IL-1β, which are components of the innate immune system, the IL-17 family might have evolved to bridge innate and adaptive immunity.

Receptor and signaling

So far, no receptor binding to IL-17D has been identified.

Cellular sources and targets

IL-17D is highly expressed in skeletal muscle, brain, adipose tissue, heart, lung, and pancreas.[E172] Lower levels of expression were found in bone marrow, fetal liver, kidney, lymph node, placenta, spleen, thymus, tonsil, resting CD4^{+} T cells, and resting CD19^{+} B cells. Interestingly, while IL-17A and IL-17F are expressed in T cells on activation, IL-17D in contrast is poorly expressed in activated CD4^{+} T cells and activated CD19^{+} B cells. Both resting and activated CD8^{+} T cells as well as resting and activated CD14^{+} monocytes show low levels of IL-17D. The expression of IL-17D has also been analyzed in zebrafish (*Danio rerio*) and was observed in intestines and gills in both normal and LPS-stimulated tissues.[E175] Expression in noninduced conditions has not been observed for other members of the IL-17 family, indicating that IL-17D may have a unique role under normal conditions. In chicken, however, IL-17D expression was increased after *Eimeria maxima* infection in CD4^{+}, CD8^{+}, and TCR1^{+} intestinal intraepithelial lymphocytes, whereas decreased expression was seen in TCR2^{+} cells,[E176] suggesting some differences between species.

Similar to IL-17C, no receptor for IL-17D has been identified so far, although some cellular targets have been identified. Among them are myeloid progenitor cells like granulocyte/macrophage, erythroid, and granulocyte/erythroid/monocyte/megakaryocyte progenitors.[E172] Like other family members, IL-17D acts on epithelial cells and chicken fibroblasts.[E172,E176] Furthermore, IL-17D was shown to modulate human umbilical vein endothelial cells (HUVECs) and subepithelial myofibroblasts.[E146,E172] Taken together, although differences between species may exist, IL-17D seems to be expressed mainly by immune cells and to act on many different tissue cells, similar to IL-17A and IL-17F. The conditions under which IL-17D is expressed, however, appear to be different.

Role in immune regulation and cellular networks

Interestingly, IL-17D has been shown to suppress myeloid progenitor cell proliferation.[E172] At a dose of 200 ng/mL, IL-17D inhibited granulocyte/macrophage, erythroid, and granulocyte/erythroid/monocyte/ megakaryocyte progenitor colony formation by an average of 39%, 32%, and 38%, respectively. However, IL-17D did not influence the proliferation of resting normal PBMCs or CD5^{+} T cells. Like other family members, IL-17D acts on epithelial cells and stimulates them to produce IL-6 and IL-8. The same effect was also observed in chicken fibroblasts.[E176] Furthermore, in HUVECs, which normally do not produce GM-CSF, significant secretion of GM-CSF was observed on stimulation with IL-17D. IL-17D was also shown to induce IL-6, IL-8, LIF, and MMP-3 secretion in subepithelial myofibroblasts, although the effects were modest compared with IL-17A and IL-17F.[E146] Taken together, IL-17D seems to act on tissue cells in ways

similar to IL-17A and IL-17F, although under different conditions, suggesting nonoverlapping roles for these cytokines.

Role in host defense or other immune-regulatory conditions

The fact that IL-17D is evolutionary highly conserved strongly suggests an important role for this cytokine in the defense of pathogens. Indeed, the bacterial component LPS upregulates the lamprey homolog of IL-17D (*LampIL-17*) in the skin, mainly in basal layer epithelial cells.[E173] Similar observations have been made in Pacific oyster, *C gigas*.[E174] Hemocytes from oysters injected with bacteria showed a very large and rapid increase in the IL-17D homolog *CgIL-17*. The rapid induction on encountering pathogens suggests it to be a very early response gene that may be responsible for the stimulation of other immune genes in oyster. In chicken, levels of the IL-17D transcript were significantly increased in jejunum, bursa, lung, and spleen after infection with *E maxima*, the parasite causing avian coccidiosis.[E176] The greatest increase was noted in CD4^{+} intestinal intraepithelial lymphocytes. These reports support an important role for IL-17D in the defense of bacteria and parasites. It remains to be determined whether IL-17D plays a similar important role in host defense in human beings, or whether its function can be covered by other IL-17 family members that do not exist in lower species.

Because IL-17D has been shown to induce proinflammatory and granulocyte-attracting factors, it can be supposed to play a role similar to the one observed for its family members. However, only few reports addressed the function of IL-17D in disease. One of them identified IL-17D in 16 of 19 nodules of patients with RA.[E166] Interestingly, IL-17A, which has an important role in RA, was present in only 1 nodule of 19, suggesting that IL-17D might take over its job in tissues where IL-17A is not expressed. In contrast, IL-17D was not detected in synovial fluid or in PBMCs of patients with RA.[E138] Another study finds IL-17D to be increased in inflammatory cardiomyopathy, a cardiac phenotype characterized by dilation and dysfunction of the ventricles.[E177] Because IL-17D stimulates production of IL-6, IL-8, and GM-CSF in human endothelial cells, its upregulation may enhance the activation of the endothelium and contribute to the inflammation. This hypothesis, however, awaits confirmation. In a third study, IL-17D has been detected in nasal granulomas of patients with Wegener granulomatosis, a disease characterized by an inflammation of blood vessels that leads to damage in important organs of the body.[E178] The role of IL-17D in this disease is still unknown, although a contribution to the observed inflammation can be hypothesized from the functions observed in other studies. Therefore, the proinflammatory nature together with the broad expression pattern make lL-17D likely to be involved in many inflammatory disorders, acting in organs where IL-17A is not expressed. However, much work is needed to investigate this interesting and relevant issue.

Role in allergic disease

No role for IL-17D in asthma or allergy has been described.

IL-17F
Discovery and structure

IL-17F has been identified, on the basis of its sequence homology to IL-17A, as the last member of the IL-17 cytokine family so far.[E179,E180] IL-17A and IL-17F show the highest degree of homology, 50% identical on the protein level. Although the other family members are located to different chromosomes, IL-17A and IL-17F are syntenic on mouse chromosome 6, suggesting a common regulatory mechanism. Two isoforms of IL-17F have been identified, a longer and a shorter form (ML-1).[E179,E180] The crystal structure of IL-17F has been solved.[E100] It reveals that IL-17 family members adopt a monomer fold typical of cysteine knot growth factors such as TGF-β, nerve growth factor, or bone morphogenetic proteins. In contrast with these factors, in which the cysteine knot is formed by 6 cysteines, the knot in IL-17 family members consists of 4 cysteines. The structural features of IL-17F suggest that it forms homodimers, with each monomer forming a flat interface that is covalently linked by a disulfide bridge.[E100] Given the high sequence homology, it is not surprising that heterodimers consisting of an IL-17A monomer and an IL-17F monomer exist.[E101,E181,E182]

Receptor and signaling

Like IL-17A, IL-17F binds to the receptor IL-17RA, although with more than 10-fold lower affinity.[E100] IL-17RA consists of a 293–amino acid long extracellular domain, a 21–amino acid transmembrane domain, and a 525–amino acid long cytoplasmic tail.[E99] As described for all other known cytokine receptors, IL-17RA is apparently expressed as a preformed, multimeric complex before ligand binding.[E105] Binding of IL-17A or IL-17F to this complex leads to a conformational change followed by the dissociation of the intracellular domains. Both IL-17A and IL-17F have been shown to bind with high affinity to IL-17RC, another family member of the IL-17 receptors.[E183] Apparently, both IL-17RA and IL-17RC are required for efficient IL-17F signaling, at least under certain conditions.[E184] The signaling cascade downstream involves MAPKs[E107] as well as NF-κB and PI3K-Akt pathways.[E108] NF-κB activator 1 binds to the cytoplasmic tail of IL-17RA and thereby acts as a critical adaptor for IL-17RA signaling.[E109,E110] Furthermore, TNF receptor-associated factor 6-mediated ubiquitination of the receptor is critical for IL-17F signaling.[E185]

Cellular sources and targets

In accordance with the close localization of IL-17A and IL-17F on chromosome 6, there are no reports showing a discordant expression to date. Like IL-17A, both isoforms of IL-17F have been found in activated memory T cells, later defined as T$_H$17 cells.[E112] The shorter isoform has also been detected in blood basophils and mast cells, whereas the longer isoform was expressed by monocytes.[E179,E180]

The receptor for IL-17F, IL-17RA can be found in various tissues like lungs, spleen, kidney, and liver.[E99] On the cellular level, it is detected in fibroblasts, epithelial cells, vascular endothelial cells, B and T lymphocytes, myelomonocytic cells, and marrow stromal cells.[E102,E117] Expression of the IL-17RC, also important for IL-17F signaling, is found in human prostate, cartilage, kidney, liver, heart, and muscle.[E104]

Role in immune regulation and cellular networks

Like IL-17A, IL-17F acts on a large variety of cells and induces a similar panel of proinflammatory cytokines. IL-17F was shown to induce IL-6 and IL-8 in epithelial and endothelial cells and fibroblasts,[E100] but also CXC-chemokines like CXCL1 (Gro-α) and epithelial cell-derived neutrophil-activating protein 78.[E186]

Endothelial cells stimulated with IL-17F respond with increased expression of IL-2, TGF-β, and monocyte chemoattractant protein 1.[E179] Other studies report induction of MIP-1β/CCL4, IL-1β, G-CSF, GM-CSF, and IP-10.[E187-E190] The potency of IL-17A/IL-17F heterodimers in the induction of IL-6 and CXCL1 in one study demonstrating an intermediate activity for the heteromer compared with the homodimers.[E181] Therefore, similar to IL-17A, IL-17F has a highly proinflammatory and chemoattractant potential.

Role in host defense or other immune-regulatory conditions

The protective role of IL-17F against infection has not been as extensively studied as for IL-17A. However, given the high potential in the recruitment and activation of neutrophils, it can be assumed that IL-17F contributes to host defense in a similar way. This idea is supported by the observation that IL-17A and IL-17F are both induced on infection by gram-negative bacteria like *K pneumoniae*.[E191]

Given the fact that IL-17F induces a similar panel of genes, signals via the same receptor, and is induced under similar conditions as IL-17A, it can be assumed to be involved in psoriasis and RA as well. Although the role of IL-17F in disease is not extensively studied, a recent report investigated the potency of IL-17F in the induction of the neutrophil attractant chemokine IL-8 and found that IL-17F was a stronger inducer of IL-8 than IL-17A.[E192] IL-17F induced IL-8 in both human epidermal keratinocytes (HEKs) and mouse skin, where neutrophilia was also observed. Furthermore, the study identified elevated levels of IL-17F in lesional skin of patients with psoriasis, supporting a role of IL-17F in this disease. IL-17F's potency to attract neutrophils has also been shown by another report. By using an adenoviral gene transfer method, IL-17F was introduced to the mouse airways, resulting in BAL neutrophilia and inflammatory gene expression in the lung.[E171] Elevated levels of IL-17F mRNA have been detected in inflamed colonic lesions of patients with Crohn disease.[E193] Although the exact role of IL-17F in the disease is still unknown, it can be assumed to be similar to that of IL-17A, namely to contribute to the characteristic chronic inflammation and to interfere with tissue integrity. Surprisingly, a recent study shows that IL-17A, but not IL-17F, was required for the initiation of EAE, providing evidence that IL-17A and IL-17F might act differently in some situations.[E194]

Although these studies suggest an involvement for IL-17F in inflammation in diseases like psoriasis and Crohn disease, the role of IL-17F in other inflammatory disorders like RA and MS awaits further elucidation.

Role in allergic disease

Several reports support a role for IL-17F in allergic asthma. The shorter isoform of IL-17F (ML-1) was observed in allergen-specific T cells, mast cells, and basophils, and it was increased after allergen challenge in subjects with asthma, suggesting a function in allergic inflammatory responses.[E180] Further evidence comes from studies using mouse models. IL-17F was induced in bronchial epithelial cells and infiltrating inflammatory cells on challenge with ovalbumin.[E195] Pulmonary gene transfer of an IL-17F expression construct induced pulmonary neutrophilia and amplified antigen-induced allergic response.[E196] Interestingly, another study found that mice deficient in IL-17F, but not

IL-17A, had defective airway neutrophilia in response to allergen challenge.[E194] In contrast with IL-17A–deficient mice, IL-17F–deficient mice displayed enhanced T$_H$2 cytokine production and eosinophil function, suggesting a diverse effect of IL-17A and IL-17F.

Therefore, IL-17F seems to contribute to allergic disease by attracting neutrophils, a phenomenon also observed for IL-17A as well as IL-17A/IL-17F heterodimers.[E101] IL-17F has an influence on goblet cell hyperplasia and pulmonary mucus hypersecretion because it enhances mucin gene expression. The observation that TGF-β is induced by IL-17F in human endothelial cells might be a hint of an involvement in airway remodeling, commonly observed in severe asthma.

Functions as demonstrated in IL-17F–deleted mice, receptor-deficient mice, and human mutations and polymorphisms

A recent study analyzed mice deficient in IL-17F and revealed several differences between IL-17A and IL-17F.[E194] In contrast with IL-17A, IL-17F was not required for the initiation of EAE. In addition, IL-17F deficiency resulted in reduced colitis, whereas IL-17A KO mice developed more severe disease. Mice deficient in IL-17F, however, had defective airway neutrophilia in response to allergen challenge but displayed enhanced type 2 cytokine production and eosinophil function. It therefore seems that IL-17F functions differently from IL-17A, at least in certain conditions.

It should be kept in mind that IL-17F signals via IL-17RA and that effects observed in IL-17RA–deficient mice could be ascribed to functions of IL-17A, IL-17F, or both. Therefore, the increased susceptibility of IL-17RA KO mice to *K pneumoniae*, *T gondii*, *C albicans*, and *P gingivalis* infection might be, at least partially, an effect of impaired IL-17F signaling.[E129-E132]

Because IL-17F is located to a genomic region linked to asthma and asthma-related phenotypes, it has been tested for associations between SNPs and asthma.[E197] A total of 50 SNPs and 2 insertions/deletions were detected in IL-17F. Interestingly, an IL-17F sequence variant in which 1 histidine is substituted with arginine (His161Arg) is associated with protection against asthma.[E198] This variant of IL-17F lacks the ability to activate the signaling pathway and thereby antagonizes wild-type IL-17F activity. Consistent observations have been made in a study investigating the His161Arg variant in chronic fatigue syndrome, in which a lower frequency of this protective IL-17F variant was detected in patients.[E199] Association of this variant with IBD is controversially discussed. One study describes His161Arg variant as a risk factor for ulcerative colitis,[E200] whereas another report found no association of the polymorphism with this disease.[E193] Although most reports concentrated on the His161Arg SNP, analysis of the variants Ala126Gly, Gly155Ala, and Ala161Gly revealed that certain combinations of these SNPs might influence the susceptibility of Behçet disease.[E201]

IL-18
Discovery and structure

IL-18, a member of IL-1 superfamily, was first described 1989 as an IFN-γ–inducing factor, and later the gene was cloned and termed IL-18.[E202] IL-18 shares structural features with IL-1. IL-18 also lacks a signal peptide, and it is synthesized as a 24-kd biologically inactive precursor, named pro–IL-18, that requires IL-1β for caspase-1 cleavage to become a biologically

active molecule. On activation of caspase-1 by TLR triggering, pro–IL-18 is processed to an active mature form, which can be released from the cell.[E203]

Receptor and signaling

The IL-18 receptor complex (IL-18R) consists of a heterodimer containing 2 chains, which are members of the IL-1R family. Both are required for initiation of signal transduction.[E204] The α-chain of IL-18R is required for ligand binding, whereas the β-chain is required for signaling. The ligand binding IL-18α–chain is abundantly expressed on the surface of T cells, NK cells, macrophages, epithelial cells, chondrocytes, and a variety of other cells. On binding of IL-18 to IL-18Rα, IL-18Rβ is recruited into a signaling complex and induces signaling pathways shared with other IL-1 receptor family members. After approximation of cytoplasmatic TIR domains, the adaptor molecule Myd88 is recruited, which leads to activation of the kinase IRAKs followed by interaction with TRAF6, which activate IKK. This results in activation of IκB and consecutively of NF-κB.[E205,E206] There is a second signaling pathway known that involves activation of MAPK p38 and PI3K in neutrophils.[E207]

Cell sources and targets

A wide range of cells, including macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes, and DCs, expresses IL-18.[E208] IL-18 alone induces only small amounts of IFN-γ in naive T cells, whereas the combination with IL-12 induces high amounts of IFN-γ.[E209] In addition, IL-18 can promote either T_H1-cell or T_H2-cell responses in early stages of differentiation, depending on the ambient cytokine milieu.[E210,E211] Moreover, IL-18 induces IL-13 production in T cells and NK cells together with IL-2.[E212] IL-18 can also promote the expression of Fas ligand in NK cells and consequently enhance NK cell cytotoxity.[E213] The biological activity of IL-18 can be neutralized by IL-18 binding protein (IL-18BP), which binds to mature IL-18 with a high affinity. It does not bind pro–IL-18 and other members of the IL-1 family.[E214]

Role in immune regulation and cellular targets

In contrast with all other members of the IL-1 family, the extracellular domain of IL-18BP is made up of only 1 immunoglobulin-like domain, and its amino acid sequence is only distantly related to the ligand-binding chain IL-18Rα.[E215] IFN-γ induces the gene expression of IL-18BP in several IEC lines and human keratinocyte cell lines. The gene induction of IL-18BP by IFN-γ was also observed in cultures of colonic biopsy specimens.[E216] These findings are consistent with the previous work of Fantuzzi et al[E217] showing reduced expression of IL-18BP in IFN regulatory-1–deficient mice. In summary, by inducing IL-18 BP, IFN-γ appears to trigger a negative feedback loop that limits IFN-γ–dependent and IFN-γ–independent actions of IL-18.

Role in host defense and autoimmune diseases

IL-18 plays an important role in host defense. It enhances both innate and acquired immunity. As described, IL-18 can enhance the function of NK cells and development of T_H1 cells. Both cell types are important for the protection and defense against microbes. Moreover, IL-18 enhances the production and secretion of IFN-γ, which plays a key role in the bacterial defense. The critical function of IL-18 in host immunity to intracellular microbial infections was demonstrated in IL-18–deficient mice infected with *Leishmania major*. These mice showed a reduced resistance to *L major* infection, whereas the administration of IL-18 and IL-12 inhibited the expansion of *L major*.[E218] In this context, it was shown that IL-18 is contributes to the NK-cell response in visceral leishmaniasis.[E219] In addition, IL-18 is important for viral clearance because of its potent activation of CD8-positive T cells.[E220] IL-18 also seems to be important for the protective immunity against *Mycobacterium tuberculosis* because IL-18 lack in mice contributes to high susceptibility to *M tuberculosis*.[E221]

IL-18 plays also important roles in several autoimmune disorders, in which IL-18 expression is often increased and correlates with disease severity in human beings as well as in experimental mice models. For example, in IL-18–deficient mice, collagen-induced arthritis was less severe compared with wild-type mice.[E222] Blocking of IL-18 by administration of recombinant IL-18BP in mice with collagen-induced arthritis resulted in a clear reduction of the disease severity compared with placebo-treated mice.[E223] Furthermore, *in vitro* IL-18 neutralizing inhibited TNF-α, IL-6, and IFN-γ secretion by macrophages. In human beings, the importance of IL-18 in RA was also proven by several studies. In 1999, it was first shown by Gracie et al[E224] that in the joints of patients with RA, significantly higher amounts of IL-18 mRNA and protein were found than in those of patients with osteoarthritis. These results were later confirmed by other groups, and interestingly, elevated levels of IL-18 in the serum of patients with RA are also present. Serum and synovial fluid IL-18 levels as well as synovial tissue IL-18 expression were correlated with disease activity in patients with RA and juvenile idiopathic arthritis.[E225] Moreover, polymorphisms in the promoter region of the IL-18 gene have been found and were associated with RA.[E226] In addition, it was shown that the mechanism of the impaired NK-cell function in systemic-onset juvenile idiopathic arthritis involves a defect in IL-18Rβ phosphorylation.[E227] IL-18 could be an interesting target in the treatment of RA and one opportunity for antibody-based biological therapies in RA.

In addition to RA, IL-18 is important in Crohn disease. In experimental mouse models of colitis, the inflammatory pathology correlates with increased levels of tissue and serum levels of IL-18, whereas anti–IL-18 treatment resulted in a dose-dependent reduction of the severity of colitis.[E228] In addition, it was not possible to induce significant colitis in the IL-18–deficient mice, whereas in IL-18 transgenic mice, IL-18 overproduction exacerbates the development of colitis.[E229] Mice deficient in caspase-1, which cleaves IL-1β and IL-18, showed a near complete resistant to induction of experimental colitis, reflected by significantly reduced clinical scores and almost absent histologic signs of colitis. In parallel, a reduced spontaneous release of the proinflammatory cytokines IL-18, IL-1β, and IFN-γ from total colon cultures of those mice was observed.[E231] Similar inhibition of colitis by reduction of IL-18 expression was shown by treatment with inhibitors of caspase-1.[E232]

In chronic Crohn disease lesions, a local increase of IL-18 expression has been demonstrated compared with uninvolved areas or normal controls.[E233] In addition, chronic lesions displayed intense transcription of IL-18–induced cytokines, IFN-γ, IL-1β, TNF-α, and IL-8, and a marked increase in IL-18R–positive immune cells was observed.[E234]

IL-18 also plays important roles in many other diseases like diabetes and psoriasis. In a murine model of insulin-dependent

diabetes, IL-18 is upregulated and can promote diabetes development in mice.[E235] In human beings also, a pathogenic role for IL-18 in development is described, and recently, an association between serum levels of IL-18 and glycemic control was demonstrated.[E236] High levels of IL-18 have also been detected in keratinocytes of patients with psoriasis and in the serum. The expression of IL-18 correlated with disease severity.[E237,E238] Although keratinocytes under nonpathologic conditions produce pro–IL-18, they are not able to convert it to mature IL-18 because of the lack of caspase-1.[E239] However, in keratinocytes, caspase-1 can be induced by immunologic and inflammatory stimuli that result in secreting of biologically active IL-18.[E240]

Role in allergic diseases

IL-18 induces the production of IFN-γ in T_H1 cells, B cells, and NK cells, thereby stimulating T_H1-mediated immune responses and inhibiting IgE synthesis.[E241] Therefore, it is reasonable to assume an important role for IL-18 in response to allergens. IL-18 polymorphisms have been implicated in allergic rhinitis[E242] and in atopic eczema.[E243] Recently, it was demonstrated that a functional polymorphism of IL-18 is associated with the severity of bronchial asthma.[E244] In addition, IL-18 serum levels correlated inversely with peak expiratory flow, suggesting that IL-18 might reflect the disease activity in asthma exacerbations.[E245] In addition, airway hyperresponsiveness and airway remodeling were inhibited in IL-18–deficient mice in comparison with wild-type mice.[E246]

IL-18 in mice and IL-18 mutations

IL-18–deficient mice were more susceptible to *L major* infection and showed uncontrolled disease progression, which was accompanied by a depressed T_H1-cell response.[E218] In this context, it was shown that IL-18–deficient mice are also more susceptible to viral infections with a profound impairment in the ability of NK cells to mediate cytotoxic activity.[E247]

IL-19
Discovery and structure

IL-19 was first isolated from an EBV-transformed B-cell library in 2000 and was described as a novel IL-10 homolog consisting of 177 amino acid residues showing 21% identity with IL-10, and the *IL-19* gene has a similar intron-exon structure.[E248]

Human *IL-19* is located on chromosome 1q31-32 and contains 6 introns and 7 exons, whereas only 5 of these exons (exons 3-7) encode for the IL-19 protein.[E249] Two different mRNA species have been identified with different 5'-sequences. The shorter form of the IL-19 mRNA encodes a protein with a classic signal peptide targeted for secretion, whereas in the longer form, a 38–amino acid sequence is added to the N-terminus of the protein, which may affect its secretion.[E248]

Its predicted molecular weight is ∼21 kd, but because of N-linked glycosylation, secreted IL-19 has an apparent molecular weight of ∼35 to 40 kd. Despite the relative low amino acid similarity between IL-19 and IL-10, their 3-dimensional structure is highly similar. Unlike IL-10, IL-19 contains 6 conserved cysteine residues and is therefore secreted as a functional monomer (as is described for IL-20). Crystallographic studies demonstrated that the IL-19 protein contains 7 amphipathic helices that form a unique helical bundle.[E250]

Cellular sources and targets

IL-19 mRNA is expressed in monocytes within 4 hours after stimulation with LPS and GM-CSF. Prepriming of monocytes with IL-4 and IL-13 enhances LPS-induced IL-19 expression, whereas prepriming of monocytes with IFN-γ inhibits LPS-induced IL-19 expression.[E248] Low levels of IL-19 mRNA expression were also observed in B cells.[E251] Recently the expression of IL-19 was found to be induced in airway epithelial cells in response to IL-17A, IL-4, and IL-13 treatment, and elevated IL-19 levels were observed in airway epithelia from patients with asthma.[E252,E253] Immunohistochemical staining of a tissue microarray revealed that IL-19 is expressed in a large number of tissues, whereas macrophages, epithelial cells, and endothelial cells were the major cell types positive for IL-19.[E254]

Receptor and signaling

IL-19 binds to and signals through a heterodimeric receptor complex formed by IL-20R1 and IL-20R2.[E255] These receptor chains were not detected on blood-derived immune cells, but several tissues including skin were positively stained for IL-20R1 and IL-20R2.[E256] IL-19 forms a stable complex with both receptor chains.[E255] IL-19 binding to its receptor leads to the activation of STAT1 and STAT3.[E257] From its crystal structure, it became apparent that the residues that interact with the receptor are on helix B, loop BC, helix C, helix G, and the C-terminal β-strand.[E250]

Role in immune regulation and cellular networks

Murine IL-19 induces the production of IL-6 and TNF-α in monocytes and induced apoptosis and reactive oxygen species production in these cells, providing evidence for a role in inflammatory responses.[E249] Furthermore, IL-19 was shown to induce the expression of IL-4, IL-5, IL-10, and IL-13 by activated T cells, indicating a role for IL-19 in the induction of T_H2 responses.[E258] IL-19 has been primarily associated with psoriasis and allergic disorders.

Role in psoriasis

TNF-α and IL-6 are the major effector cytokines in the pathogenesis of psoriasis, and their expression in monocytes is induced by IL-19. A study aimed at elucidating the role of IL-19 in psoriasis revealed that serum levels in patients with psoriasis were decreased whereas epidermal expression of IL-19 was increased compared with healthy individuals.[E259] Several studies have demonstrated an association between SNPs in the IL-19 and IL-20 genes and increased risk of developing psoriasis, as discussed in the section covering IL-20.

Role in allergic disease

Elevated serum levels of IL-19 have been reported in patients with asthma as well as in a mouse model for asthma. Furthermore, IL-19 was shown to induce the expression of T_H2 cytokines from activated T cells.[E258] Later it was found that IL-19 expression is higher in airway epithelia from patients with asthma than epithelia from patients with chronic obstructive pulmonary disease or cystic fibrosis as well as healthy individuals.[E253] It was further shown that IL-19 expression can be enhanced by IL-4, IL-13, and IL-17A in normal human bronchial epithelial cell lines in a STAT6-dependent way.[E253] Long-term exposure of naive T cells to IL-19, IL-20, and IL-22 downregulates IFN-γ expression but upregulates IL-4 and IL-13 expression. This indicates that these cytokines may function to polarize naive T cells to T_H2 cells.[E260]

Functions as demonstrated in IL-19–deficient or transgenic mice

So far, transgenic overexpression of IL-19 has not been reported. However, unpublished observations mentioned in a study describing the receptor complexes for IL-19, IL-20, and IL-24 indicated no overt skin phenotype in transgenic mice over-expressing IL-19.[E257] *IL-19-/-* mice have a normal phenotype and show no developmental abnormalities. However, they are more susceptible to experimental acute colitis induced by dextrone sul-fate sodium. This correlates with increased macrophage infiltra-tion of the colonic mucosa, whereas B-cell recruitment was impaired. Furthermore, higher levels of proinflammatory cyto-kines were expressed by *IL-19-/-* mice–derived macrophages on LPS stimulation. These data indicate a protective role for IL-19 in this particular model.[E261]

IL-20
Discovery and structure

IL-20 was discovered in 2001 through EST database screening for sequences encoding amphipathic helices together with a signal sequence.[E262] The human *IL-20* gene maps to chromosome 1q32 (together with IL-10, IL-19, and IL-24), and the encoded protein shows 28% amino acid sequence identity to IL-10 but shows the highest homology (40%) with IL-19. Both mouse and human IL-20 consist of 176 amino acids.[E262] Mature IL-20 contains 6 conserved cysteine residues that prevent the formation of an intercalating dimer such as formed by IL-10. As a result, this protein exists as a functional monomer.[E262]

Cellular sources and targets

Like IL-19, IL-20 is expressed mainly by LPS-stimulated monocytes as well as epithelial and endothelial cells.[E256,E263] Furthermore, IL-20 (together with IL-28 and IL-29) is highly ex-pressed by DCs in response to LPS stimulation.[E264] IL-20 expres-sion at the mRNA level was observed in keratinocytes in psoriatic lesions as well as in NHEK and human keratinocyte line T cells.[E262,E265] IL-20 plays a role in epidermal function, as was clearly demonstrated by the abnormal skin phenotype of IL-20 transgenic mice (described in more detail below).[E262] Further-more, IL-20 specifically enhances colony formation by CD34+ multipotential progenitors, suggesting a role for this cytokine in hematopoiesis.[E266] IL-20 might contribute to the activation or for-mation of lymphatic vessels as well through activation of lym-phatic endothelial cells.[E267]

Receptor and signaling

Two receptor complexes for IL-20 have been identified: IL-20R1/IL-20R2 (shared with IL-19 and IL-24) and IL-22R1/IL-20R2 (shared with IL-24).[E255,E257,E262] The receptor complex most commonly activated by IL-20 appears to be IL-20R1/IL-20R2. However, IL-22R1 expression is found in some tissues where IL-20R2 is absent, suggesting a predominant role for IL-22R1/IL-20R2 there.[E257] Interestingly, a complete IL-20 receptor complex has not been found in blood-derived immune cells. Fur-thermore, high levels of IL-20R1, IL-20R2, and IL-22R1 were found on epithelial cells and stromal cells in skin, lung, pancreas, and breast tissues, suggesting that their ligands act mainly on tis-sue resident cells.[E256]

Binding of IL-20 to its receptor complexes leads to activation of STAT1 at supraphysiological concentrations (EC_{50} 800 PM/L)

and STAT3 at much lower concentrations (EC_{50} 1-5 PM/L), sug-gesting that STAT3 activation is the most relevant signal transdu-cer.[E257] IL-20 induces the proliferation of endothelial cells (HUVECs and human mammary epithelial cells), an effect that was abolished when IL-10 was simultaneously applied. Further-more, IL-20 treatment of HUVECs induced the phosphorylation of ERK1/2, p38 kinase, and JNK, suggesting a potential role for these molecules in IL-20–mediated signal transduction.[E268]

Role in host defense and angiogenesis-dependent disorders

IL-20 was shown to induce the expression of psoriasin and β-defensin–2 in keratinocytes, indicating a function in clearance of bacterial infection.[E264] Moreover, several observations have suggested that IL-20 plays a role in the pathogenesis of psoriasis. Important information was obtained from the transgenic overex-pression of IL-20 in mice, which leads to skin abnormalities in-cluding hyperkeratosis, thickened epidermis, and a compact stratum corneum, as well as growth retardation and death within the first days after birth.[E262] These skin abnormalities as well as the direct activation of STAT3 by IL-20 observed in a keratinocyte cell line provided the first indications that this cytokine is in-volved in epidermal function and possibly psoriasis.[E262] Further-more, all receptor chains involved in IL-20 binding are expressed in human skin, and their expression is increased in psoriatic skin.[E257,E265] Another finding supporting a role for IL-20 (and IL-19) in the pathogenesis of psoriasis is that their mRNA is ex-pressed in psoriatic lesions, whereas no expression was detected in uninvolved psoriatic skin.[E265] In a human skin xenograft trans-plantation model in which human psoriatic plaques or nonlesional skin biopsies were transplanted onto immunodeficient mice, blocking of IL-20 signaling led to psoriasis resolution. On the other hand, mice engrafted with nonactivated PBMCs that re-ceived continuous IL-20 infusion developed psoriasis in nonle-sional skin xenografts.[E269]

In addition to its putative role in psoriasis, IL-20 appears to play a role in other angiogenesis-dependent disorders such as ather-osclerosis and RA, because it was shown that IL-20 promotes angiogenesis.[E268] Furthermore, IL-20 strongly induced endothe-lial cell vessel tube formation and is beneficial for the re-estab-lishment of vessel networks in an ischemic hind-limb rat model.[E270] Therefore, IL-20 can be considered a promising can-didate for therapeutic treatment of ischemic disorders.

Functions as demonstrated in IL-20–deficient or transgenic mice and human mutations

As mentioned, transgenic mice overexpressing IL-20 have shown that IL-20 plays an important role in skin biology and may be involved in the pathogenesis of psoriasis.[E262] Several SNPs in the IL-19 and IL-20 genes have been linked with increased risk of developing psoriasis. The IL-19 and IL-20 haplotype CACCG-GAA was shown to be a significant susceptibility factor for psori-asis, whereas a protective effect has been described for the IL-20 and IL-24 haplotypes CAAAC, TGGGT, and CGAGT.[E271,E272]

IL-21
Discovery and structure

IL-21 was identified and cloned in a screen searching for a ligand to the already identified IL-21 receptor.[E273] IL-21 consists of 131 amino acids forming a 4-helix bundle cytokine domain. It

shares significant homology to IL-2, IL-4, and IL-15 and belongs to the same cytokine family, namely the family γc cytokines. IL-21 has been mapped to chromosome 4q26-q27, adjacent to IL-2. Because the IL-15 gene lies in the same cluster, these 3 highly related genes may have arisen by gene duplication. Human IL-21 has a predicted molecular weight of 15 kd and shows 57% identity to murine IL-21.

The 3-dimensional structure of IL-21 has been solved by nuclear magnetic resonance spectroscopy.[E274] As predicted, the structure is dominated by a central 4-helical bundle, arranged in an up-up-down-down topology, as observed for other cytokines. Interestingly, 1 segment of the IL-21 molecule apparently exists in 2 distinct and interchangeable states.[E274]

Receptor and signaling

The IL-21R was discovered as an orphan receptor and was first named *novel IL receptor*.[E273,E275] On the basis of its sequence homology to the IL-2 receptor β-chain, it was related to the γc cytokine family. Cytokines of this family bind to a complex formed by a common γc and an individual receptor component. Therefore, the functional receptor of IL-21 consists of γc and the IL-21R.[E276,E277] IL-21 signals via the Jak-STAT pathway and involves Jak1 and Jak3.[E276,E277] It can activate Stat1 and Stat3, and to a lesser extent Stat5a and Stat5b.[E278,E279] Experiments using Stat3 KO mice suggest Stat3 to be the most important STAT protein in IL-21 signaling.[E279] The cytoplasmic domain of IL-21R contains 6 tyrosine residues. One of them, Tyr510, can be phosphorylated and serves as a docking site for both Stat1 and Stat3. Besides the Jak/STAT pathway, PI3K and MAPK pathways seem to be involved.

Cellular sources and targets

IL-21 is produced by T cells and NK T cells.[E273,E280] More recently, IL-21 was attributed to the T$_H$17 subset of CD4$^+$ T cells.[E281,E282] Similarly, its receptor IL-21R was detected on CD4$^+$ T cells and NKT cells, but also on CD8$^+$ T cells, B cells, DCs, macrophages, and keratinocytes.[E273,E275,E283-E286] High expression of the IL-21R was observed on B cells, even in the resting state.[E283] It is expressed at low levels at the pre–B-cell state of development and through the first transitional stage, increasing at the second transitional stage.[E287] Mature follicular B cells express high basal levels of IL-21R, which can be further increased by signals through the B-cell receptor or through CD40.[E288] In contrast with follicular B cells, marginal zone B cells have low levels of IL-21R, whereas this receptor is absent on plasma cells.[E283]

Within the T-cell lineage, IL-21R is induced during transition from double-negative to double-positive lymphocytes. Although both mature CD4$^+$ and CD8$^+$ T cells express low levels of IL-21R, the expression is increased on TCR stimulation or IL-21 signals.[E276,E283] Given the broad range of IL-21R expression, IL-21 signaling seems to play an important role in the communication of many immune cells.

Role in immune regulation and cellular networks

IL-21 has been shown to reduce IgE class-switching *in vitro*.[E289] However, regulation of IgE by IL-21 seems to be context-dependent, because IL-21 was shown to decrease IgE when combined with phytohemagglutinin and IL-4, but in contrast induced IgE in combination with anti-CD40 and IL-4.[E290] The exact mechanism of this regulation remains to be determined.

Another finding in which IL-21 leads to a context-dependent outcome is apoptosis. IL-21 was found to enhance proliferation of human B cells stimulated via CD40, but to inhibit it on anti-IgM or IL-4 stimulation.[E273] Whether IL-21 induces proliferation or apoptosis therefore depends on the method of B-cell activation. Proliferation dominates in B cells that are activated via B-cell receptor stimulation together with costimulatory signals, whereas apoptosis is observed in B cells on TLR activation, for example stimulation with LPS or CpG.[E283,E291,E292] Therefore, IL-21 plays an important role in the regulation of B-cell expansion: it prevents expansion of B cells receiving nonspecific TLR signals but promotes proliferation of specifically activated B cells, thereby supporting the important versus deleterious antibody response. In addition, IL-21 is implicated in plasma cell differentiation through induction of B-lymphocyte–induced maturation protein 1, a master transcription factor for terminal differentiation to plasma cells. Taken together, IL-21 is important for B-cell function, affecting antibody isotype balance, proliferation, and apoptosis as well as differentiation to plasma cells.

IL-21 was also found in CD4$^+$ cells. Although all effector T$_H$-cell subsets, T$_H$1, T$_H$2, and T$_H$17 cells, can express IL-21, T$_H$17 cells produce by far the highest levels.[E281,E282] Induction of IL-21 by IL-6 in T$_H$17 cells leads to a further autocrine upregulation of IL-21.[E293] IL-21 plays a crucial role in the development of T$_H$17 cells because it induces the IL-23R, which is not expressed in naive T cells.[E282,E293] IL-23 signaling is important for the expansion and stabilization of T$_H$17 cells and for their effector function.[E294]

Interestingly, IL-21 has little or no effect on proliferation of naive or memory CD8$^+$ cells but strongly synergizes with IL-7 or IL-15 in the expansion of these cells.[E295] Synergy of IL-21 and IL-15 was also observed for the induction of granzyme B, an enzyme mediating cytolytic function of CD8$^+$ cells. Furthermore, IL-21 seems to be important in maintaining costimulatory functions of the surface proteins CD28 and CD62L[E296] and to enhance production of perforin.[E297]

An influence of IL-21 was observed on NK cells.[E298] The actions of IL-21, however, are dependent on the maturation stage. IL-21 enhanced *in vitro* generation of NK cells from bone marrow precursors and proliferation of committed immature NK cells in response to suboptimal IL-2 or IL-15 doses.[E299] Similar to its effect on NK cells, IL-21 can increase the proliferation of NKT cells when combined with either IL-2 or IL-15.[E280] Furthermore, IL-21 upregulates production of IL-4, IL-13, and granzyme B by NKT cells, thereby enhancing their effector function.

In contrast with the stimulatory effect of IL-21 on most of the immune cells, DCs are rather inhibited by IL-21. For example, when bone marrow precursor cells are cultured in the presence of GM-CSF and IL-15, they develop into mature DCs. In the presence of IL-21, however, the DCs maintain an immature phenotype, characterized by low MHC II expression.[E284] Moreover, IL-21–primed DCs have an inhibitory effect on the T-cell response, even when the priming is only for 2 hours.

Role in host defense or other immune-regulatory conditions

The fact that IL-21 increases effector functions of both CD8$^+$ T cells and NK cells suggests that it might have a positive effect on tumor regression. Several studies addressed this question in animal models. IL-21 was found to inhibit growth of melanomas,

fibrosarcomas,[E300] and pancreatic carcinomas.[E301] In both studies, the effect was predominantly mediated by NK cells rather than by CD8^{+} cells, whereas a third study showed a fully CD8^{+} T-cell–dependent prevention of tumor initiation in mammary carcinoma.[E302] NK-cell–mediated tumor killing on IL-21 treatment, however, seems to depend on the expression of NKG2D ligands on the surface of the target cells,[E303] limiting a future IL-21 anti-cancer therapy to certain types of tumors. In the case of CD8^{+} T-cell–mediated tumor killing, it has been shown by several studies that IL-21 is more potent than IL-2 or IL-15, but synergized efficiently with these cytokines in tumor regression.[E295,E304] These reports suggest that IL-21–mediated activation of NK cells and cytotoxic T cells can be exploited in combination with other chemotherapies. IL-21 has now entered clinical trials, and phase I results are promising.[E305] At the end of the study, 1 patient reached complete remission, whereas 9 of 29 patients achieved stable disease. Furthermore, in contrast with IL-2 and IFN-α therapies, low toxicity is observed for IL-21, making it to a valuable tool in cancer therapies.

Several reports addressed the involvement of IL-21 in autoimmune disease, but the exact role is still not fully clear in most of the diseases, and investigations are challenge by IL-21's pleiotropic function. High levels of serum IL-21 were detected in patients with SLE, and these levels correlated with disease severity,[E306] consistent with observations reported by a study using mouse models of SLE.[E292] Although neutralization of IL-21 could delay the progression of the disease, it should be kept in mind that IL-21 might also have a beneficial effect in this disease by inhibiting activation of self-reactive B cells.

In EAE, IL-21 seems to contribute to the inflammation, because mice that received IL-21 before induction of EAE had more severe disease accompanied by higher numbers of inflammatory T cells in the central nervous system.[E307] This effect is probably a result of the induction of T_H17 cells, a population that plays a major role in EAE. Consistently, IL-21 or IL-21R KO mice have a 10-fold reduced number of IL-17–producing cells and markedly reduced EAE progression.[E281,E282] A similar role of IL-21 might be found in RA, a disease likewise dominated by T_H17 cells. Higher levels of IL-21R are found in patients with RA, suggesting a role for IL-21 in the disease.[E308,E309] However, as in SLE, the mechanisms by which IL-21 contributes to the disease are not fully clear, and IL-21 might have both adverse as well as beneficial effects.

Role in allergic disease

IL-21's role in allergy and asthma has not been extensively studied. However, *in vivo* injection of IL-21 has been shown to prevent antigen-specific IgE but not IgG_{2a} production.[E289] IL-21 did not affect T_H2-cell differentiation or IL-4 production from CD4^{+} T cells but inhibited IL-4–induced germline Cε transcription in B cells. Although further investigations need to be done, these results suggest a beneficial effect of IL-21 in allergic diseases.

Functions as demonstrated in IL-21–deleted mice and receptor-deficient mice

Although IL-21R is induced during B-cell development, it is apparently not essential for B-cell development, as suggested by experiments using IL-21R KO mice. No defects in B-cell numbers have been observed in these mice, either in bone marrow or in the periphery.[E298] However, IL-21R KO mice have reduced serum

IgG_1 levels, whereas IgE is increased, an unexpected result because IgG_1 and IgE are usually coordinately regulated. Similar to the B-cell development, IL-21 signaling is not required for CD4^{+} T-cell and NK-cell development, because IL-21R KO mice exhibit normal CD4^{+} T cells and NK cells.[E298] Likewise, development of CD8^{+} cells is not affected in IL-21R KO mice. However, expansion and cytotoxicity of CD8^{+} T cells are impaired in these animals,[E295,E310] consistent with IL-21's antitumor activity. Both IL-21 and IL-21R KO mice have a 10-fold reduced number of IL-17–producing cells and, as a consequence, a markedly reduced EAE progression,[E281,E282] underlining the importance of IL-21 and IL-17A in inflammatory conditions. Taken together, IL-21 seems not to be crucial for the development of immune cells but to play a role at later stages and under certain immune-regulatory conditions.

IL-22
Discovery and structure

IL-22 was originally identified in mice as a gene induced by IL-9 in T cells, and it was termed *IL-10–related T-cell–derived inducible factor*.[E311] The human gene encoding IL-22 is located on 12q15, close to IL-26 and IFN-γ.[E312] The secreted IL-22 is 146 amino acids in length, is approximately 70 kd in weight, and shares 80.8% identity with mouse IL-22.[E313] As a member of the IL-10 family, it has 22.8% identity with IL-10 and shares the antiparallel α-helical structure with its family members.[E314] Four cysteine residues, 3 of which are conserved between IL-10 and IL-22, form intramolecular disulfide bridges. IL-22 is heavily glycosylated, which does not seem to be important for its tertiary structure, but does seem to be important for receptor binding.[E314,E315]

Receptor and signaling

The IL-22R complex is built of IL-22R1 and IL-10R2, the second chain of the IL-10 receptor.[E311,E313,E316] IL-22R1 has a long intracellular tail containing 4 putative STAT recruiting sites.[E316] Evidence suggests that IL-22 undergoes conformational change during the interaction with its receptor chains.[E315,E317] Recently, the crystal structure of the IL-22/IL-22R1 complex has been solved, and residues important for binding have been identified.[E318,E319]

IL-22 signaling occurs mainly via the Jak/STAT pathway. Which of the Stat and Jak molecules are involved and whether MAPKs are activated seems to depend on the cell type analyzed, although Stat3 appears to be generally involved.

Interestingly, a soluble form of IL-22R also exists, the IL-22 binding protein (IL-22BP).[E320-E322] Although soluble receptors are generated most often by proteolytic cleavage or alternative splicing, IL-22BP is encoded by an independent gene. IL-22BP is mainly expressed by resting DCs and to a lesser extent by activated DCs, resting and activated T and B cells, and activated mast cells.[E256] It binds to IL-22, but not to other members of this cytokine family. *In vitro*, IL-22BP can inhibit the function of IL-22 and is therefore frequently used in *in vitro* experiments as a naturally occurring antagonist. However, the situation *in vivo* might be different, and it remains to be elucidated whether IL-22BP also inhibits IL-22 signaling under physiological conditions or whether it instead positively regulates its function by prolonging its half-life.

Cellular sources and targets

IL-22 has been found in activated T cells and, at lower levels, in activated NK cells.[E251] Among T cells, IL-22 is mainly expressed

by memory CD4^{+} cells. More recently, IL-22 has been shown to be specifically produced by T$_H$17 cells.[E135,E136,E323] Similarly, a very recent report identifies a distinct subset of IL-22–producing NK cells located in mucosa-associated lymphoid tissues of mice and human beings, referred to as NK-22 cells.[E324] In contrast, no expression of IL-22 has been found in monocytes and B cells.

The IL-10R2 chain is ubiquitously expressed, as expected from its role as common part of several cytokine receptors. Thus, the IL-22R1 is likely to determine which cells are targets for IL-22. Interestingly, IL-22R1 could not be detected on primary immune cells like monocytes, skin-derived mast cells, macrophages, DCs, T cells, B cells, and NK cells.[E325] In contrast, some organs like kidney, small intestine, liver, colon, and lung, and particularly pancreas and skin, showed expression of IL-22R1. Consistently, IL-22R1 has been found in several epithelial cell lines corresponding to these tissues, as well as in primary keratinocytes. Interestingly, both components of the receptor, IL-10R2 and IL-22R1, are upregulated by IFN-γ.

Role in immune regulation and cellular networks

Investigations addressing the functions of IL-22 rapidly revealed that, despite the structural relation, IL-22 is not functionally related to IL-10. Initial studies observed an upregulated production of acute-phase reactants and IL-10 in several cells lines,[E326] suggesting a functional role for IL-22 in inflammation. *In vitro* treatment with recombinant IL-22 or overexpression of IL-22 promoted cell growth and survival in a hepatocellular cell line.[E327] These reports analyzing immortalized cell lines give hints for a role of IL-22 in the acute phase of infections as well as in proliferation of certain cells. Further investigations using primary cells are required in this area.

Role in host defense or other immune-regulatory conditions

Consistent with the high expression of the IL-22 receptor on keratinocytes, IL-22 increases the antimicrobial defense of these cells by enhancing the expression of β-defensin 2 and β-defensin 3, psoriasin, calgranulin A, and calgranulin B.[E137,E325] IL-22 also contributes to skin immunity by synergizing with IL-17A and IL-17F in the induction of antimicrobial peptides in keratinocytes.[E136] A role of IL-22 in the defense of several bacteria has been found. IL-22 is important for the defense of *Citrobacter rodentium*,[E328] a bacterium that induces the appearance of NK-22 cells in the lamina propria.[E324] Furthermore, IL-22 is increased on infection with *M tuberculosis* and *K pneumoniae*, suggesting a role for IL-22 in the defense of these bacteria.[E329,E330]

IL-22 may also play a role in defense against viruses, although there are some inconsistencies. For example, IL-22 overproduction has been found in individuals with resistance to HIV-1.[E331] In viral hepatitis, hepatocytes upregulate IL-22.[E332] Although no effect on virus replication has been observed in this disease, IL-22 might prevent and repair liver injury.[E327]

Finally, because chronic mucocutaneous candidiasis was found to be associated with significantly lower IL-22 levels, the inability to clear *C albicans* might be a result of a defect in IL-22 production.[E333] Taken together, these studies support an important role for IL-22 in the defense of different pathogens.

Because keratinocytes are a major target for IL-22, its role in keratinocyte-associated diseases has been studied. Indeed, one study found an important role for IL-22 in psoriasis by mediating dermal inflammation and acanthosis.[E135] Consistently, in a mouse model of psoriasis, neutralization of IL-22 prevented development of the disease, reducing acanthosis (thickening of the skin), inflammatory infiltrates, and expression of T$_H$17 cytokines.[E334] In human being, T cells isolated from psoriatic skin produced higher levels of IL-22, and supernatants of lesional psoriatic skin-infiltrating T cells induced an inflammatory response by normal human epidermal keratinocytes, resembling that observed in psoriatic lesions.[E335] Another study investigates the influence of 2 different drugs on IL-22 and finds that etanercept but not acitretin is able to reduce IL-22 levels, accompanied by a lower psoriasis area and severity index.[E336]

T$_H$17 cells are a major effector population in IBD. Because IL-22 is produced by this helper cell subset, its expression has been analyzed in IBD. Indeed, increased levels of IL-22 have been found in patients with IBD, and IECs express functional receptors for IL-22.[E337-E339] Although further investigations are needed to clarify fully the role of IL-22 in this disease, it seems to have adverse effects by contributing to inflammation, but also beneficial roles by promoting wound healing. Such a repair effect of IL-22 is also observed in hepatitis. Injection of recombinant IL-22 attenuated liver injury,[E327] whereas hepatocytes from mice deficient in IL-22 were highly sensitive to the detrimental immune response associated with hepatitis,[E340] suggesting that IL-22 serves as a protective molecule counteracting the destructive effects of the immune response and limiting tissue damage.

The results of studies addressing the role of IL-22 in cancer differ. One study observes prolonged survival of the hosts on IL-22, although neither metastasis nor tumor growth was affected.[E341] In another study, IL-22 treatment of mice with breast cancer led to decreased tumor size and reduced tumor cell proliferation,[E342] whereas more recent studies suggest an adverse effect of IL-22 in cancer. Overexpression of IL-22 protected lung cancer cell lines from starvation-induced and chemotherapeutic drug–induced apoptosis, whereas administration of IL-22 RNA interference plasmids significantly inhibited tumor cell growth.[E343] Expression of IL-22 and IL-22R has been found on anaplastic large cell lymphoma, and it was associated with proliferation of these cells.[E344] Besides the antiapoptotic and proliferative effects, IL-22 has been shown to induce inducible nitric oxide synthase (iNOS) in colon carcinoma cells, a gene involved in inflammation and carcinogenesis.[E345] The differences in the results are most likely a result of the different type of tumors analyzed. Further investigations are required to draw conclusions about which types of cancer IL-22 might target as a drug.

Role in allergic disease

To date, few reports have investigated the role of IL-22 in allergic diseases. Inflamed skin of nickel-challenged individuals with allergy was observed to contain infiltrating cells expressing IL-22 and IL-22R.[E346] Another study reports that T$_H$17 cells induce airway hyperresponsiveness in steroid-resistant asthma. It remains to be determined whether this effect is a result of IL-22 or other T$_H$17 cytokines.[E347]

Functions as demonstrated in IL-22–deleted mice, receptor-deficient mice, and human mutations

The role of IL-22 in host defense is underlined by studies investigating IL-22–deficient and IL-22R–deficient mice. IL-22 KO mice have an increased intestinal epithelial damage, systemic

bacterial burden, and mortality on infection with *C rodentium* because of a defective induction of antimicrobial proteins belonging to the regenerating gene family.[E328] In contrast, the other IL-10 family members, IL-19, IL-20, and IL-24, were all dispensable for host defense against this bacterium, suggesting a unique role for IL-22.

Six SNPs have been found in the gene encoding IL-22.[E348] Two of these seem to correlate with treatment response and viral clearance, respectively, consistent with the reports suggesting a role for IL-22 in the defense of viruses. It remains to be elucidated whether these or other SNPs have an influence on the defense of other pathogens and whether they correlate with certain disease frequencies.

IL-23
Discovery and structure

IL-23 is a type I heterodimeric cytokine that consists of a 19-kd 4-fold helical core α-subunit (IL-23p19) that is disulfide-linked to an additional 40-kd distinct β-subunit (IL-12p40).[E349] The IL-23p19 subunit has been mapped to the long arm of human chromosome 12 and the mice chromosome 10. The protein shows 70% homology between mice and human beings and has an overall sequence identity of approximately 40% to the p35 subunit of IL-12.[E349]

Receptor and signaling

Because of a common p40 subunit, IL-23 and IL-12 also share the IL-12Rβ1 subunit in their receptor complex. A second subunit (called IL-23R) is required for specific recognition of p19, and the heterodimer forms the high-affinity IL-23 receptors. The IL-23R gene has been localized on the human chromosome 1 and on the mice chromosome 6. Because it is a member of the IL-6/IL-12 receptor family, the IL-23R consists of an extracellular N-terminal immunoglobulin-like domain and 2 cytokine receptor domains that bind to the IL-23p19.[E350] The IL-12β1 subunit contains 3 membrane-proximal fibronectin type III and 2 cytokine receptor domains that interact with IL-12/23p40.[E351] Stimulation of the receptor complex activates Jak2 and Tyk2, resulting in phosphorylation of the receptor complex and formation of docking sites for STATs (1, 3, 4, and 5). The STATs are subsequently dimerized, phosphorylated, and translocated into the nucleus, activating target genes.

Cellular sources and targets

The secretion of p19 depends on its ability to partner with IL-12p40 via a disulfide bond, and therefore, coexpression of both subunits in 1 cell is required to generate the formation of the biologically active IL-23. IL-23 is mainly produced by phagocytic cells, macrophages, and activated DCs from peripheral tissues including the skin, intestinal mucosa, and lungs. Production of both subunits of IL-23 is stimulated through activation of TLRs by their ligands (including LPS, peptidoglycan, CpG DNA, and poly I:C). Such interactions result in increased expression of p40 and p19, consequently enhancing the release of IL-23. Some evidence suggests that activation of DCs through TLR2 preferentially induces IL-23 synthesis and an agonist of C-type lectin dectin-1, β-glucan curdlan, does so without inducing IL-12p70.[E352] Other factors such as prostaglandin E2, extracellular nucleotides, and GM-CSF can modulate IL-23 production by antigen presenting cells both in mice and human beings.[E353] *B pertussis*, producing the pertussis toxin that blocks Gαi-linked G-protein–coupled receptors and leads to an increase of cyclic adenosine monophosphate, enhances IL-23. In addition, IL-23 production can be enhanced via CD40-CD40 ligand interaction, resulting in increased production of IL-23, and creating a potent positive feedback for augmenting IL-23 production by APC. However, such stimulation is dose-dependent and time-dependent.[E352]

Role in immune regulation and cellular networks

In contrast with IL-12, which stimulates both naive and activated T cells, IL-23 acts only on memory and effector T cells. In addition to high levels of the IL-23 receptor complex expression on activated and memory T cells, the receptor is expressed on various cell populations, including NK and NKT cells, eosinophils, monocytes, macrophages, DCs, and epithelial cells such as keratinocytes.[E349,E350] Because TCR stimulation is not sufficient to induce IL-23R expression, additional stimulations are required to promote IL-23 responsiveness. After IL-23 stimulation, several inflammatory molecules are produced, including IL-17A, IL-17F, IL-6, IL-22, TNF, CXCL1, and α3 integrin. Thus, IL-23 has initially been identified as a T_H17-cell–promoting factor.[E143,E354] Recent reports clarified this role of IL-23. It was shown that TGF-β and IL-6 are required for the differentiation of naive T cells into IL-23R–positive IL-17–producing T cells.[E355-E357] IL-6 induces the production of IL-21, which signals in an autocrine fashion to upregulate its own expression and to induce the expression of IL-23R in a STAT3 and retinoic acid-related orphan receptor γt–dependent manner.[E293] IL-23, in synergy with TGF-β, further amplifies RORγt expression and production of IL-17. Despite this initial assumption, IL-23 is dispensable for the *in vitro* polarization of naive T cells into T_H17 effectors. However, after IL-6/TGF-β–mediated commitment of T_H17 cells, subsequent exposure to IL-23 is necessary for full differentiation and effector function of T_H17 cells.

In addition to its role in T_H17-cell development, IL-23 activates NK cells, enhances T-cell proliferation, and regulates antibody production.[E358] The IL-23/IL-17 pathway is associated with local tissue inflammation that produces swelling, heat, and pain and sets up an environment with heightened immune responses. Therefore, it was proposed that IL-23 might play a critical role in driving an early inflammatory immune response to pathogens or injury by directly inducing IL-17 production and early neutrophil recruitment. Dysregulation of the IL-23/IL-17 immune axis has been linked to immunopathology and autoimmune inflammation, and the generation of IL-23p19 KO mice indicated that IL-23, but not IL-12, plays a crucial role in the development of several autoimmune models.[E359]

Under physiological conditions, IL-23 is constitutively expressed in ileal mucosa, and IL-17–producing cells are highly enriched in intestinal tissues.[E360] It is therefore not surprising that numerous studies have confirmed a role for IL-23 in contributing to the development of several intestinal diseases. Significant upregulation of local and systemic IL-23 production was observed in *H pylori*–induced gastric ulcers and gastric cancer in human and in mouse models. A 20-fold increase of T_H17 cells and IL-17–expressing macrophages was observed in lesions of patients with Crohn disease compared with controls, which may be a result of the increased expression of IL-23.[E361] Furthermore, the development of spontaneous IBD in IL-10–deficient mice was completely prevented by crossing these mice with

IL-23p19–deficient mice.[E362] This demonstrates that IL-23 is required for the induction of colitis.

Functions as demonstrated in IL-23–deleted mice and receptor-deficient mice

The IL-23/IL-17 immune axis has also been implicated in the pathogenesis of experimental encephalitis and collagen-induced arthritis in mice. IL-23–driven IL-17–producing cells are highly potent at inducing central nervous system immune pathology.[E143] The IL-23p19 KOs can still generate T$_H$1 lymphocytes and IFN-γ but are resistant to EAE, a model for human MS. Similarly, CIA studies revealed that the IL-23–deficient mice are resistant to the development of bone and joint pathology during exacerbated arthritis because of the absence of CD4$^+$ T cells that make IL-17.[E363] High levels of IL-17 also correlated with the severity of disease in patients with MS and RA.[E361]

Multiple SNPs are located in the IL-23R generation and show distinct correlation patterns to diseases. Polymorphisms in the IL-23R represent one of the strongest associations in Crohn disease, and they have also been linked to the pathogenesis of ulcerative colitis, psoriasis, ankylosing spondylitis, and myocardial infarction.[E364-E366] The arginine residue at position 381 is the fifth amino acid internal to the transmembrane domain in the cytoplasmic tail of the IL-23R and is highly conserved between species. The glutamine allele of Arg381Gln is much less common than the arginine allele, and it confers approximately 3-fold protection against the development of Crohn disease. In addition to Arg381Gln, several other markers in IL-23R and in the intronic region between IL-23R and the adjacent IL-12RB2 demonstrated independent evidence for association with the disease.[E366] This suggests the presence of at least 2 independent risk alleles in the region. Similar protective effects for Arg381Gln in IL23R have been reported in psoriasis cohorts, and a strong association with psoriasis was observed for SNPs within the p40 gene region.[E365,E367] Recently, clinical trials using monoclonal anti–IL-23 therapy have shown promising results in the treatment of Crohn disease.[E368]

IL-24
Discovery and structure

IL-24 was identified in 1995 through subtractive hybridization studies by using cDNA libraries from human melanoma cells. IL-24 was expressed in healthy melanocytes, whereas its expression was abolished in melanoma cells.[E369] As a result, IL-24 was initially named *melanoma differentiation-associated gene 7*.

The gene encoding IL-24 localizes (together with the genes encoding IL-10, IL-19, and IL-20) to chromosome 1q32 and is composed of 7 exons and 6 introns. IL-24 shares 19% amino acid identity with IL-10, and like the other members of the IL-10 family, IL-24 has a predicted 3-dimensional structure containing 6 α-helices. IL-24 consists of 206 amino acids, and its predicted molecular weight is 23.8 kd.[E370] IL-24 possesses 3 consensus N-linked glycosylation sites, and as a result of extensive N-linked glycosylation, the apparent molecular weight of secreted human IL-24 is ~35 kd.[E371] Unlike most of the other IL-10 family members, human IL-24 must be glycosylated to maintain biological activity and solubility. Furthermore, a single unique disulfide bond is required for secretion and activity.[E372] So far, it is not clear whether IL-24 exists as a functional monomer, a homodimer, or both.

Receptor and signaling

IL-24 is the ligand for 2 heterodimeric receptor complexes: IL-22R1/IL-20R2 or IL20R1/IL-20R2. These receptor complexes were identified through a screening experiment in which combinations of putative R1 and R2 types of the IL-10 family (IL10R2, IL-20R1, IL-22R1, and IL-20R2) were expressed in transfected COS cells. IL-24 bound to cells that were transfected with the IL-20R2, and this binding was strongly enhanced when IL-20R2 was cotransfected with IL-20R1 and IL-22R1.[E371] The binding of IL-24 to either receptor complex results in the activation of STAT1 and STAT3. Like IL-19–mediated and IL-20–mediated STAT3 activation, IL-24–mediated STAT3 activation occurs at physiological concentrations, whereas STAT1 activation occurs at much higher concentrations.[E257] An indication for alternative signaling pathways for IL-19, IL-20, and IL-24 came from growth inhibition experiments with the carcinoma cell line ovarian carcinoma-3, which expresses all 3 receptor complexes involved in binding of these ligands. IL-19 and IL-24 induced growth inhibition in this cell line in a STAT-independent manner, suggesting that other signaling pathways must be activated.[E257]

Cellular sources and targets

IL-24 is expressed in normal melanocytes but is strongly downregulated in metastatic melanomas.[E369] Furthermore, IL-24 was found to be expressed by T cells, monocytes, and NHEK cells as well as B cells.[E256,E373,E374] A recent report showed that anisomycin-induced and IL-1β–induced IL-24 expression in normal human keratinocytes is regulated by p38 MAPK through mRNA-stabilizing mechanisms.[E375] In line with the initial concept of IL-24 as a tumor suppressor molecule, its expression in most human tumors is very low.

Role in immune regulation and cellular networks

PBMCs stimulated with IL-24 produced high levels of IL-6, TNF-α, and IFN-γ and low levels of IL-1β, IL-12, and GM-CSF within 48 hours. This proinflammatory response can be inhibited by addition of IL-10.[E376] Therefore, IL-24 appears to play a role in an immunoregulatory loop. When added to B-cell cultures, IL-24 strongly inhibits plasma cell differentiation and promotes CD40-induced proliferation, indicating that it may play a role in the regulating the balance between plasma and memory B-cell differentiation.[E374]

Role of IL-24 as tumor suppressor

The first demonstration that IL-24 is a potent and specific inhibitor of cancer cell proliferation came from the same group that identified the IL-24 gene. They showed that transfection of a number of different cancer cell lines containing both normal and mutated p53 and retinoblastoma genes with an adenoviral vector containing the IL-24 gene induced potent suppression of proliferation of all cancer cell lines tested.[E377]

Increased levels of iNOS expression have been associated with melanoma progression. Treatment of malignant melanoma cells with recombinant IL-24 or transfection with an adenoviral vector encoding the IL-24 gene resulted in a marked reduction of iNOS, demonstrating a suppressive effect of IL-24 on iNOS expression, which supports its role as a tumor suppressor.[E378] More insight into the molecular mechanism by which IL-24 exerts cancer-specific apoptosis induction was recently gained. It was demonstrated that IL-24–mediated induction of cancer cell apoptosis depends

on receptor binding but is independent of STAT3 activation. Furthermore, the treatment of tumor cells with recombinant IL-24 leads to increased expression of endogenous IL-24 through stabilization of IL-24 mRNA. Finally, recombinant IL-24 treatment was shown to induce endoplasmic reticulum stress and reactive oxygen species production.[E379] The authors concluded that the IL-24–induced endoplasmic reticulum stress and reactive oxygen species may specifically induce apoptosis in cancer cells. These cells are likely more susceptible to such signals than normal cells, because their endoplasmic reticulum stress and reactive oxygen species levels are already elevated, and therefore a slight increase in their production may tilt the balance toward apoptosis induction.

The first *in vivo* evidence of the potential therapeutic effects of IL-24 in the treatment of cancer was provided in 2002. In this study, an IL-24–encoding adenovirus was injected in subcutaneous lung tumor xenografts in nude mice. This treatment significantly inhibited tumor growth and induced extensive apoptosis of tumor cells. Furthermore, the expression of CD31 (an angiogenesis marker) was downregulated whereas TRAIL expression was increased in treated tumors.[E380] From these results, it was concluded that treatment with an IL-24–encoding adenovirus may be a powerful therapeutic agent for the treatment of cancer. A phase 1 clinical trial in which an IL-24–encoding adenovirus was injected intratumorally in patients with advanced cancer demonstrated that this treatment is well tolerated and induces transient increases in IL-6, IL-10, and TNF-α as well as an increase in CD8^{+} T cells and induction of apoptosis in a large volume of the tumor.[E381]

Role in psoriasis

An IL-20R2–dependent mechanism for IL-23–induced skin inflammation and epidermal hyperplasia has been described. Intradermal treatment of mice with IL-23 induced epidermal thickening and mRNA expression of *IL-19* and *IL-20*, whereas the expression of the subunits of their receptor complexes (IL-20R1, Il-20R2, or IL-22R1) was not affected. Intradermal injection of IL-23 into *il-20r2*^{-/-} mice significantly inhibited epidermal thickening compared with wild-type mice, whereas the skin phenotype of treated *il-19*^{-/-} and *il-20*^{-/-} mice did not differ from wild-type animals. This suggests a role for IL-20R–mediated signaling in the IL-23–mediated initiation of psoriasis in which IL-19 and IL-20 appear to be functionally redundant.[E382]

Functions as demonstrated in IL-24 transgenic mice

IL-24 transgenic mice share many of the phenotypic features with IL-20 and IL-22 transgenics, including epidermal hyperplasia, neonatal lethality, and abnormal keratinocyte differentiation.[E383] This again indicates that there may be a certain degree of redundancy in the epidermal functions of these 3 related cytokines.

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FROM IL-25 TO IL-37 AND IFN-γ

IL-25
Discovery and structure

IL-25 was first described in 2001 by Hurst et al.[E1] The protein consists of 177 amino acids and has a molecular mass of 17.6 kd in mice and 16.7kd in human beings. Because of its homology to IL17A, IL-17B, and IL-17C (16% to 18% homology), it has also been named IL-17E.[E1,E2] The strongest identity exists at the C-terminal part (20% to 30%). Little is known so far about the structure of IL-25. It is encoded on chromosome 14q11.1.

Receptor and signaling

IL-25 binds to the IL-17RB and IL-17RA to form a heteromeric receptor complex.[E3] IL17RB$^{-/-}$ mice develop phenotypically normally. In contrast with wild-type splenocytes, splenocytes from IL17RB$^{-/-}$ mice did not produce IL-5 or IL-13 in response to IL-25 stimulation.[E3] IL17RA$^{-/-}$ mice presented almost the same pattern as was seen in IL17RB$^{-/-}$. Intranasal challenge with IL-25 resulted in high numbers of eosinophils, neutrophils, lymphocytes, CCL2, CCL11, IL-5, IL-13, IL-9, and IL-10 mRNA. This was not observed in IL-17RA$^{-/-}$ and IL17RB$^{-/-}$ mice. Moreover, the receptor KO mice did not display features of IL-25–induced inflammation in the lung. In conclusion, both receptors are assumed to be involved in IL-25 signaling.

Cellular sources and targets

IL-25 is produced by T$_H$2-polarized T cells[E4] and in *in vitro* cultured mast cells[E5] and epithelial cells.[E6,E7] Recently, eosinophils and basophils from atopic individuals have also been described as sources of IL-25. Basophils may maintain reactivity of T$_H$2 central memory cells that express the IL-25R on stimulation by the innate immune system.[E8] IL-25 is found at very low levels in various tissues (brain, kidney, lung, prostate, testis, spinal cord, adrenal gland, trachea at an mRNA level). Highest expression levels were detected in the gastrointestinal tract and uterus.

Role in immune regulation and cellular networks

Intraperitoneal injection of IL-25 leads to eosinophilia, splenomegaly, and an increase of splenic plasma cell numbers. Moreover, IgE and IgG$_1$ increases.[E4] IL-25 induces T$_H$2-associated cytokines (IL-13 in all tissues; IL-4 and IL-5 in spleen). Nevertheless, it is important to mention that IL-25 leads to pathological changes solely in mucosal tissues, despite gene expression in various other tissues. IL-25 administration induced epithelial hyperplasia in the esophagus and the nonglandular part of the stomach. Epithelial cells contained eosinophilic cytoplasmatic inclusions in gastric glands and pyloric epithelial cells. Furthermore, inflammatory infiltrates of eosinophils, neutrophils, and mononuclear cells in the epithelium and lamina propria of esophagus and stomach and sometimes in the serosa and submucosa are described. Within the small and large intestine, goblet cell hypertrophy and hyperplasia occur, and epithelia of the large biliary tract in the liver and the large pancreatic ducts were often vacuolated and contained eosinophilic cytoplasmic inclusions.[E4] Administration of IL-25 does not result in an increased IL-6 expression in the spleen, stomach, or small intestine. No changes of IL-1α, TNF-α, IL-10, or IFN-γ are described. In addition, IL-25 mRNA expression is not upregulated on IL-25 treatment.

IL-25 had no impact on IL-4, IL-5, and IL-13 production of naive T cells or B cells in the presence of LPS or CD40 ligand.

IL-25–dependent actions are attributed to an IL-4, IL-5, IL-13–producing non–T-cell/non–B-cell population (NTNB) that is ckit^{pos} FcεR1^{neg}. The NTNB ckit^{pos} FcεR1^{neg} cells were described as small agranular cells with limited cytoplasm and no marker expression of mature NK cells, mast cells, basophils, or eosinophils. Recently, 3 publications added significant information regarding these effector cell populations by demonstrating a key role of IL-25 in the initiation of T$_H$2-type responses.[E9] Saenz et al[E10] reported a lineage-negative multipotent progenitor cell population they called MPP^{type2}. This subset is Lin^{neg}c-Kit^{int}Sca-1^{pos}, expands on IL-25 administration in the gastric lymphatic tissue and can give rise to cells of the monocyte/macrophage and granulocyte lineage. MPP^{type2} cells lead to T$_H$2-type responses and favor helminth expulsion.[E10] A similar fraction that also responds to IL-25 has been described in the fat-associated lymphoid cluster.[E11]

Neill et al[E12] defined a Lin^{neg}ICOS^{pos}ST2^{pos}IL-17RB^{pos}IL-7Rα^{pos}MHC II^{pos} IL-13–producing leukocyte subset that expanded on IL-25 and/or IL-33 administration. They were named nuocytes according to their cytokine predominance. Nuocytes represent the predominant IL-13–producing subset 5 days after *N brasiliensis* infection and are crucial for worm expulsion. Transfer of nuocytes into IL-17RA$^{-/-}$ established features of IL-25–evoked T$_H$2-type responses and established an IL-25 response in the recipient mice.

A crucial role of IL-25 on T$_H$9 cells has been suggested. IL-17RB is upregulated on T$_H$9 cells, and IL-25 is capable of IL-9 induction in differentiated T$_H$9 cells but not naive cells.[E13] In addition, IL-25 may interact with the IL-17A pathway. IL-25$^{-/-}$ mice not only displayed problems in reducing *Trichuris muris* burden but also increased their IL-17A and IFN-γ levels.[E14] Moreover, IL25$^{-/-}$ mice are highly susceptible to experimental autoimmune encephalomyelitis, most likely via an upregulation of IL-23.[E15] Treatment with IL-25 resulted in increased IL-13 secretion that opposed IL-17A–induced EAE.

Role in allergic disease

Recent data suggest a crucial role for IL-25 in asthma. IL-25 is expressed in the lungs of sensitized mice on antigen inhalation. In contrast, administration of an soluble IL-25R inhibited antigen-induced eosinophil recruitment, CD4$^+$ T-cell recruitment, IL-5 and IL-13 production, and goblet cell hyperplasia.[E16] Administration of anti–IL-25 mAbs reduced IL-5 and IL-13 production, eosinophilic infiltration, goblet hyperplasia, and AHR. Interestingly, this antibody successfully in the prevented AHR during allergen challenge.[E9] Blocking of IL-25 before sensitization led to an abrogation of AHR after methacholine challenge.[E17] A transgenic model with exclusive expression of IL-25 in the lung induced the recruitment of eosinophils and CD4$^+$ T cells on allergen-specific stimulation compared with allergen-challenged wild-type mice with comparable numbers of neutrophils and macrophages. IL-4, IL-5, and IL-13 were increased in the BAL fluid, whereas IFN-γ was undetectable. Mucus secretion, thymus and activation-regulated chemokine, and eotaxin levels were also enhanced. However, IL-25 expression itself did not induce airway inflammation. Recently, IL-17RB–expressing CD4$^+$ NKT cells were described to be responsible for airway hyperreactivity in an asthma model in mice.[E18,E19]

Functions as demonstrated in IL-25–deleted mice and receptor-deficient mice

IL-25–deficient mice display a rather normal phenotype. T_H2 effector functions are normal with the exception of eosinophils. However, IL-25^{-/-} mice fail to expel *N brasiliensis* efficiently because of subtle changes in the onset of T_H2 cytokine responses.[E9] In wild-type animals, the increase of NTNB that is ckit[pos]FcεR1[neg] precedes the increase in T_H2 CD4 cells. Because of the prolonged presence of high T_H2 cytokine levels, IgE is finally higher, and the number of mast cells in mice with parasitic infestation is higher in IL-25^{-/-}–deficient mice. IL-25 deficiency does not lead to a delay in goblet cell hyperplasia and has no effect on basophil counts. However, there is a deficit in circulating eosinophils (nonB nonT, CCR3^{+}, side scatter high). The delayed onset of T_H2 response to worms can be restored on addition of IL-25. However, IL-25 itself is not sufficient to expel the worms by its presence in IL-4^{-/-}, IL-5^{-/-}, IL-9^{-/-}, IL-13^{-/-} mice. Response to the parasite is characterized by a delayed onset and permanently high levels of these T_H2 cytokines because of persistent parasitic burden in IL-25–deficient mice.[E9]

IL-25–overexpressing mice displayed splenomegaly, lymphadenopathy, and a strong increase of eosinophils and B cells in peripheral blood.[E20] Because B cells decrease in parallel in the bone marrow, it could be assumed that IL-25 contributes to the release of premature B cells into the periphery. These B cells did not proliferate on IL-25 exposure, but they upregulated their IL-17E receptor expression. In accordance with the increased B-cell frequencies in the periphery, IgM, IgG, and IgE were elevated. In addition, cytokine levels of various cytokines were substantially increased (IL-2, IL-4, IL-5, IL-6, IL-10, IFN-γ, G-CSF, GM-CSF, and eotaxin).[E20] Pan et al[E21] reported similar results. However, their transgenic mice showed marked growth retardation and a more pronounced inflammation of organs. Experiments with adenovirus expressing IL-25 or IL-25 alone resulted in T_H2-like reactions with elevation of mRNA of IL-4, IL-5, and IL-13 and production of the chemokines CXCL5, thymus and activation-regulated chemokine, and eotaxin. In addition, vascular changes (rather distal) in the lung with moderate media hypertrophy, presence of eosinophils in the lumen, and infiltrates with eosinophils and monocytes beneath the endothelium within the vessel wall and adjacent to the vessels were described. In bronchi and larger bronchioles, epithelium is thickened and contains large amounts of mucus. Epithelial cells sometimes contained eosinophilic inclusions in the cytoplasma.[E1]

In conclusion, IL-25 seems to be a potent inducer of T_H2 immunity in the lung and in the intestine. It directly affects responder cell populations that give rise to monocyte/macrophage and granulocyte lineage, ultimately contributing to T_H2 responses and increased T_H2 responses in T cells.

IL-26
Discovery and structure

IL-26 was discovered in a study investigating the phenotypic changes of T cells after transformation by *H saimiri*. With the technique of subtractive hybridization for cloning cDNA transcripts that are specifically present in transformed human T cells and not in untransformed cells, IL-26 was identified and initially termed AK155.[E22] IL-26 shows 24.7% identity to IL-10 and is suggested to have a closely related structure consisting of 6 α-helices. The observed molecular weight of monomeric IL-26 is 19 kd. Gel electrophoresis under native conditions revealed that IL-26 spontaneously forms dimers.

The gene encoding IL-26 is located on chromosome 12q15, in proximity to the genes for IFN-γ and IL-22. Therefore, common regulatory mechanisms can be expected. Interestingly, several groups failed to identify a murine homolog of IL-26, and apparently this gene is missing in mice and rat. Only for exon 5, a section sharing weak homology with human IL-26 could be detected. This sequence is disrupted by several stop codons. Unexpectedly, IL-26 has been found in zebra fish, chicken, and frog, suggesting an evolutionary conservation despite the lack of IL-26 in rodents.[E23,E24]

Receptor and signaling

The receptor for IL-26 consists of 2 chains.[E25,E26] One chain is the IL-10R2, which also belongs to other receptor complexes of this cytokine family, namely the receptors for IL-10, IL-22, IL-28, and IL-29. The second chain is the IL-20R1, which is also required for binding the cytokines IL-19, IL-20, and IL-24. Because IL-26 is suggested to form dimers, it is likely to bind to 2 IL-10R2 and 2 IL-20R1 chains, although this has not been proven yet. IL-26 seems to bind first to IL-20R1, thereby inducing dimerization of the receptor chains. This dimerization activates the Jak/STAT signaling pathway, resulting in rapid phosphorylation of STAT1 and STAT3.

Cellular sources and targets

IL-26 expression has been found to be restricted to memory T cells after TCR stimulation, and to NK cells.[E27] Among the T cells, CD4^{+} cells produced higher levels of IL-26 than CD8^{+} cells. Recently, IL-26 has been found to be specifically expressed by the T_H17 subset of T cells,[E28,E29] a subset involved in many inflammatory and autoimmune disorders. The finding that IL-26 is expressed by these cells expands the research of T_H17-dominated diseases and underlines a difference between human and mouse T_H17 cells, because IL-26 is not present in mice. Similar things have been observed in NK cells. A recent study identified a distinct subset of human NK cells that specifically express IL-22 and that have therefore been termed NK-22 by the authors.[E30] This subset, located in mucosa-associated lymphoid tissues, such as tonsils and Peyer patches, also produces IL-26, but in contrast with T_H17 cells, no IL-17A and IL-17F. The coexpression of IL-22 and IL-26 is therefore commonly observed and not surprising, considering the close chromosomal location of these genes.

Because the IL-10R2 chain is ubiquitously expressed, fitting to its role as common part of several cytokine receptors, it is likely that the IL-20R1 chains account for the cell specificity of IL-26 signaling.[E27] In contrast with IL-10R2, IL-20R1 is not detected in immune cells, but on several epithelial cell lines and many tissues like skin, testis, heart, placenta, salivary gland, and prostate.[E31,E32] Activation of STAT1 or STAT3 on IL-26 stimulation has been observed, for example, in the colorectal adenocarcinoma cell line HT-29 or the epithelial keratinocyte line HaCaT.[E25,E26] It therefore seems that although immune cells are major producers of IL-26, its targets are nonimmune cells like epithelial cells from various tissues.

Role in immune regulation and cellular networks

To date, few studies addressed the role of IL-26 in immune regulation. One report describes IL-26 to enhance secretion of IL-8 and IL-10 as well as surface expression of CD54 by epithelial

cells.[E25] Another study investigated the influence of on B cells and found an inhibition of IgG and IgA production.[E33] More recently, IL-26 has been shown to induce proinflammatory cytokines like TNF-α, IL-6, and IL-8 in IEC lines and to inhibit proliferation of these cells.[E34] Further analyses are required to get a clear picture of IL-26's role in immune regulation and cellular networks.

Role in host defense or other immune-regulatory conditions

Few reports investigating the role of IL-26 in human diseases have been published so far. The lack of IL-26 in mice makes functional investigations more difficult, because the role of IL-26 cannot be studied in KO mice. The finding that IL-26 is expressed by T_H17 cells lead to the hypothesis that IL-26 might be involved in inflammatory diseases, because T_H17 cells play a key role in many of these disorders. One study analyzed the infiltration of various inflamed tissues by T_H17 cells by isolating CD4^{+} T cells from lesions of patients with various chronic inflammatory diseases.[E35] The tissues analyzed include samples from patients with psoriasis vulgaris, RA, or Crohn disease, as well as bronchial biopsies taken from patients with severe asthma. T cells from all of these tissues were characterized by the expression of T_H17-specific genes, among them IL-26. Supernatants of the cells induced expression of genes associated with inflammation in primary keratinocytes. Whether IL-26 contributed to this effect remains to be determined. Another study investigates the function of IL-26 in Crohn disease and reports expression of both IL-26 receptor subunits IL-20R1 and IL-10R2 by several IEC lines.[E34] IL-26 decreases proliferation of these cells and increases expression of proinflammatory cytokines. Furthermore, IL-26 serum protein expression was higher in patients with Crohn disease compared with controls, suggesting a role of IL-26 in this disease, although IL-26 expression might also just indicate a high number of T_H17 cells without having a direct effect. In Crohn disease as well as in other inflammatory disorders like psoriasis, RA, or MS, it remains to be determined whether the role of IL-26 is distinct from the functions of the other T_H17 cytokines IL-17A, IL-17F, and IL-22, and whether it synergizes with these cytokines in maintaining inflammation.

Role in allergic disease

So far, no role for IL-26 in asthma or allergy has been described.

Functions as demonstrated in IL-26–deleted mice, receptor-deficient mice, and human mutations

Because of the lack of IL-26 in mice, no studies investigating IL-26–deficient mice have been performed.

In human beings, the genomic region where the genes for IL-26, IL-22, and IFN-γ are located is polymorphic. Two microsatellite polymorphisms have been found at the IL-26 locus.[E36] The first is located in the third intron and the second in the 3' region of the gene. Therefore, these polymorphisms do not affect the amino acid sequence of the protein, but they can be used as genetic markers. Further studies revealed an association between the polymorphisms in this region and the protection of some male individuals from MS.[E37,E38] One marker located 3 kb 3' from the IL-26 gene was significantly associated with RA in women. Therefore, polymorphisms in the 12q13-15 region may contribute to sex-based differential susceptibility to this disease.

Interestingly, the original reason why a correlation with inflammatory disorders has been analyzed was the presence of the IFN-γ gene in this chromosomal region. Only later, it became apparent that T_H17 cells, as a main player in inflammatory diseases, express IL-26, which is also located to this region.

IL-27

Discovery and structure

IL-27 is a member of the IL-12–related cytokine family. This heterodimeric cytokine consists of the p28 protein and EBI3 subunits. The IL-27 p28 chain (also named IL-27A or IL-30), as a member of the long-chain 4-helix bundle cytokines, is homologous to the helical p35 subunit of IL-12. The EBI3 subunit (IL-27B) is related to IL12p40 and structurally resembles the soluble IL-6R.[E39] The IL-27 p28 gene is located on chromosome 16 in human beings and on chromosome 7 in mice and contains 202 residues. The EBI3 gene is on human chromosome 19 and mice chromosome 17 and contains 229 amino acids. IL-27 differs from other cytokines in that its subunits are not linked by a disulfide bond, which theoretically allows the production of the 2 subunits by distinct cells, followed by extracellular association.

Receptor and signaling

IL-27 mediates its effect through an heterodimeric receptor composed of a WSX-1 subunit (also termed IL-27Ra or T-cell cytokine receptor), which is an orphan class 1 cytokine receptor that is homologous to the 2 chain of the IL-12R, and gp130, which is shared by several cytokines (eg, IL-6, IL-11, ciliary neurotrophic factor, LIF, cardiotropin-like cytokine, OSM, and cardiotropin-1). WSX-1 confers ligand specificity and the gp130 signaling subunit that activates the Jak-STAT signal transduction pathway.[E40] Consistent with the actions of IL-27 on T cells, WSX-1 is highly expressed on T cells. However, WSX-1 and gp130 are coexpressed on a variety of cells and tissues. The pattern of STAT activation by IL-27 depends on the cell type and the activation state. In resting lymphocytes, IL-27 activates STAT1, STAT3, STAT5, and low amounts of STAT4.[E41,E42] Decreased activation of STAT1 was observed in fully activated relative to resting CD4^{+} T cells.[E43] In myeloid cells, IL-27–induced phosphorylation of STAT1 and STAT3 has been observed.[E40,E44] The function of IL-27 also depends on the STAT activation. STAT1 plays a key role in early regulation of T_H1-cell differentiation[E45] and is also necessary for mediating the suppressive effects of IL-27 on T_H17[E46-E48] and T_H2 differentiation.[E42] Both STAT1 and STAT3 are required for IL-27–induced IL-10 production in T cells, but their activation has not been linked to IL-27 function in the myeloid lineage.[E49,E50]

Cellular sources and targets

IL-27 is expressed predominantly by APCs, including DCs and macrophages, and by endothelial cells. The production of both subunits can be induced by TLR ligands such as LPS, poly I:C, and intact *Escherichia coli*.[E39] In addition, signaling via CD40L and IL-1β can upregulate the EBI3 subunit, whereas p28 has been shown to be upregulated by IFN-γ.[E51]

Role in immune regulation and cellular networks

IL-27 was first described as a T_H1–polarizing cytokine because of its action, alone or in synergy with IL-12, to promote IFN-γ production in a STAT1-Tbet–dependent manner. Mice genetically

deficient in WSX-1 were shown to be impaired in IFN-γ production and T_H1 differentiation, with higher susceptibility to infection with intracellular pathogens such as *L major* or *T muris*.[E52,E53] This leads to the conclusion that IL-27 was essential for the development of T_H1 immunity.

However, other reports indicated that IL-27 could also act as an inhibitor of the T_H2 immunity. A strong and accelerated T_H2 response was developed in WSX-1^{−/−} mice challenged with *T muris*.[E54] In asthma and glomerulonephritis models, the absence of IL-27 signaling led to an exacerbated T_H2 response.[E55,E56] The inhibitory role of IL-27 on the T_H2 response may in part be a result of its capacity to inhibit expression of the T_H2 lineage-specific transcription factor GATA3.[E42]

Studies to determine the natural antagonists of T_H17-cell activity led to the discovery that IL-27 can directly antagonize the development of T_H17-cell responses and limit IL-17–cell—driven inflammation in the central nervous system.[E47,E48] The lack of IL-27 signaling resulted in an increase in the number of IL-17–producing $CD4^+$ T cells in the CNS and was associated with exacerbated clinical disease. IL-27 also limits T_H17-cell–mediated uveitis and scleritis and was suggested to contribute to immune privilege.[E46] IL-27 inhibition of the development of T_H17 cells was also shown *in vitro*.[E43,E57]

Functions as demonstrated in IL-27–deleted mice and receptor-deficient mice

IL-27 is a pleiotropic cytokine with a wide range of activity on the T-cell responses that are not limited to a precise T_H-cell subset. It is known that IL-27 has the capacity to regulate T-cell proliferation, and this might explain why IL-27 can act on diverse subsets of T cells. $CD4^+$ T cells from IL-27R^{−/−} mice show enhanced proliferation after activation *in vitro*.[E52,E58,E59] This inhibition of T-cell proliferation might be a result of inhibition of IL-2 production because increased expansion of $CD4^+$ T cells has been observed during acute infection with *T gondii* and was associated with high production of IL-2.[E59,E60] IL-27 has been shown to regulate directly the production of IL-2 by $CD4^+$ T *in vitro*.[E59,E61]

In addition to controlling the production of the cytokine IL-2, recent studies underlined a role of IL-27 in promoting IL-10 synthesis.[E49,E50] *In vitro*, supernatant of IL-27–activated $CD4^+$ T cells contained higher levels of IL-10 than the unstimulated cells, and *in vivo*, *T gondii*–infected IL-27R^{−/−} mice displayed a reduced capacity to produce IL-10. Furthermore, it seems that IL-27–mediated inhibition of EAE depends on IL-10 production.

In line with the regulatory function of IL-27, the IL-27R is highly expressed on regulatory T cells, which are known to play a prominent role in limiting inflammation.[E62] However, the role of IL-27 is not clearly defined and seems to be species-specific. IL-27R^{−/−} mice display normal number of regulatory T cells, and the expression of the specific transcription factor for Treg cells, FOXP3, is inhibited by IL-27 in *in vitro*–stimulated mice $CD4^+$ T cells.[E57,E62] In contrast, TGF-β–induced FOXP3 expression is enhanced by IL-27 in *in vitro*–differentiated human Treg cells. Further studies are needed to clarify the significance of IL-27 in Treg-cell development.

Another key regulatory function of IL-27 might be to regulate early inflammatory events during acute infections, because IL-27 neutralization protects mice against lethal septic peritonitis by enhancing the influx and oxidative-burst capacity of neutrophils.[E63] Because of its similarity to other members of the IL-6/

IL-12 family, IL-27 was also thought to have a role in IBD. In fact, overproduction of IL-27 was observed in patients with Crohn disease or ulcerative colitis, and IL-27R was required for the induction of experimental DSS-induced colitis.[E64-E66] However, another study showed that EBI3 was dispensable for TNBS-induced colitis.[E67] Recently, it was shown that in contrast with the IL-10^{−/−} mice that are highly susceptible, the double IL-10/IL-27^{−/−} mice were resistant to spontaneous and helminth-induced colitis.[E68] A IL-27–promoting effect on the onset of IBD was a result of its function on both T_H1 and T_H2 responses.

Both IL-27^{−/−} (EBI3^{−/−}) and IL-27R^{−/−} mice have been generated to investigate the function of IL-27 *in vivo*. However, the phenotypes of both mice lines are not exactly similar. The discovery of the new IL-35, which shares the EBI3 subunit with IL-27, may explain this discrepancy.[E69]

Recently, 4 SNPs were identified in the IL-27p28 sequence: -964A/G, 2905T/G, 4603G/A, and 4730T/C.[E70,E71] The polymorphism at position -964A/G is most likely to be associated with asthma.[E70] Both -964A/G and 2905T/G gene polymorphisms may have a protective action against chronic obstructive pulmonary disease.[E71] The AG genotype of -964A/G had a 2.2-fold decrease risk and the TG genotype of the IL-27p28 2905T/G had a2.85-fold decrease risk of chronic obstructive pulmonary disease. However, further studies are needed to characterize the molecular mechanism involved in susceptibility to these diseases.

IL-28 AND IL-29
Discovery and structure

The most recently discovered members of the IL-10 family are IL-28A, IL-28B, and IL-29 (alternatively termed IFN-λ2, IFN-λ3, and IFN-λ1, respectively). Like IL-20, IL-28A, IL-28B, and IL-29 were discovered through database mining. At the amino acid level, these novel cytokines are closely related to type I IFNs, whereas their genetic intron-exon structure is similar to that of IL-10 family cytokines.[E72,E73] Human *IL-28A*, *IL-28-B*, and *IL-29* map to the chromosomal location 19q13.13.[E73] IL-28A and B are almost identical (96% amino acid identity), and both contain 6 exons, whereas IL-29 contains 5 exons.[E73] These gene structures are common for IL-10 family cytokines, and this distinguishes *IL-28* and *IL-29* from genes encoding type I IFNs, which consist of only 1 exon.

Receptor and signaling

IL-28A, IL-28B and IL-29 all signal through the same receptor complex, which is composed of a single IL-28R1 (alternatively named IFN-λR1, cytokine receptor family 2-12, or Ludwig Institute for Cancer Research) chain and an IL-10R2 chain.[E72-E74] The IL-28R1 chain is made up of a 200–amino acid extracellular domain, a transmembrane domain, and a 223–amino acid intracellular domain. Two alternatively spliced forms of IL-28R1 have been identified, which yield either a putative secreted form of the extracellular domain or a form that is incapable of signaling.[E73] The IL-10R2 chain is ubiquitously expressed, whereas the expression of IL-28R1 is subject to a certain degree of regulation, because it was not detected in fibroblasts and endothelial cells.[E73] Signaling through IL-28R1 requires the recruitment of Jak1 and induces the phosphorylation of STAT1, STAT2, STAT3, STAT4, and STAT5.[E72,E74,E75] The IL-28R1 and IL-10R2 are expressed on a wide range of melanoma cell lines as well as primary melanoma tumors. Incubation of melanoma cell

lines with IL-29 leads to phosphorylation of STAT1 and STAT2 and subsequent induction of IFN-regulated transcripts. Furthermore, IL-29 was shown to enhance bortezomib-induced and temozolomide-induced apoptosis synergistically.[E76]

Role in immune regulation and cellular networks

From their similarity to IFNs, it was expected that IL-28 and IL-29 would play a role in the defense against viral infection. Accordingly, *IL-28* and *IL-29* gene expression was very low in untreated PBMCs, whereas a marked increase in their expression could be induced by poly I:C as well as viral infection, which suggests a role in antiviral immunity for these cytokines.[E72] IL-28–mediated and IL-29–mediated antiviral activity has been observed against a broad range of viral infections *in vitro* and *in vivo*.[E72,E73,E77,E78] Furthermore, both cytokines could inhibit hepatitis B and C viral replication, suggesting that they may be therapeutically useful in the treatment of these viral infections.[E79]

Activated monocytes express IL-29, and during their maturation to DCs in response to bacterial stimuli, IL-20 and IL-28A are produced as well. The coexpression of IL-20, IL-28, and IL-29 in maturing DCs supports are role for these cells in the amplification of the innate immune response of tissue resident cells like keratinocytes, which show a strongly enhanced response to TLR2 and TLR3 stimulation after treatment with IL-20 and IL-29.[E80]

Potential role in allergic and autoimmune diseases

In response to IL-28 and IL-29 stimulation, monocyte-derived DCs upregulate the expression of their IL-28R1 chain, rendering them responsive to IL-28 and IL-29 stimulation. When treated with IL-28 and IL-29 during their development, monocyte-derived DCs display a tolerogenic phenotype with expression of high levels of class I and II MHC molecules but low levels of costimulatory molecules and promote Treg-cell expansion. IL-28 and IL-29 can thus promote the development of tolerogenic DCs.[E81] In addition, IL-29 appears to play a role in the regulation of the T_H1/T_H2 response. When naive T cells were cocultured with allogenic myeloid DCs (mDCs) that were matured in the presence of IL-29, a strong decrease in the amount of secreted IL-13 was observed, whereas the secretion of IFN-γ was not affected. This observation indicates that IL-29 modulates mDCs in a way that leads to a preferential decrease in the production of the T_H2 cytokine IL-13.[E82] IL-29 can also act directly on naive and memory CD4$^+$ cells by inhibiting GATA3 expression, thereby inhibiting IL-4–induced T_H2 polarization.[E83] An indirect feedback loop between T_H2 cells and plasmacytoid DCs (pDCs) may exist, because it was shown that IL-4 induces IL-1Ra secretion from monocytes. This monocyte-derived IL-1Ra in turn acts on pDCs and induces the expression of IL-29, which leads to suppression of T_H2 responses.[E84] Up to 60% of human tonsil, colon, and lung mast cells express IL-29. Stimulation with LPS and poly I:C as well as allergens can induce the release of IL-29, whereas extrinsic IL-29 induces mast cells to release IL-4 and IL-13 but not histamine. These findings indicate a potential role for IL-29 in the pathogenesis of allergic inflammation.[E85]

IL-28 may play a protective role in autoimmune disease as well. Administration of a vaccine containing a portion of the encephalitogenic proteolipid protein (PLP$_{139-151}$) coupled to ovalbumin-peptide and reovirus pσ1 conferred protection against PLP$_{139-151}$–induced EAE via induction of IL-10–producing FoxP3$^+$ Treg cells and IL-4–secreting FOXP3$^+$ T_H2 cells. However, after depletion of Treg cells, the pσ1-based protection against EAE was associated with an increased expression of

FOXP3 on CD25$^-$CD4$^+$ T cells producing IL-28. IL-28 could have a protective role in EAE and may therefore be a candidate for an alternative therapy for autoimmunity.[E86]

IL-30

Alternative designation for the p28 subunit of IL-27 (see the section on IL-27).

IL-31
Discovery and structure

IL-31 is a 4-helix bundle cytokine that is closely related to the IL-6–type cytokines OSM, LIF, and cardiotrophin-1. It was first cloned in 2004[E87] and is encoded on chromosome 12q24.31 in human beings. The mature protein has a molecular mass of 24 kd.[E88]

Receptor and signaling

A detailed analysis of the IL-31 interaction with its receptor complex has been published recently.[E89] IL-31 signals through a heterodimeric receptor complex that consists of IL-31RA and OSMRβ. Four splice variants of IL-31RA have been described so far (v1-4) in human beings.[E87] The short isoform (v2) displays strong inhibitory functions. IL-31RA belongs to the gp130 family, is expressed on CD14$^+$ cells, and is upregulated on stimulation with IFN-γ and LPS. Importantly, IL-31RA is constitutively expressed in keratinocytes and epithelial cells, but expression is consistently lower than those of OSMRβ in keratinocytes and epithelial cells from other sources. Recently, loss of IL-31RA on keratinocyte differentiation has been described.[E90] Moreover, mRNA of IL-31 RA was detected in skin-infiltrating macrophages (CD68$^+$), IECs, and a subset of small neurons. Some IL-31RA expression has been described on CD4 T cells. However, these cells lack the expression of OSMRβ.[E87]

On stimulation with IL-31, primary cells natively expressing IL-31RA mainly signal via the STAT3 pathway, whereas diverse human epithelial cell lines displayed activation of various signaling pathways including STAT1, STAT3, STAT5, and PI3K with a preferential engagement of STAT3, ERK, JNK, and Akt pathways. In general, the mode of activation resembles those of the IL-6R–specific signal transduction. A negative feedback loop via SOCS3 is suggested.

Cellular sources and targets

Messenger RNA and protein expression of IL-31 has been detected in human beings in activated CD4$^+$ T cells, which are in most cases of the T_H2 type and at lower levels in CD8$^+$ T cells. The main target cells of IL-31 are keratinocytes, epithelial cells, dorsal root ganglia, eosinophils, basophils, and monocytes.

Role in immune regulation and cellular networks

IL-31 induces the release of IL-6, IL-8, CXCL1, CXCL8, CCL2, and CCL8 by eosinophils[E91]; upregulates chemokine mRNA expression (CCL1, CCL4, CCL17, CCL19, CCL22, CCL23, CCL25, CXCL1) in keratinocytes; and leads to the expression of growth factors like VEGF and chemokines in epithelial cells.[E87] In epithelial cells, changes in cell morphology, inhibition of proliferation, and inhibition of apoptosis take place. Thus, IL-31 may play a part in attenuation of proliferation and the induction of regeneration if inflammation occurs. The impact of IL-31 on dorsal root ganglia remains to be investigated in detail. The fact that IL-31RA has also been detected in afferent fibers in

the spinal cord and the dermis of the skin may suggest nociceptive functions.[E92]

Role in allergic disease

IL-31 expression is increased in skin biopsies of patients with atopic dermatitis, allergic contact dermatitis,[E93] and prurigo nodularis.[E94] Serum IL-31 levels are higher in chronic spontaneous urticaria[E95] and patients with AD and correlate with Scoring Atopic Dermatitis scores.[E96] In addition, IL-31 is significantly higher expressed in anti-CD3 or Staphylococal enterotoxin A-stimulated T cells from donors with allergy and healthy donors and is mainly restricted to CD45RO cutaneous lymphocyte antigen⁺ cells.[E97] Recently a common IL-31 haplotype was reported that is associated with a higher risk of developing nonatopic eczema.[E98]

In vivo mouse data applying a monoclonal anti–IL-31 antibody in NC/Nga mice suggest a moderate impact on initial scratching behavior that vanished on chronification. The intervention had no impact on severity of dermatitis, weight gain, or histologic findings.[E99]

The impact of IL-31 on asthma has not been reported in detail so far. There is evidence pointing toward an upregulation of IL-31 mRNA in PBMCs and IL-31 in the sera of patients with asthma.[E100] In addition, IL-31 induced protein expression of EGF, VEGF, and MCP1/CCL2 in a bronchial epithelial cell line.[E101] In 2 mouse models (BALB/c, C57BL/6) of airway hyperresponsiveness, IL-31mRNA was upregulated in the lung on antigen challenge.[E87]

Moreover, IL-31 has also been suggested to play a role in IBD. In a colon cancer cell line, IL-31 and IL-31RA expression was upregulated on LPS and TNF-α, IL-1β, and IFN-γ exposure. Furthermore, IL-31 upregulated IL-8 production in this cell line. Interestingly, mRNA of IL-31 was higher in patients with Morbus Crohn and ulcerative colitis, and a correlation between the degree of IL-8 expression and IL-31 was observed in the respective lesions.[E102] However, a recent study could not detect a correlation between IL-31 and colitis ulcerosa.[E103]

Functions as demonstrated in IL-31–deleted mice and receptor-deficient mice

IL-31RA–deficient mice developed normally with no apparent pathologies. Importantly, they lack the dermatitis-like phenotype described. In mouse models with *S mansoni* egg- and *trichuris*–induced inflammation, IL-31RA⁻/⁻ mice displayed significantly enhanced T_H2-type responses and granuloma formation and accelerated worm expulsion. Consequently, T_H2 counterregulatory properties are suggested.[E104, E105]

Transgenic overexpression of IL-31 leads to alopecia, chronic pruritus that induces skin lesions, conjunctivitis, and swelling around the eye because of excessive scratching.[E87] In addition, an inverse T/B-cell ratio with a relative increase of activated memory T cells with relatively unchanged IgE and IgG concentrations has been described. This pathology closely resembles the situation of patients with nonatopic dermatitis. Skin histology shows similar patterns (hyperkeratosis, acanthosis, inflammatory cell infiltration, an increase in mast cells) as seen in nonatopic dermatitis. Intradermal injection of IL-31 via osmotic pumps causes inflammatory infiltrates filled with eosinophils, neutrophils, monocytes, and lymphocytes and enlarged lymph nodes within days. This nonatopic dermatitis–like phenotype could also be achieved in RAG1⁻/⁻ and mast cell–deficient mice.

In conclusion, IL-31 is a relatively new cytokine that is considered to be associated with a T_H2 response and is most likely involved in the pathogenesis of atopic dermatitis. However, the role of IL-31 in other diseases, its exact mechanisms, and its physiological role remains to be evaluated in detail.

IL-32

Discovery and structure

IL-32 was originally described as a transcript termed *NK cell transcript 4* (NK4) found in activated NK cells and T cells.[E106] On expression of the recombinant form of the NK4 transcript, it became clear that NK4 encoded for a protein with many characteristics of a cytokine. Therefore, the name was changed to IL-32, although IL-32 lacks sequenced homology to currently known cytokine families. The gene encoding IL-32 is located on human chromosome 16p13.3 and is organized into 8 exons. Six isoforms of IL-32 exist because of mRNA alternative splicing. The isoforms α, β, γ, and δ are expressed in several tissues and cell types, whereas the 2 isoforms ε and ζ were abundantly expressed only in activated T cells.[E107] IL-32 splice variants do not possess a typical hydrophobic signal peptide at the N-terminus, suggesting that IL-32 is not secreted.

Receptor and signaling

Although a receptor for IL-32 is not known so far, recombinant IL-32 induces various proinflammatory cytokines such as human TNF-α, IL-8, and MIP-2 in many cells, especially in monocytes, macrophages, and PBMCs, by activating the signal pathway of NF-κB and p38 MAPK.[E108] In this context, it has been recently demonstrated that silencing endogenous IL-32 by short hairpin RNA impairs the induction of the proinflammatory cytokines TNF-α and IL-1β in monocytes, suggesting that IL-32 is an intracellular cytokine.[E11]

Cellular sources and targets

IL-32 is found in several tissues and cell types. Moderate-state levels of mRNA are present in the thymus, small intestine, and colon, and high steady-state levels of mRNA could be detected in the spleen and peripheral blood leucocytes.[E108] Activated T lymphocytes and NK cells mainly produce IL-32, whereas primary human B cells stimulated with IgM or anti-CD40 do not express significant IL-32.[E107] Moreover, epithelial cells are a dominant and widespread source of IL-32. IL-32 was expressed in human lung epithelial cell lines and IEC lines on stimulation with TNF-α, IFN-γ, IL-1β, and IL-18.[E108,E109] Recently, IL-32 was detected in endothelial cells stimulated with IL-1β and keratinocytes stimulated with TNF-α and IFN-γ.[E110,E111] Moreover, a subset of immature monocyte-derived DCs constitutively expressing IL-32 was identified, suggesting a role of IL-32 in the immune response mediated by DCs.[E112] Primary human T cells stimulated with anti-CD3 synthesize IL-32 with a molecular weight of 25 kd, which on Western blot is found in lysates but not in supernatants. Similar findings were reported for 293T cells transfected with either IL-32γ or IL-32β.[E107] In contrast, it was reported that overexpression of IL-32α or IL-32β in COS cells resulted in secreted IL-32.[E108] It remains unclear which of the IL-32 isoforms are secreted from a particular cell type and, moreover, the type of stimuli that induce the secretion.

Role in immune regulation and cellular networks

It was shown by overexpression of IL-32β in HeLa cells that high levels of intracellular IL-32β induce apoptosis.

Cotransfection of the same HeLa cells with short-hairpin RNA coding for IL-32 resulted in a 50% decrease in the expression of the IL-32 protein in parallel with decreased cell death. Furthermore, the expression of IL-32 is upregulated in activated T cells, suggesting that IL-32 is specific for T cells undergoing apoptosis and could be involved in activation-induced cell death in T cells, probably via its intracellular actions.[E107] Moreover, high levels of IL-32 were observed in stromal cells from patients with myelodysplastic syndrome and low levels in patients with myeloproliferative disorder. Cotransfection of stromal cells with IL-32 small interfering RNA, which resulted in a decrease in the expression of the IL-32 protein, significantly reduced apoptosis in leukemia cells, suggesting that IL-32 in stromal cells appears to deliver proapoptotic signals to leukemia cells.[E113] Recently, the role of IL-32 in keratinocyte apoptosis in the context of atopic dermatitis was demonstrated.[E111] Downregulation of IL-32 by IL-32 small interfering RNA in human primary keratinocytes and artificial skin equivalents could decrease apoptosis markedly. Moreover, IL-32 was detected in chronic atopic dermatitis skin lesions, which are characterized by infiltrations of activated T cells inducing keratinocyte apoptosis. In THP-1 cells infected with *M tuberculosis*, IL-32 can influence the production of proinflammatory cytokines as well as apoptosis via its intracellular actions, suggesting that this cytokine has a dual function: induction of proinflammatory cytokines and induction of apoptosis.[E114] In an attempt to isolate a putative IL-32 receptor, proteinase 3 (PR3) has been identified as a specific IL-32α binding protein. The binding of IL-32α to PR3 is independent of its enzymatic activity. PR3 cleaves IL-32α, resulting in the formation of 2 peptides of 16 kd and 13 kd. These two cleavage products of IL-32α showed enhanced biological activity in the induction of MIP2 and IL-8 from mouse and human monocytes.[E115] Recently the biological activity between the 4 isoforms α, β, γ, and δ was compared. The γ isoform of IL-32 showed the highest activity in inducing TNF-α, MIP2, and IL-6, although all isoforms were biologically active.[E116] Moreover, IL-32 is synergizing with nuclear oligomerization domains (NODs) for the release of IL-1β and IL-6 in PBMCs.[E117] Although a mouse homolog of IL-32 has not so far been reported, IL-32 induces TNF-α and MIP2 in a mouse macrophage cell line.

Role in allergic disease

IL-32 is present in many inflammatory diseases, and it is assumed that IL-32 also has important functions during allergic inflammation. The role of IL-32 in atopic dermatitis has been described. IL-32 contributes to the pathophysiology of atopic dermatitis. Its expression in keratinocytes and serum levels correlated with disease severity of atopic dermatitis independent of atopy status.[E111]

Role in host defense or other immune-regulatory conditions

Proinflammatory cytokines can be induced by bacterial products via pattern recognition receptors. Two important families of microbial receptors are the cell-surface TLR and the intracellular NOD receptor family. IL-32 has the property to amplify the release of IL-1β and IL-6 induced by the intracellular pattern recognition receptor NOD2. In contrast, IL-32 does not influence the cytokine production induced via cell-surface TLRs.[E117] IL-32 was specifically induced by mycobacteria through a caspase-1

and IL-18–dependent production of IFN-γ[E118] and enhances the clearing of THP-1 cells infected with mycobacteria.[E114] Furthermore, the expression of IL-32 is increased in response to HIV infection. IL-32 plays an important role in suppressing HIV because a significant increase in HIV replication was observed by knockdown of IL-32 in HEK 293T cells.[E119] IL-32 not only contributes to host responses through the induction of proinflammatory cytokines but also directly affects specific immunity by differentiating monocytes into macrophagelike cells mediated through a caspase-3–dependent mechanism. In addition, IL-32 reversed GM-CSF/IL-4–induced DC differentiation to macrophagelike cells.[E120]

IL-32 plays an important role in autoimmune disease. It is highly expressed in RA synovial tissue biopsies and is associated with disease severity.[E121] Synovial staining of IL-32 also correlated with indices of synovial inflammation as well as the synovial presence of TNF-α, IL-1β, and IL-18. Moreover, in synovial biopsies from patients with RA, the level of IL-32 staining correlated with systemic inflammation. Injection of recombinant human IL-32 into the knee joints of naive mice resulted in joint swelling, infiltration, and cartilage damage. However, in TNF-α–deficient mice, IL-32–driven joint swelling was absent and cell influx was markedly reduced, suggesting that IL-32 activity is TNF-α–dependent. Transgenic mice overexpressing human IL-32 demonstrated that splenocytes from such mice produced more TNF-α, IL-1β, and IL-6 in response to LPS stimulation and contained more TNF-α in serum. In such mice, exacerbation of collagen-induced arthritis was observed that could be negated by TNF-αa blockade. This finding further supports the proposed TNF-α dependence of IL-32 activity.[E122]

IL-32 plays also important roles in Crohn disease and IBD, which are chronic intestinal disorders of unknown etiology. Both are characterized by disruption of the epithelial barrier and the formation of epithelial ulceration. One reason for the epithelial damage is insufficient bacterial killing, on the basis of genetics factors such as mutation in the NOD2 gene. IL-32 acts in a synergistic manner with NOD2-specific muropeptides for the release of proinflammatory cytokines. This effect was absent in colon cells of patients with Crohn disease with a NOD2 gene mutation, suggesting a pivotal role of IL-32 in the pathogenesis of Crohn disease.[E117] In addition, it was demonstrated that IL-32α expression was enhanced in colon cells on stimulation with IFN-γ, TNF-α, and IL-1β. There was a markedly enhanced expression of IL-32α in colon epithelial cells of patients with IBD compared with healthy controls or samples of ischemic colitis.[E109]

IL-32 models in mice

Although IL-32 is only present in tissues from human beings and absent in rodents, there a IL-32–overexpressing mouse model available. In transgenic mice overexpressing human IL-32, splenocytes produced more TNF-α, IL-1β, and IL-6 in response to LPS stimulation and contained more TNF-α in serum. In these mice, an exacerbation of collagen-induced arthritis was observed that could be negated by TNF-α blockade.[E122] Recently it was demonstrated in the context of vascular inflammation that overexpression of IL-32 in mice leads to increased inflammatory cell infiltration, vascular leakiness, and tissue damage in lungs, which results in a significant acceleration of animal death compared with wild-type controls.[E123]

IL-33

Discovery and structure

IL-33 was first mentioned in 2003 by Baekkevold et al[E124] as nuclear factor from high endothelial venules. It belongs to the IL-1 cytokine family and has been demonstrated to be a potent inducer of T_H2-type responses via its receptor, the IL-1R–related protein ST2.[E125]

IL-33 is a β-trefoil fold protein with a molecular weight of 30 kd. The protein contains a highly conserved N-terminal homeodomain-like helix-turn-helix DNA-binding domain.[E124] It localizes to the nucleus, associates with heterochromatin and mitotic chromosomes, and exhibits potent transcriptional repressor activities. Thus, the cytokine is mainly localized within the nucleus.[E126,E127] This N-terminal domain shows homology to the transcription factors engrailed and pou. IL-33 is encoded at chromosome 9p24.1 (human) or 19qC1 (mouse).[E125] Human and mouse IL-33 share 48% homology.

Initially, cleavage by caspases-1 into an active 18-kd cytokine was considered to take place.[E126,E128] Recently it became evident that full-length IL-33 is active via its IL-1–like domain at the carboxyterminus, and inactivation takes place mainly via cleavage by the caspases 3 and 7.[E129-E131]

Receptor and signaling

IL-33 binds to its receptor ST2, which was initially described as an orphan receptor, has been linked to T_H2-type inflammatory processes, and is expressed on T_H cells with T_H2-type polarization, DCs, and mast cells.[E132-E136] ST2 belongs to the IL-1R family and is encoded on chromosome 2q12 and is highly conserved across species. The glycosylated form has a molecular weight of 60 to 70 kd that corresponds to the secreted form. Four isoforms have been described so far: the soluble form of ST2 (sST2), ST2L, ST2V, and STLV.[E137-E139]

The trans-membrane form ST2L displays a similar structure to the IL-1RI, which consists of 3 extracellular immunoglobulin domains and an intracellular TIR domain.

ST2-dependent signals induced via IL-33 result in signaling through the NF-κB or MAPKs.[E125,E140,E141] Signaling occurs via recruitment of a coreceptor, IL-1RacP, or via T1ST2 homodimerization.[E142,E143] IL-1RacP KO mice do not respond to externally administered IL-33.[E142] *In vitro*, IL-33/ST2 signaling has been demonstrated in a ST2-transfected 293 cell line, which resulted in phosphorylation of IκBα and activation of Erk1/2, p38, and JNK and on mouse mast cells that naturally express ST2. The signaling patterns were similar to IL-1 stimulation through IL-1R.

The soluble form of ST2 has been reported to be released by cardiac myocytes, lung alveolar epithelial cells, fibroblasts, macrophages, and monocytes in the presence of LPS, TNF-α, IL-1, or T_H2 clones. It is actively involved in negative regulation of IL-33–induced actions via inhibition of binding of IL-33.[E144-E146] Consequently, administration of sST2 fusion protein attenuates inflammation in an asthma model in mice.[E133] In addition, sST2 levels are elevated in various diseases (SLE, RA, idiopathic pulmonary fibrosis, asthma).[E145,E147-E152]

Role in immune regulation and cellular networks

IL-33 is assumed to act as an "alarmin" that is considered to be upregulated in response to inflammation, released by necrotic cells, and inactivated during apoptosis.[E129-E131] However, the mechanisms of release need further investigation.

In concert with TSLP and IL-25, IL-33 is considered to be the most potent inducer of T_H2-type inflammation on mucosal tissues.[E153] Target cell populations are classically considered to be basophils, mast cells, eosinophils, NK, NKT cells, and T_H2 lymphocytes and, on the basis of recent literature, DCs and nuocytes.[E12,E125,E154]

Nuocytes are IL-13–producing lineage markers[neg] ICOS[pos] ST2^{pos} IL17RB^{pos} and IL17Rα^{pos} cells that are amplified via IL-33 and IL-25 and enhance T_H2-type T-cell responses. In addition to IL-13, nuocytes also produce considerable amounts of IL-5, IL-4, IL-6, IL-10, and GM-CSF and are able to induce worm expulsion in IL-13$^{-/-}$IL-4$^{-/-}$ mice.[E12]

In vitro–polarized T_H2 cells produce enhanced amounts of the T_H2-type cytokines IL-5 and IL-13 in the presence of IL-33.[E125] Naive T cells do not express the receptor ST2 *per se*. Evidence suggests that a STAT5 inducer may be required for ST2 upregulation.[E155]

In mast cells, numerous proinflammatory cytokines like IL-1β, IL-6, IL-13, and TNF-α are induced by IL-33. Basophils and eosinophils respond to IL-33 via activation enhanced integrin expression.[E156-E159] In addition, bone marrow–derived mouse DCs express low levels of ST2 on their surfaces. IL-33 upregulates MHC II and CD86 and induces IL-6 in the absence of IL-12. These IL-33–treated DCs are able to elicit a robust T_H2 phenotype in naive T cells with high IL-13 and IL-5 production.[E154]

Role in autoimmunity and other diseases

Several mouse model systems like autoantibody-induced arthritis,[E160,E161] IL-13–dependent cutaneous fibrosis,[E162] and ulcerative colitis[E163] link IL-33 and autoimmune diseases. Moreover IL-33 is abundantly expressed in synovial fluid of patients with RA.[E126] Administration of a sST2-Fc fusion protein reduced the severity of collagen-induced arthritis and resulted in lower serum IFN-γ and TNF-α levels without an upregulation of T_H2-type cytokines.[E164]

Soluble ST2 levels are also elevated in case of severe trauma or sepsis.[E146] External application of sST2 induced a downregulation of proinflammatory cytokines and increased survival in mice.[E165] This is in line with the observation that ST2-deficient mice fail to develop endotoxin tolerance.[E166]

IL-33 and in particular its ligand ST2 have been linked to cardiovascular disease.[E167] Cardiac fibroblasts and cardiomyocytes express IL-33 and sST2 when exposed to biomechanical strain or angiotensin II. Mice that undergo myocardial infarction display elevated sST2 in the serum and ST2 mRNA in cardiomyocytes. Levels decrease within the following days. Soluble ST2 represents an independent risk factor for 30-day mortality after myocardial infarction in human beings. Thus, it may act as a biomarker for myocardial infarction. Interestingly, sST2 levels are also significantly higher in patients with chronic heart failure and seem to be an independent marker for dyspnea related to acute congestive heart failure. IL-33 may serve as a rescue factor because cardiac hypertrophy was reduced and survival prolonged in mice after aortic constriction.[E167] In addition, IL-33 administration led to reduced aortic atherosclerotic plaque formation in mice with a germline deletion of apolipoprotein A. The opposite effect was observed with sST2 application.[E168]

Role in allergic disease

The impact of the IL-33/ST2 system has been linked to asthma development in mice. Although contradictory data are

available,[E169] several studies have shown the blocking of T_H2-type inflammation in asthma in mice by either transfer of sST2 or administration of neutralizing antibodies.[E124,E126] IL-33 may also be involved in mast cell activation in allergic asthma.

Administration of exogenous IL-33 leads to lymphocyte-independent airway hyperreactivity and goblet cell hyperplasia in mice.[E125] Repeated treatment with IL-33 (daily intraperitoneal application for 7 days) resulted in mRNA upregulation of IL-4, IL-5, and IL-13 (strongest upregulation) in the thymus, the spleen, the liver, and the lung *in vivo*. This treatment also induced eosinophilia, increased numbers of mononuclear and plasma cells, and induced splenomegaly with elevated serum levels of IgA, IL-5, and IL-13, whereas IL-1α, IL-2, IL-10, IL-12, IFN-γ, and TNF-α were not altered. Epithelial hyperplasia (esophagus, small intestine) has been described in the gastrointestinal tract. Eosinophilic and monocytic infiltration together with hypertrophy and enhanced mucus secretion in bronchi and larger bronchioles occurs. In addition, media hypertrophy of small and medium arteries of the lung has been reported.[E125] IL-33 amplifies alternative macrophage activation in the lungs of mice in an IL-13 and IL-4Rα–dependent manner and thereby increases airway inflammation.[E170] The number of IL-33–positive epithelial cells was significantly higher in lung epithelial cells of individuals with asthma[E170] and in skin biopsies of patients with atopic dermatitis.[E141] In a mouse model, IL-33 induced acute anaphylactic shock.[E141]

Pre-exposure with sST2 in mice reduced allergen-specific proliferation of T cells.[E144] Interestingly, sST2 levels in serum of patients with acute eosinophilic pneumonia or acute exacerbations of asthma are elevated compared with healthy controls.[E151,E152] A recent report suggested potent sST2 production by lung alveolar epithelial cells and lung bronchus epithelial cells in response to IL-1α, IL-1β, and TNF-α in a human endotoxin model.[E146]

Functions as demonstrated in IL-33–deleted mice and receptor-deficient mice

ST2 KO mice show a normal T_H2-cell maturation but an altered antigen-specific T_H2-type response. In case of *N brasiliensis* infestation, IL-4 and IgE responses are mounted compared with the wild-type control. However, there is a lack of pulmonary granuloma formation in the lung in case of intravenous *S mansoni* application without apparent clinical deterioration. In a model of ventricular pressure overload, ST2 deficiency led to increased rates of ventricular fibrosis and cardiomyocyte hypertrophy that resulted in enhanced chamber hypertrophy and reduced ejection fraction.[E167] In addition, ST2-deficient mice cannot develop endotoxin tolerance.[E166]

IL-37
Discovery and structure

IL-37 was first described in 2000 by Kumar et al[E171] as *IL-1 family member 7* (IL-1F7). It maps to the IL-1 family cluster of genes on chromosome 2.[E172] IL-37 has 5 different splice variants (IL-1F7a-e) with a molecular weight of 17 to 24 kd.[E173,E174] IL-37b (IL-1F7b), which is the largest and includes 5 of the 6 exons, shares significant sequence homology with IL-18. Only IL-37b and IL-37c containing exons 1 and 2 express an N-terminal prodomain, which includes a potential caspase-1 cleavage site.[E175]

Receptor and signaling

IL-37b precursor is cleaved by caspase-1 into mature IL-37b. Both of them bind to the IL-18R α-chain with lower affinity than that of IL-18. However, the binding of IL-37 to IL-18R α-chain does not function as a receptor antagonist of IL-18.[E175] IL-37b also binds to IL-18BP, which is the natural antagonist of IL-18, and enhances the IL-18–neutralizing capacity of the IL-18BP.[E176]

Mature IL-37b translocates into the nucleus by caspase-1 and forms a functional complex with Smad3, which affects gene transcription.[E177] The phosphorylation of STATs 1 to 4, which are involved in signal transduction for proinflammatory cytokines, are suppressed by IL-37b. IL-37b also suppresses both c-Jun, which is a part of the IL-1–inducible proinflammatory transcription factor AP-1, and phosphorylation of p38 MAPK, which contributes to several proinflammatory signaling cascades. Moreover, IL-37b increases phosphorylation of GSK-3α/β, which renders this kinase inactive.[E178-E182]

Cell sources and targets

The IL-37 transcripts are detected in human tissues such as lymph node, thymus, bone marrow, placenta, lung, testis, uterus, and colon tumor, and in human cell lines such as THP-1, U937, A431, IMTLH, KG-1, HL60, HPBMC, HPT-4, and NHDC.[E183] The protein is found in monocytes, tonsil plasma cells, and breast carcinoma cells.[E175,E176] IL-37 acts by an intracellular mechanism in translocating to the nucleus by forming a functional complex with Smad3.[E177,E180] It suppresses TLR-induced proinflammatory cytokines and DC activation.

Role in immune regulation and cellular networks

TGF-β and several TLR ligands such as LPS and Pam_3CSK_4 highly induce IL-37 in PBMCs. Proinflammatory cytokines IL-18, IFN-γ, IL-1β, and TNF moderately increase it, whereas it is inhibited by IL-4 plus GM-CSF.[E180]

The siRNA knockdown of LPS-induced IL-37 shows the increases of proinflammatory cytokines in human PBMCs. Meanwhile, the TLR-induced proinflammatory cytokines are reduced both in a mouse macrophage RAW cell line stably expressing the human IL-37b (RAW-IL-37) and in human monocyte cell line THP-1 and epithelial cell line A549 overexpressed by IL-37b.[E180]

IL-37b–overexpressing THP-1 cells show not only the suppression of cellular adhesion and migration regulators such as focal adhesion kinase, Pyk2, and paxillin but also the reduction of kinases, which affect cellular proliferation and differentiation, including the MAPK p38α and multiple STAT transcription factors. In addition, IL-37b–overexpressing RAW–IL-37 cells show striking morphologic differences such as loss of pseudopodia and vacuolization. Thus, IL-37b also regulates postreceptor signal transduction in a specific fashion.[E180]

Role in host defense and autoimmune diseases

IL-37 is not constitutively expressed in tissues from healthy subjects. However, it is highly expressed in synovial tissue from individuals with active RA, suggesting that IL-37 mediates a negative feedback mechanism to suppress excessive inflammation.[E180]

Functions as demonstrated in IL-37 transgenic mice and Smad3 knockdown *in vivo*

IL-37b transgenic mice are protected from LPS-induced shock. They show the lower proinflammatory cytokines and the less LPS-induced DC activation. The siRNA knockdown of Smad3

shows the reduction of the anti-inflammatory function, especially in IL-37 transgenic mice, indicating the functional link between IL-37 and Smad3.[E180]

IFN-γ
Discovery and structure

The unique member of the type II IFN family, IFN-γ, was first identified in the 1960s for its distinctive antiviral activity against the Sindbis virus in phytohemagglutinin-stimulated human leukocyte cultures.[E184] Both human and mouse genes are encoded by a single-copy gene. The human IFN-γ gene is located on chromosome 12 and the mouse gene on chromosome 10.[E185-E187] Despite the fact that the genomic structure is highly conserved among all species and consists of 4 exons and 3 introns, the interaction of IFN-γ and its receptor is species-specific and is restricted to the receptor extracellular domains. The human protein contains 166 residues that include a cleaved hydrophobic signal sequence of 23 amino acids. A 34-kd homodimer, noncovalently linked by 2 glycosylation sites, represents the active form of the protein.[E188,E189]

Receptor and signaling

The crystal structure of IFN-γ has been resolved, and it was predicted that a single IFN-γ molecule interacts with 2 IFN-γ receptor molecules.[E190] The functional IFN-γ receptor consists of 2 ligand-binding IFNGR1 (or IFNGRα) chains located on human chromosome 6 and on mouse chromosome 10, and 2 signal-transducing IFNGR2 (or IFNGRβ) chains located on human chromosome 21 and on mouse chromosome 16.[E191,E192] Both chains belong to the class II cytokine receptor family, and IFNGR2 is usually the limiting factor in IFN-γ responsiveness, because the IFNGR1 chain appears to be constitutively expressed. Because of the lack of intrinsic kinase or phosphatase activity, the IFNGR1 chain is constitutively associated to Jak1 and the IFNGR2 chain to Jak2 to assure the signal transduction. IFN-γ signaling leads to the activation of STAT1 molecules, their translocation into the nucleus, and their binding to a defined γ-activated site to initiate the transcription. IRF family members, including IRF-1, IRF-2, and IRF-9, are also involved in IFN-γ signaling.[E193-E195]

Cellular sources and targets

A number of cell populations from both the innate (eg, NK cells, NKT cells, macrophages, myelomonocytic cells) and adaptive immune systems (eg, TH1 cells, CTL and B cells) can secrete IFN-γ. Its production is controlled by APC-secreted cytokines, mainly IL-12 and IL-18. IL-12 promotes the secretion of IFN-γ in NK cells, and the combination of IL-12 and IL-18 further increases IFN-γ production in macrophages, NK cells, and T cells. The TH2-inducing cytokine IL-4, as well as IL-10, TGF-β, and glucocorticoids, negatively regulate the production of IFN-γ.[E196]

Role in immune regulation and cellular networks

As a member of the IFN family, IFN-γ has the ability to "interfere" with viral infection. In contrast with the type I IFN response that is triggered directly by viral infection, IFN-γ can also act as a secondary mediator. The immunomodulatory activities of IFN-γ are important later in the response for the establishment of an antiviral state. IFN-γ exerts its antiviral effects mainly via the induction of key antiviral enzymes

including the double-stranded RNA activated protein kinase, 2'-5' oligoadenylate synthetase (2-5 synthetase), and the double stranded RNA-specific adenosine deaminase.[E197-E199]

In addition to its antiviral activity, IFN-γ coordinates a broad range of biological functions. As the major product of fully differentiated TH1 cells, IFN-γ promotes cytotoxic activity by both direct and indirect mechanisms. Directly, together with IL-12 and IL-27, IFN-γ participates in the events taking place during the commitment of naive CD4+ T cells toward a TH1 phenotype.[E200] Indirectly, IFN-γ can regulate antigen processing, and via its ability to inhibit cell growth, IFN-γ can reduce the TH2-cell population and thus contribute to TH1-cell differentiation.

The ability to regulate MHC class I and II protein expression is a major physiological role of IFN-γ. Within the class I antigen-presentation pathway, IFN-γ induces expression of new proteasome subunits, LMP2, MECL-1, and LMP7, to form an inducible proteasome. This is a mechanism by which IFN-γ can increase the quantity, the quality, and the repertoire of peptides for class I MHC loading.[E200] IFN-γ also induces the proteasome regulator PA28, which associates with the proteasome, alters proteolytic cleavage preference, and allows more efficient generation of TAP-compatible and MHC-compatible peptides to increase the overall efficiency of class I MHC peptide delivery.[E201] In addition to inducing TAP transporter, which is vital for the transport of the peptide from the cytosol to the ER lumen, IFN-γ upregulated the class I MHC complex.[E202] Upregulation of cell-surface class I MHC antigen presentation by IFN-γ is important for host response to intracellular pathogens.

IFN-γ can also promote peptide-specific activation of CD4+ T cells in professional and nonprofessional APCs via the upregulation of the class II antigen-presenting pathway. By inducing the expression of several key molecules, IFN-γ upregulates the quantity of peptide:MHC class II complexes on the surface of the cell. Among these crucial molecules, there is the invariant chain; the constituents of the MHC complex itself; cathepsins B, H, and L, which are lysosomal proteases implicated in peptide production for loading; DMA and DMB, which function to remove CLIP from the peptide binding cleft to render it available to peptide loading; and class II transactivator, a key transcription factor for the regulation of expression of genes involved in the MHC II complex.[E203-E205]

Inhibition of cell growth is another important feature of IFN-γ. IFNs inhibit proliferation primarily by increasing protein levels of cyclin-dependent kinase inhibitors of the Cip/Kip family. IFN-γ induces the cyclin-dependent kinase inhibitors p21 and p27 that inhibit the activity of CDK2 and CDK4, respectively, causing the cell cycle to arrest at the G1/S checkpoint.[E206-E209]

IFN-γ also shows proapoptotic affects. Rapid STAT1 activation after IFN-γ treatment of cells bearing high levels of IFNGR can induce apoptosis in an IRF-1–dependent manner.[E210] Many of the proapoptotic effects of IRF-1 are mediated by the IRF-1–induced caspase-1 (IL-1b–converting enzyme). IFN-γ also induces a number of other proapoptotic molecules including the antiviral enzyme protein kinase R, the death-associated proteins, and cathepsin D. IFN-γ may enhance cell sensitivity to apoptosis by increasing the surface expression of Fas/Fas ligand and of the TNF-α receptor.[E211-E213]

IFN-γ can also modulate the immune response by controlling AICD of CD4+ T cells through modulation of signaling by the death receptor Fas.[E214] CD4+ T cells that lack IFN-γ or STAT1 are resistant to AICD, and IFN-γ was proposed to increase

CD4^{+} T-cell apoptosis through a mitochondrial pathway,[E215] which requires the production of caspases. Retrovirus-mediated expression of caspase-8 could restore the sensitivity of Stat1-deficient T cells to AICD.[E214] However, a recent study challenged this mechanism of action of IFN-γ by showing a function for IFN-γ in controlling CD4^{+} T-cell death in ways that do not seem to involve Fas or its ligand or to require the production of caspases.[E216] This study provides evidence suggesting that mycobacterial infection–induced CD4^{+} T-cell death is a result of autophagy and that Irgm1, also called LRG47, is an IFN-inducible GTPase that seems to suppress IFN-γ–induced autophagy in CD4^{+} T cells. The expression of several members of the family of the antiapoptosis protein Bcl-2 was not affected by either IFN-γ or the absence of Irgm1, which suggests a lack of involvement of the mitochondrial cell death pathway.

IFN-γ is a key cytokine in bridging the innate and the adaptive arms of the immune system. In addition to its role in the development of a T$_H$1-type response, IFN-γ plays a role in the regulation of local leukocyte-endothelial interactions. IFN-γ regulates this process by upregulating expression of numerous chemoattractant (eg, IP-10, MCP-1, MIG, MIP-1a/b, and RANTES) and adhesion molecules (eg, ICAM-1 and VCAM-1).[E217-E221]

IFN-γ was originally called *macrophage activated factor*, and enhanced microbial killing ability is observed in IFN-γ–treated macrophages. It is via induction of the NADPH-dependent phagocyte oxidase (NADPH oxidase) system (called *respiratory burst*), production of nitric oxide intermediates, tryptophan depletion, and upregulation of lysosomal enzymes that IFN-γ mediates this antimicrobicidal function, which also occurs in neutrophils.[E222,E223] IFN-γ can effectively prime macrophages to respond to LPS and other TLR agonists. TLR4 transcription and subsequent surface expression are increased by IFN-γ, thus enhancing LPS-binding ability in macrophages. LPS-dependent signaling is enhanced by IFN-γ via the induction of MD-2 accessory molecule, MyD88 adaptor, and IRAK expression.[E224,E225] IFN-γ was recently identified as a modulator of the cooperation between TLR and Notch pathways. By inhibiting Notch2 signaling and downstream transcription, IFN-γ abrogates Notch-dependent TLR-inducible genes, which represents another way IFN-γ can modulate effector functions in macrophages.[E226]

Functions as demonstrated in IFN-γ–deleted mice and receptor-deficient mice

Because IFN-γ is a multipotent cytokine that plays an important role in both the innate and the adaptive immune response, it is not surprising that its deficiency is associated with the pathogenesis of several diseases. Low levels or IFN-γ correlate with an increased susceptibility to intracellular pathogen infection with subsequent tissue destruction, as well as tumor development. Patients with acquired IFN-γ deficiency, caused by serum autoantibodies that specifically neutralized the biological activity of IFN-γ, show defects in the T$_H$1-cytokine pathway together with disseminated tuberculosis and nontuberculous mycobacterial infections.[E227-E230] On the other hand, early IFN-γ production in response to live parasite stimulation correlates with a protective immunity to symptomatic malaria in Papua New Guinean children.[E231]

IFN-γ may also play an important role in the pathogenesis of type 1 diabetes, as suggested by the decreased levels of IFN-γ observed in newly diagnosed patients with diabetes.[E232] The cellular arm of the immune system is implicated in the pathogenesis of the disease, and diabetes can be induced by the transfer of T$_H$1 CD4^{+} T cells expressing cytokine in a nonobese mouse model of autoimmune diabetes. Decreased apoptosis of activated T cells in nonobese diabetes mice is a feature or the outcome of the loss of IFN-γ–mediated immune suppression.[E233]

IFN-γ also has a role in the pathogenesis of RA. Arthritis onset and severity are reduced under conditions in which IFN-γ is neutralized or in mice deficient in IFN-γ, suggesting a role of IFN-γ in the initiation of the disease.[E234] Similarly, in another model of autoimmune disease, EAE, the disease is enhanced in IFN-γ–deficient mice.[E235,E236] However, IFN-γ can also inhibit the inflammatory process at a later stage of the disease, and it was proposed that this was a result of the ability of IFN-γ to suppress IL-17 secretion. However, it seems that IL-17 production is dispensable for the exacerbation of the disease and that IFN-γ mediates this inhibition via its antiproliferative and proapoptotic effects on activated T cells.[E235,E237]

Despite the important functions of IFN-γ in the immune system, both IFN-γ^{-/-} and IFNGR^{-/-} mice showed no obvious developmental defects, and their immune systems appeared to develop normally.[E238] However, these mice show deficiencies in natural resistance to several bacterial, parasitic, and viral infections. IFN-γ^{-/-} mice have suppressed splenic NK-cell activity, uncontrolled splenocyte proliferation, reduced MHC II expression and antimicrobial products by macrophages. IFNGR^{-/-} mice show a deficiency in IgG$_{2a}$ production; increased susceptibility to vaccinia virus, *Listeria monocytogenes*, pseudorabies virus, and *M bovis*; and increased resistance to endotoxic shock. Localized site inflammation, increased CTL activity, lymphocyte infiltration and severe tissue destruction has been observed in transgenic mice.[E239-E243]

The biological effects of IFN-γ are widespread, and polymorphism in the IFN-γ or IFNGR genes has been associated with susceptibility to several diseases including pulmonary tuberculosis, MS, myasthenia gravis, and arthritis manifestation. For example, mutation in the IFN-γ gene has been shown to lower the body's ability to resist mycobacterial infection.[E244]

Complete IFNGR1 deficiency is a result of homozygous recessive mutations or heterozygous mutations affecting the extracellular domain of the IFNGR1 gene and preventing the expression of the receptor at the cell surface.[E245] In the patients with mutations in IFNGR2, the cell surface expression of IFNGR1 is normal, but functional response to IFN-γ is lacking.[E246,E247] Inactivating mutations of the human IFNGR1 or IFNGR2 chains, resulting in defective expression or function of the IFN-γ receptor, show severe susceptibility to poorly virulent mycobacteria, often a BCG infection.[E248]

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