Fundamentals of allergy and immunology

Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases

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There have been extensive developments on cellular and molecular mechanisms of immune regulation in allergy, asthma, autoimmune diseases, tumor development, organ transplantation, and chronic infections during the last few years. Better understanding the functions, reciprocal regulation, and counterbalance of subsets of immune and inflammatory cells that interact through interleukins, interferons, TNF-α, and TGF-β offer opportunities for immune interventions and novel treatment modalities in the era of development of biological immune response modifiers particularly targeting these molecules or their receptors. More than 60 cytokines have been designated as interleukins since the initial discoveries of monocyte and lymphocyte interleukins (called IL-1 and IL-2, respectively). Studies of transgenic or gene-deficient 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 essential information about their functions. Here we review recent developments on IL-1 to IL-38, TNF-α, TGF-β, and interferons. We highlight recent advances during the last few years in this area and extensively discuss their cellular sources, targets, receptors, signaling pathways, and roles in immune regulation in patients with allergy and asthma and other inflammatory diseases. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

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Since the discovery of IL-1 in 1977, approximately 360,000 published scientific articles have referred to interleukins. Secreted proteins that bind to their specific receptors and play a role in intercellular communication among leukocytes are named interleukins. The nomenclature has been continuously evolving, and assignments of new members to the IL-1 family have been taking place (see Table E1 in this article's Online Repository at www.jacionline.org).[1] Interleukins are assigned to each family based on sequence homology and receptor chain similarities or functional properties (Fig 1). We have learned in the last decades since the discovery of T_H subsets[2,3] that almost all immune cells display different functional subsets characterized by distinct surface receptors and cytokine profiles, such as CD4 and CD8 T cells, B cells, innate lymphoid cells (ILCs), natural killer (NK) cells, and dendritic cells (DCs).[4-6]

Investigations of the mechanisms of immune and inflammatory cell functions have identified a growing list of interleukins. Their interactions among different cell types that contribute to their effector and suppressive functions are shown in Table I. Phenotypes of cytokine- or receptor-deficient, as well as cytokine-overexpressing, transgenic mice and mutations and relevant polymorphisms in human subjects are listed in Table E2 in this article's Online Repository at www.jacionline.org. Association of cytokines

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Abbreviations used
AIT: Allergen-specific immunotherapy
APC: Antigen-presenting cell
Breg: Regulatory B
γc: Common γ chain
CRS: Chronic rhinosinusitis
DC: Dendritic cell
FOXP3: Forkhead box P3
ILC: Innate lymphoid cell
KO: Knockout
NK: Natural killer
Ra: Receptor antagonist
TLR: Toll-like receptor
Treg: Regulatory T
TSLP: Thymic stromal lymphopoietin
TSLPR: TSLP receptor

with diseases together with anticytokines/anticytokine receptor treatment options are shown in Table II. Fig 1 shows receptor families and common use of receptors between interleukins. Cytokine-driven differentiation of T-cell subsets is shown in Fig 2. The intensive interaction of cytokines and other mediators with cell subsets during type 2 inflammation, which takes places in patients with asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis (CRS), and helminth infections, is shown in Fig 3.

In the main text below we present a functional approach in subgrouping these cytokines, linking various categorization systems. First, we describe different cell subsets named or defined by the main cytokines produced. Next, we describe the cytokine families based on their sequence homology and evolutionary relationship, common receptor chains, or major function of the whole group. Groups of cytokines are listed in Table E1 in this article's Online Repository. Additionally, all of the interleukins have been listed in numeric order, with an extensive emphasis on their structure, receptors, cellular sources, targets, signaling pathways, and roles in immune regulation in patients with allergy, asthma, and other inflammatory diseases in the text portion in this article's Online Repository at www.jacionline.org.

EFFECTOR CD4 T-CELL SUBSETS

$CD4^+$ T cells are divided into distinct subsets according to their cytokine profile.[2] They differentiate from naive T cells, and their cytokine expression profile depends on the types of antigen-presenting cells (APCs), the type of the initial innate immune response, the adjuvanticity of the molecules presented with the antigen, and the existence and dose of many small molecules and other cytokines in the microenvironment.[7] $CD4^+$ naive T cells can differentiate into T_H1, T_H2, T_H9, T_H17, T_H22, and follicular effector T cells, as well as different subsets of regulatory T (Treg) cells.[4,8,9] Based on their respective cytokine profiles, responses to chemokines, and interactions with other cells, these T-cell subsets can promote the development of different types of inflammatory responses (Fig 2). Both innate and effector mechanisms play essential roles during the development of allergic disease.[10]

Effector T_H2 cells produce IL-4, IL-5, IL-9, and IL-13.[11] In addition, thymic stromal lymphopoietin (TSLP), IL-25, IL-31, and IL-33 contribute to the development and intensity of T_H2 responses and inflammation.[12-14] These cytokines have roles in the production of allergen-specific IgE, eosinophilia, mucus, tissue migration of T_H2 cells and eosinophils, regulation of tight junctions, and epithelial barrier integrity.[15-18] They are essential players in immune response to helminths.[19] T_H1 cells produce IFN-γ, which protects against intracellular pathogens and plays a role in activation and chemokine production of resident tissue cells and activation-induced cell death of skin keratinocytes, mucosal epithelial cells, and T cells.[20-22]

The discovery of T_H17 cells has enabled a novel approach to inflammatory processes, autoimmunity, and immune response to extracellular infections. T_H17 cells are characterized by their expression of IL-17A, IL-17F, IL-6, IL-8, TNF-α, IL-22, and IL-26.[23,24] There is still an ongoing debate and no clear distinction between T_H17 and T_H22 cells in human subjects because the main cytokine of T_H22 cells, IL-22, can be produced by T_H17 cells.[25] The combination of TGF-β and IL-4 reprograms the differentiation of T_H9 cells, which produce IL-9 and IL-10.[26] These cells show a distinction to T_H2 cells and might represent a clinically relevant T-cell subset linked to food allergy.[27] Follicular helper T cells represent a large subset of effector T cells in lymphoid tissues and provide help to B cells.[28,29] They support the differentiation of antigen-specific B cells into memory and plasma cells.

Treg CELLS AND OTHER REGULATORY CELLS

Treg cell subsets have distinct phenotypes and include constitutive and inducible subsets of $CD4^+CD25^+$ forkhead box P3 $(FOXP3)^+$ Treg cells and type 1 Treg cells.[30,31] Allergen tolerance and allergen-specific immunotherapy (AIT) are one of the most representative areas in which Treg cells display their major role.[32-34] The production of IL-10 and TGF-β from other cells is decisive for their immune regulatory functions. Subsets of $CD8^+$ T cells, γδ T cells, IL-10–producing B cells, IL-10–producing NK cells, DCs, and macrophages might contribute to immune suppression or regulation.[3,35]

ILC SUBSETS

Immune responses in populations of lymphoid cells that lack rearranged antigen receptors and markers for myeloid and lymphoid lineages, such as T, B, and NK cells, show similarities to T_H1, T_H2, and T_H17/T_H22 types of immune responses. These cells are defined as ILC1s, ILC2s, and ILC3s. ILC1s mainly produce IFN-γ, ILC2s produce IL-5 and IL-13,[36] and ILC3s produce IL-17 and IL-22.[5] ILCs control the mucosal environment through close interaction with epithelial cells and other tissue cells, cytokine production, and induction of chemokines that recruit suitable cell populations to initiate and promote distinct types of immune response development and tissue inflammation.[14] These cells can be detected in several body fluids and tissues, such as sputum, peripheral blood, nasal polyps, and the esophagus, for their characterization in patients with allergy and asthma.[36,37]

MAST CELLS AND BASOPHILS

Mast cells and basophils play a crucial role in type I allergy, as well as in innate and adaptive immune responses.[38] Recent studies in human and mouse models have shown that basophils perform nonredundant effector functions and significantly contribute to

the development and progression of T_H2 cytokine–mediated inflammation.[38,39] Mast cells are localized at the interface with the external environment, such as the skin, respiratory tract, conjunctiva, and gastrointestinal tract. Mast cells contribute to the maintenance of tissue homeostasis, with important roles in wound repair, revascularization, and protective responses to bacterial infection and venoms. They synthesize many interleukins and release them on activation through IgE cross-linking or innate immune response receptors.[38,40]

EPITHELIAL CELLS

Airway epithelial cells, gut epithelium, keratinocytes, and other epithelia are at the interface of the human body and the environment. Thus they form a complex physicochemical barrier and the first line of defense against environmental cues, such as viruses, bacteria, fungi, parasites, allergens, and inorganic particles. Epithelial cells regulate both innate and adaptive immunity, among others, through the production of various costimulatory molecules, chemokines, cytokines, and lipid mediators in response to environmental stimuli sensed by the rich panel of intracellular sensors, such as Toll-like receptors (TLRs), NOD-like receptors, melanoma differentiation-associated protein 5, and retinoic acid–inducible gene 1.[41] After sensing of allergens, epithelial cells can produce IL-1α, IL-25, IL-33, TSLP, and GM-CSF.[41] These cytokines start to orchestrate T_H2 immunity. However, when allergens have additional protease activity and/or are accompanied by microbial components, such as endotoxins or inorganic particles, epithelial secretory responses can lead to mixed T_H2 and T_H17 immunity or even T_H1 responses.[42,43] In response to viruses, epithelial cells produce a wide range of mediators, such as type I interferons, GM-CSF, RANTES/CCL5, and IFN-γ–induced protein 1/CXCL10.[44] These mediators orchestrate further downstream innate and adaptive antiviral immune responses.

PHENOTYPES AND ENDOTYPES OF CHRONIC DISEASES AND INTERLEUKINS AS THERAPEUTIC TARGETS

It is generally expected that drug development in the next decades will show a significant shift from chemicals to biological agents.[45] The new era of drug development is now leading to development of biomarkers and endophenotyping of diseases for better patient care, which is called stratified medicine, precision medicine, or personalized medicine.[46] Distinguishing phenotypes of a complex disease will help to cover the observable clinically relevant properties of the disease but do not show a direct relationship to disease etiology and pathophysiology. In a complex disease, such as asthma, different pathogenetic mechanisms can cause similar disease symptoms; however, they might require different treatment methods.[47]

These putative pathophysiologic mechanisms identifying disease subgroups are addressed by the term endotype. Classification of complex diseases based on the concept of endotypes provides advantages for epidemiologic, genetic, and drug-related studies.[48] Accurate endotyping with biomarkers reflects the natural history of the disease and aims to predict treatment response. Accordingly, recent studies have focused on better understanding of endotypes of allergic diseases, allergen-specific immunotherapy (AIT), asthma, CRS,[49] and chronic obstructive pulmonary disease and development of biomarkers to stratify patients that also include novel interleukins and microRNAs that regulate their expression.[50] Many cytokines and their receptors have been therapeutic targets in clinical studies, and several anticytokine antibodies and/or cytokine receptor antagonists (Ras) have been approved and registered (Table II). Because several clinical trials with anticytokine approaches did not fulfill the primary outcomes in patients with highly heterogeneous diseases, such as asthma, there is a hope that implementing the endotype concept of these diseases will help to tailor the right treatment to the right patient.

THE IL-1 FAMILY

IL-1 was first described as a protein that induced fever and was called human leukocytic pyrogen, which comprises 2 major proteins: IL-1α and IL-1β.[51] Although IL-1α and IL-1β have minimal sequence homology, they were thought to have similar biological properties; however, these properties are becoming more distinct because of different clinical responses to biological targeting of these 2 interleukins. There are fundamental differences in their localization, maturation, and secretion.[51] IL-1α is translated into pro–IL-1α, an already biologically active form, whereas IL-1β is translated into pro–IL-1β, which has no biological activity, until it is processed by the activation of inflammasome and caspase-1. IL-1α and IL-1β exert similar effects by binding to the IL-1 type I receptor. They can also bind to the IL-1 type II receptor, which acts as a decoy receptor and is not involved in signal transduction. The IL-1 family of cytokines comprises 11 members, including 7 proinflammatory agonists (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ) and 4 defined or putative antagonists (IL-1Ra, IL-36Ra, IL-37, and IL-38) exerting anti-inflammatory activities.

IL-1Ra and IL-1 are synthesized and released in response to the same stimuli.[52] IL-1Ra lacks the IL-1 receptor accessory protein interacting domain, so that its binding to IL-1 type I receptor inhibits IL-1 signaling.[53] Therapies under development for some inflammatory disorders involve neutralization of IL-1 activity through administration of IL-1Ra and anti–IL-1 neutralizing mAbs.[54] IL-1Ra–deficient mice spontaneously have chronic inflammatory polyarthropathy (see Table E2). In a phase 1 clinical study IL-1Ra has reduced inhaled LPS-induced airway neutrophilia as a candidate for the treatment of neutrophilic asthma.[55] The balance between expression levels of IL-1 family cytokines and activation and inhibition of inflammasomes, their Ras, and functional and decoy receptors, is decisive in the generation of proinflammatory and/or homeostatic functions.[56,57]

IL-18

IL-18 is a member of the IL-1 family expressed by a range of inflammatory cell types.[58] Assembly of the inflammasome in cells activates caspase-1 and, subsequently, proteolysis and release of the cytokines IL-1β and IL-18, as well as pyroptotic cell death.[54] Although it was originally discovered as an inducer of IFN-γ production, IL-18 alone induces only small amounts, 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 disease activities of rheumatoid arthritis and Crohn disease.

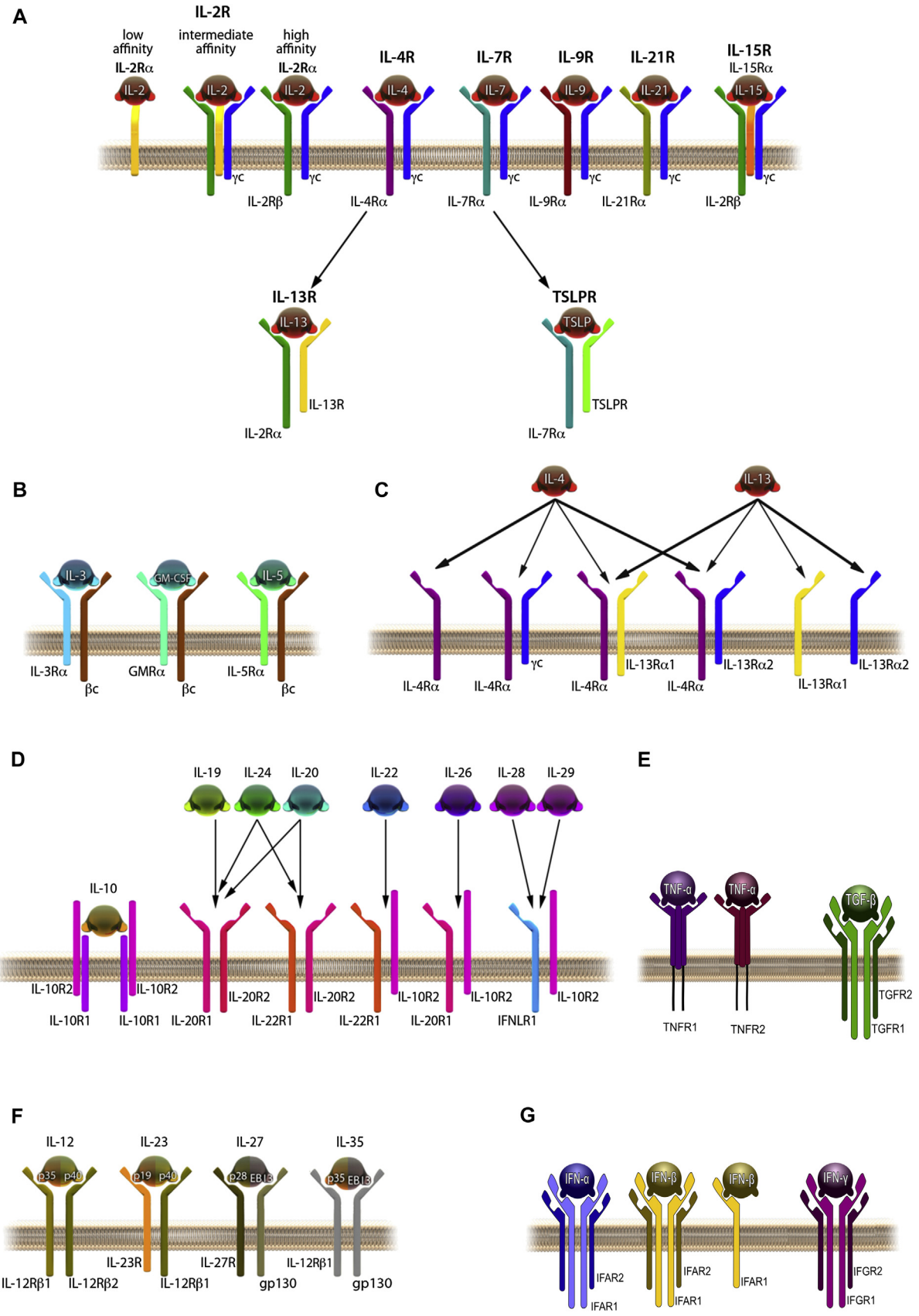

FIG 1. Cytokine receptors. **A,** Receptors of the IL-2 family, which is composed of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Receptors contain the common cytokine receptor γ chain (CD132, γc). IL-13R shares IL-4Rα with

IL-18–deficient mice are more susceptible to bacterial infections than normal mice and have uncontrolled disease progression that is accompanied by reduced T_H1 cell responses (see Table E2). IL-37, a recently described cytokine, requires the receptors IL-18Rα and IL-1R8 to carry out its signal transduction.[59]

IL-33

As a member of the IL-1 family, IL-33 is a potent inducer of type 2 responses in T cells and ILCs through its receptor, ST2.[60,61] 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. Levels of soluble ST2 are increased in patients with inflammatory conditions, such as systemic lupus erythematosus, rheumatoid arthritis, 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. *IL33-IL1RL1* pathway polymorphisms are associated with asthma and specific wheezing phenotypes; most of the single nucleotide polymorphisms are associated with intermediate-onset wheeze, a phenotype closely associated with allergic sensitization.[62] In addition, infection of the respiratory epithelium with rhinovirus can antagonize tolerance to inhaled antigen through combined induction of TSLP, IL-33, and OX40 ligand.[63] As an interesting recent finding, IL-33 can impair barrier function of the skin by downregulating filaggrin expression.[17]

IL-36

IL-36 is another proinflammatory family member of IL-1 and a common mediator of innate and adaptive immune responses. It is inhibited by IL-36Ra[64] and uses mitogen-activated protein kinase and nuclear factor κB pathways, exerting proinflammatory effect *in vivo* and *in vitro*. IL-38 binds to IL-36 receptor, as does IL-36Ra, and has similar biological effects on immune cells. Both IL-38 and IL-36Ra have anti-inflammatory biological effects. Recently, high expression of IL-36 has been reported in transcriptomic analyses of AD lesions.[65]

IL-37

IL-37 was originally defined as IL-1 family member 7, which is found in monocytes, tonsil plasma cells, and breast carcinoma cells.[66] Recently, IL-1R8 was found to act as the coreceptor for IL-37–IL-18Rα, and this interaction was required for the anti-inflammatory function of IL-37.[59] TGF-β and several TLR ligands induce production of high levels of IL-37 by PBMCs, and proinflammatory cytokines, such as IL-18, IFN-γ, IL-1β, and TNF, moderately increase IL-37 levels.[67] IL-37b transgenic mice are protected from LPS-induced shock through reductions in proinflammatory cytokine levels and inhibition of DC activation (see Table E2).[67]

IL-38

IL-38 is also a member of the IL-1 cytokine family and shares some characteristics of IL-1Ra, binding the same IL-1 receptor type I. The *IL1F10* gene is located in the IL-1 family cluster on chromosome 2 in human subjects and mice between the genes encoding IL-36Ra and IL-1Ra. IL-38 is highly homologous to IL-36Ra and IL-1Ra, suggesting that it might act as an IL-1 family antagonist. IL-38 expression was reported in skin, tonsil, thymus, spleen, fetal liver, and salivary glands.[68] IL-38 plays a role in the pathogenesis of inflammatory diseases, exerting a protective effect in some autoimmune diseases. The effects of IL-38 might resemble those of IL-36Ra because it binds to the IL-36 receptor and inhibits its effects, particularly the T_H17 response.[53]

THE COMMON γ CHAIN CYTOKINE FAMILY

The common γ chain (γc) family consists of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 and was named for binding of these factors to the 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.[69]

IL-2

IL-2, which was discovered more than 30 years ago in supernatants of activated T cells, is mainly produced by $CD4^+$ and $CD8^+$ T cell–activated DCs and NK and NKT cells.[70] 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 γc (Fig 1). All 3 subunits are required for assembly of the high-affinity IL-2R. On T-cell activation, IL-2Rα is rapidly upregulated and participates in the formation of a high-affinity quaternary complex, which activates multiple signal transduction pathways. IL-2 is essential for the development of Treg cells, and IL-2Rα is a marker for the flow cytometric identification of Treg and regulatory B (Breg) cells in resting conditions.[71,72] IL-2 is a regulator of ILCs and acts as a B-cell growth factor, stimulates antibody synthesis, and promotes proliferation and differentiation of NK cells to increase their cytolytic functions.[73]

IL-4, and TSLPR shares IL-7R with IL-7. **B,** Receptors for IL-3, IL-5, and GM-CSF are heterodimers of a unique α chain and the common β chain (βc, CD131) subunit. **C,** Receptors for IL-4 and IL-13 consist of 2 receptor chains: IL-4Rα (CD124) and γc. IL-4 and IL-13 bind to IL-4R, which consists of IL-4Rα and the IL-13Rα1 chain. IL-13R consists of 2 subunits, IL-13Rα1 and IL-13Rα2, and signaling occurs through the IL-4R complex type II, which consists of IL-4Rα and IL-13Rα. **D,** Based on 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, as shown. **E,** TNF-α binds to TNFRI and TNFR2, and TGF-β binds to heterodimer receptor consisting of TGF-βR1 and TGF-βR2. **F,** IL-12R consists of 2 subunits: IL-12Rβ1 and IL-12Rβ3. A heterodimer of IL-12Rβ1 and IL-23R binds IL-23. IL-12Rβ2 shows homology to the gp130 subunit of IL-27R. **G,** IFN-α and IFN-β bind to the heterodimer receptor consisting of IFNAR1 and IFNAR2; in addition, IFN-β binds to IFNAR1, and IFN-γ binds to the IFN-γR1 and IFN-γR2 heterodimer.

TABLE I. Cytokines and their major functions

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-1α and IL-1β	Heterodimer	17 kDa	IL-1 type 1 receptor, IL-1 type 2 receptor	Macrophages, monocytes, lymphocytes, keratinocytes, microglia, megakaryocytes, neutrophils, fibroblasts, synovial lining cells	T cells, fibroblasts, epithelial and endothelial cells	Induction of proinflammatory proteins; hematopoiesis; differentiation T_H17 cells; development of IL-10–producing Breg cells in mouse spleens and mesenteric lymph nodes
IL-1Ra (antagonist)	Heterodimer	16.1-20 kDa	IL-1 type 1 receptor, IL-1 type 2 receptor	Monocytes, macrophages, fibroblasts, neutrophils, endothelial and epithelial cells, and keratinocytes	T cells, fibroblasts, epithelial and endothelial cells	Antagonism of IL-1
IL-2	Monomer	15.5 kDa	IL-2R	$CD4^+$ and $CD8^+$ activated T cells, DCs, NK and NKT cells, mast cells, and ILCs	$CD4^+$ and $CD8^+$ T cells, NK and B cells, and ILCs	Proliferation of effector T and B cells; development of Treg cells; differentiation and proliferation of NK cells; growth factor for B cells and stimulus for antibody synthesis; proliferation and cytokine production in ILCs
IL-3	Monomer	15 kDa	IL-3 receptor α + β c (CD131)	T cells, macrophages, NK cells, mast cells, eosinophils, stromal cells	Erythroid progenitors, granulocytes, macrophages progenitors, $CD34^+$ progenitor cells, basophils, eosinophils, megakaryocytes, monocytes, Treg and endothelial cells	Hematopoietic growth factor; activation of basophils and eosinophils; differentiation of DCs and Langerhans cells; enhancement of IL-2–induced proliferation and differentiation of B cells; improvement of antigen uptake; phagocytosis in macrophages
IL-4	Monomer	15 kDa	IL-4R type I, IL-4R type II	T_H2 cells, basophils, eosinophils, mast cells, NKT cells and γ/δ T cells	T and B cells	Induction of T_H2 differentiation; IgE class-switching; 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
IL-5	Homodimer	15 kDa	IL-5R	T_H2 cells, activated eosinophils and masts cells, T_C2 cells, γδ T cells, NK and NK T cells and $CD4^-$c-$Kit^-CD3\varepsilon^-IL2R\alpha^-$ (Peyer patches), ILC2s	Eosinophils, basophils and mast cells, Treg cells, neutrophils and monocytes	Differentiation and function of myeloid cells; increment of eosinophils chemotactic activity and adhesion capacity; involvement in remodeling and wound healing

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-6	Homodimer	19-26 kDa	IL-6R (sIL-6R) gp130	Endothelial cells, fibroblasts, monocytes/ macrophages, T cells, B cells, granulocytes, smooth muscle cells, eosinophils, chondrocytes, osteoblasts, mast cells, glial cells, and keratinocytes	Hepatocytes, leukocytes, T cells, B cells, hematopoietic cells	Induction of acute-phase proteins in hepatocytes; leukocyte trafficking and activation; T-cell differentiation, activation, and survival; B-cell differentiation and production of IgG, IgM, and IgA; hematopoiesis; involvement in osteoclastogenesis and bone resorption and recruitment of mesenchymal vascular cells; neoangiogenesis *in vivo*; synovial fibroblast proliferation and cartilage degradation; survival of cholinergic neurons and induction of adrenocorticotropic hormone synthesis
IL-7	Monomer	25 kDa	IL-7R and sIL-7R	Epithelial cells, keratinocytes, DCs, B cells, and monocytes/ macrophages	Developing B and T lymphocytes, mature T cells, NK cells, and ILCs	Proliferation of pre-B and pro-B cells (mice); megakaryocyte maturation; V(D)J recombination; naive T-cell survival; proliferation of thymocytes; development and maintenance of ILCs; synthesis induction of inflammatory mediators in monocytes
IL-8	Homodimer	16 kDa	CXCR1 and CXCR2	Monocytes, macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, fibroblasts, keratinocytes, chondrocytes, synovial cells, hepatocytes, smooth muscle and skeletal muscle cells	Neutrophils, NK cells, T cells, basophils, eosinophils, mast cells, monocytes, and endothelial cells	Chemoattractant for neutrophils, NK cells, T cells, basophils, and eosinophils; mobilization of hematopoietic stem cells; angiogenesis
IL-9	Monomer	14 kDa	IL-9R	T_H2, T_H9, T_H17, and Treg cells, mast cells, eosinophils, ILCs	B, T, and mast cells; hematopoietic cells; airway epithelial cells; airway smooth muscle cells; and intestinal epithelial cells	T and mast cell growth factor; inhibition of T_H1- cytokines; proliferation of $CD8^+$ T cells and mast cells; IgE, chemokine, and mucus production in bronchial epithelial cells

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-10	Homodimer	20.5 kDa (predicted size of precursor protein) 18.6 kDa (predicted size mature protein, monomer)	IL-10R1/IL-10R2 complex	T cells, B cells, monocytes, macrophages, and DCs	Macrophages, monocytes, T cells, B cells, NK cells, mast cells, DCs, and granulocytes	Immunosuppressive effect through APCs or direct effects on T-cell subsets; suppression of IgE and induction of IgG by B cells in human subjects
IL-11	Monomer	19 kDa	IL-11Rα + gp130	Bone marrow 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, megakaryocyte progenitors and plasmacytoma cells; protection of epithelial cells and connective tissue; induction of acute-phase proteins; inhibition of monocytes and macrophage activity; promotion of neuronal development; bone remodeling, by stimulation of osteoclasts and inhibition of osteoblasts
IL-12 (p35/p40)	Heterodimer	35 kDa (IL-12a p35) + 40 kDa (IL12b p40)	IL-12Rβ1 and IL-12Rβ2	Monocytes, macrophages, neutrophils, microglia, DCs, B cells	T cells (T^H1 cells), NK cells	Development and maintenance of T_H1 cells; activation of NK cells; support of DC maturation; induction of cytotoxicity
IL-13	Monomer	10 kDa	IL-13R1α1 and IL-13R1α2	T, NKT, and mast cells; basophils and eosinophils; and ILCs	B cells, mast cells, epithelial cells, eosinophils, smooth muscle cells, and macrophages	Switching to IgG_4 and IgE, upregulation of CD23, MHC class II on B cells, and induction of CD11b, CD11c, CD18, and CD29; CD23 and MHC class II on monocytes; activation of eosinophils and mast cells; recruitment and survival of eosinophils; defense against parasite infections
IL-14	Monomer	53 kDa	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
IL-15	Monomer	14-15 kDa	IL-15R	Monocytes, macrophages, DCs and activated $CD4^+$ T cells, keratinocytes, skeletal muscle cells, fibroblasts, various epithelial cells, bone marrow stromal cells, nerve cells	NK cells, NKT cells, monocytes, macrophages, DCs, neutrophils, eosinophils, mast cells, T cells and B cells	T-cell activation; proliferation and activation of NK cells; differentiation of γ/δ T cells; homeostasis of $CD8^+$ memory, NK, and NKT cells; enhancement of T_H2 differentiation; prevention of neutrophils and eosinophils from apoptosis

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-16	Homotetramer	56 kDa	CD4	T cells, eosinophils, mast cells, eosinophils, monocytes, DCs, fibroblasts, epithelial cells, synoviocytes	T cells, monocytes, macrophages, DCs, eosinophils, mast cells	Modulation of T-cell response; chemoattractant for $CD4^+$ T cells, $CD8^+$ T cells, monocytes, mast cells, and eosinophils
IL-17A	Cysteine knot, homodimer or heterodimer	35 kDa	IL-17RA (= IL-17R)	T_H17 cells, $CD8^+$ T cells, NK cells, NKT cells, γδ T cells, neutrophils, ILCs	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages, B and T lymphocytes, myelomonocytic cells and marrow stromal cells	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment and activation of neutrophils
IL-17B,C,D	Cysteine knot, homodimer	41, 40, and 52 kDa	For IL-17 B: IL-17RB (= IL-17H1, IL-25R) For IL-17C: IL-17RA to IL-17RE For IL-17D: SEF	IL-17B: neuronal cells, chondrocytes; IL-17C: mucosal epithelial cells; IL-17D: resting B and T cells, skeletal muscle, brain, adipose tissue, heart, lung, and pancreas	Monocytes, endothelial cells, myofibroblasts, epithelial cells	Induction of antimicrobial peptides, proinflammatory cytokines, chemokines. and metalloproteases; IL-17B: chondrogenesis and osteogenesis; IL-17C: influence on intestinal barrier function; IL-17D: suppression of myeloid progenitor cell proliferation
IL-17F	Cysteine knot, homodimer or heterodimer	44 kDa	IL-17RA (= IL-17R) and IL-17RC (= IL-17RL)	T_H17 cells, $CD8^+$ T cells, NK cells, NKT cells, γδ T cells neutrophils, basophils, mast cells, monocytes	Epithelial/endothelial cells, fibroblasts, osteoblasts, monocytes, macrophages, B and T lymphocytes, myelomonocytic cells and marrow stromal cells	Induction of proinflammatory cytokines, chemokines, and metalloproteases; recruitment and activation of neutrophils
IL-18	Heterodimer	22.3 kDa	IL-18 receptor	Macrophages, DCs, epithelial cells, chondrocytes, osteoblasts, Kupffer cells, keratinocytes, astrocytes, renal tubular epithelial cells	T cells, NK cells, macrophages, epithelial cells, chondrocytes	Induction of IFN-γ in the presence of IL-12; enhancement of NK cell cytotoxicity, promoting T_H1 or T_H2 cell responses depending on cytokine milieu
IL-19	Monomer	20.5 kDa: predicted size of precursor; 17 kDa: predicted size of mature protein; 35-40 kDa: found in transfected cells, glycosylated	IL-20R1/IL-20R2	Monocytes, keratinocytes, endothelial and epithelial cells, B cells	Keratinocytes	Induction of T_H2 cytokines; enhanced production of IL-6, TNF-α, and IL-10 in monocytes
IL-20	Monomer	20 kDa (predicted size of precursor), 17.5 kDa (predicted size of mature protein)	IL-20R1/IL-20R2 and IL-22R1/ IL-20R2	Monocytes, keratinocytes, epithelial and endothelial cells	Keratinocytes, monocytes, epithelial cells, and stromal cells in skin, lung, pancreas, and breast tissues	Role in skin biology
IL-21	Four-helix bundle, monomer	15 kDa	IL-21R	T cells (predominantly T_H17 and T_H9), NK T cells	$CD4^+$ T cells, $CD8^+$ T cells, B cells, DCs, macrophages, keratinocytes	B-cell proliferation, differentiation, and survival; T-cell growth factor; NKT cell proliferation when combined with either IL-2 or IL-15

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-22	Six anti-parallel α-helices, monomer	23 kDa	IL-22R	Activated T cells (predominantly T_H17 and T_H22 cells), NKT cells, activated NK cells, lymphoid tissue-inducer cells, ILCs	Keratinocytes and epithelial cells of kidney, small intestine, liver, colon, lung, and particularly pancreas and skin	Pathogen defense; wound healing; tissue reorganization
IL-23 (p19+p40)	Heterodimer	IL-12b p40 = 40 kDa, IL-23 p19 = 19 kDa	IL-23R	Phagocytic cells, macrophages, and activated DCs from peripheral tissues, including the skin, intestinal mucosa, and lungs	T cells (T_H17 cells), NK and NKT cells, eosinophils, monocytes, macrophages, DCs, and epithelial cells	Stimulation of production of proinflammatory IL-17; enhancement of T-cell proliferation and promotion of memory T cells; activation of NK cells; regulation of antibody production
IL-24	Homodimer and monomer	23.8 kDa (predicted size of unprocessed precursor), 18 kDa (unglycosylated mature protein), 35 kDa (observed size of secreted IL-24, glycosylated)	IL-20R1/IL-20R2 and IL-22R1/IL-20R2	Melanocytes, T cells, monocytes, normal human epidermal keratinocytes, B cells	Cancer cells	Tumor suppression
IL-25 (IL-17E)	Homodimer	19 kDa	IL-17RA and IL-17RB	T_H2 cells, mast and epithelial cells, eosinophils, and basophils from atopic subjects	T_H2 memory cells, fibroblasts, basophils, NKT cells, macrophages, and ILC2s	Induction of T_H2 responses and inhibition of both T_H1 and T_H17 cell responses; induction of IgE, IgG_1, IL-4, IL-5, IL-13, and IL-9 production
IL-26	Six α-helices, homodimer	38 kDa	IL-10R2 chain and IL-20R1 chain	Memory T cells, NK cells, activated T_H17 cells	Epithelial cells, binds heparin	Activation and regulation of epithelial cells
IL-27 (p28+EBI3)	Heterodimer	IL-27a p28 = 28 kDa; IL-27b EBI-3 = 25.4 kDa	WSX-1 and gp130	Activated DCs, macrophages, epithelial cells	T cells, NK cells	Induction of T-bet, promoting T_H1 cell differentiation; inhibition of T_H17 cells response through STAT1
IL-28A/B/IL29 (IFN-λ family)	Monomer	IL-28A = 22.3 kDa; IL-28B = 22.2 kDa; IL-29 = 21.9 kDa	IL-28R1/IL-10R2	Nucleated cell types, particularly DCs, in response to viral infection	Tissue-resident cells, primary monocytes, myeloid and plasmacytoid DCs, and $CD4^+$ cells	Downregulation of T_H2 response and upregulation of T_H1 response; induction of tolerogenic DCs and consequent promotion and expansion of Treg cells
IL-30 (p28 subunit of IL-27)	Heterodimer	28 kDa				Prevention and treatment of cytokine-induced liver injury
IL-31	Four-helix bundle	24 kDa	IL-31RA/OSMRβ	Activated $CD4^+$ T cells (mainly T_H2) and $CD8^+$ T cells, monocytes, macrophages, DCs, mast cells, keratinocytes, and fibroblasts	Keratinocytes, epithelial cells, dorsal root ganglia, eosinophils, mast cells, basophils, and monocytes	Induction of IL-6, IL-8, CXCL1, CXCL8, CCL2, and CCL8 production in eosinophils; upregulation of chemokine mRNA expression in keratinocytes and induction of growth factor and chemokine expression in epithelial cells; inhibition of proliferation and apoptosis in epithelial cells

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IL-32	Unknown	14.9-26.6 kDa	Unknown	Monocytes, macrophages, NK cells, T cells, epithelial cells	Macrophages, DCs, T cells, PBMCs, monocytes	Induction of TNF-α, IL-8, and IL-6 and apoptosis of epithelial cells
IL-33	β-Trefoil fold	30 kDa (active form = 18 kDa)	ST2	Necrotic cells, nuocytes, and fibroblasts on mechanical stress; stromal cells on cell damage; epithelial cells	Basophils, mast cells, eosinophils, DCs, macrophages, NK cells, NKT cells, T lymphocytes, B lymphocytes, endothelial cells, epithelial cells, fibroblasts, ILCs	Transcriptional repressor activity; induction of T_H2-type inflammation on mucosal tissues; maturation factor for bone marrow–derived DCs accompanied by the release of proinflammatory cytokines; enhanced integrin expression in basophils and eosinophils; inducer of ILCs
IL-34	Homodimer	39-kDa monomers	Colony-stimulating factor 1 receptor	Heart, brain, liver, kidney, spleen, thymus, testes, ovary, small intestine, prostate, and colon; most abundant in spleen	Monocytes, macrophages	Regulator of myeloid lineage differentiation, proliferation, and survival; microglial proliferation
IL-35 (p35+EBI3)	Heterodimer	60 kDa	IL-12Rβ2/gp130; IL-12Rβ2/IL-12Rβ2; gp130/gp130	Treg cells, monocytes, vascular endothelial cells, smooth muscle cells, and epithelial cells	NK cells and activated T cells	Reduction of effector T-cell proliferation; increase of IL-10 production and Treg cell proliferation
IL-36			IL-36Ra	Internal endothelial tissues and skin, bone marrow–derived macrophages	Keratinocytes and other epithelial barriers; at lower levels on DCs, naive $CD4^+$ T cells, differentiated T_H1 and T_H2 cells; very low levels on T_H17 cells	Promotion of the early inflammatory response to tissue injury or infection
IL-37	Unknown	17-24 kDa	IL-18Rα and IL-18BP	Monocytes, tonsil plasma cells, breast carcinoma cells, some colon carcinoma cells, melanomas, and lung carcinomas	DCs	Inhibition of IL-18 activity and innate immunity
IL-38		17 kDa	IL-1R1 with low affinity, IL-36R	Basal epithelia of skin, spleen, fetal liver, placenta, and thymus and proliferating B cells of the tonsils		Inhibition of the production of T_H17 response cytokines; antagonism of IL-36
IFN-α, IFN-β	Homodimer	15–21 kDa (IFN-α) and 22 kDa (IFN-β)	IFNAR	Mainly plasmacytoid DCs, but all nucleated cells can produce IFN-αβ in response to viral infection	All cells express IFNAR in low numbers	Defense against viral infection by orchestrating adaptive immune responses; stimulation of DC capability to present antigens; stimulation of macrophage antibody-dependent cytotoxicity; activation of naive T cells; promotion of development and proliferation of the B1 subset; trigger of apoptosis of tumor cells, as well as virus-infected cells

(Continued)

TABLE I. *(Continued)*

Cytokine	Structure	Size (molecular weight)	Receptors	Cell sources	Cell targets	Major functions
IFN-γ	Homodimer	40-60 kDa	IFNGR1/IFNGR2	NK and NKT cells, macrophages, myelomonocytic cells, T_H1 cells, cytotoxic T lymphocytes, and B cells	Epithelial cells, macrophages, DCs, NK cells, T and B cells	Antiviral properties; promotion of cytotoxic activity and T_H1 differentiation; upregulation of MHC class I and II; inhibition of cell growth; proapoptotic effects and control of activation-induced cell death; induction of epithelial apoptosis in skin and mucosa
TGF-β	Homodimer	25 kDa	TβR-I and TβR-II	A large variety of cells, including epithelial cells, fibroblasts, and immune cells, such as eosinophils, macrophages, and Treg cells	Epithelial and endothelial and mesenchymal and immune cells, including CD8 T cells, CD4 T cells, NK cells, monocytes, macrophages, neutrophils, and eosinophils	Coordination of the proper development of the cardiac system and bone formation; induction of epithelial and endothelial to mesenchymal transition; balance of proinflammatory and anti-inflammatory effects by decreasing the cellular growth of almost all immune cell precursors; regulation of the differentiation of several T_H cell subsets and induction of Treg cells; immune tolerance
TNF-α	Homotrimer	26 kDa membrane-bound form + 17 kDa soluble form	TNFR1 (p55/60, CD120a) and TNFR2 (p75/80, CD120b)	Activated macrophages, monocytes, $CD4^+$ T cells, B cells, neutrophils, NK cells and mast cells, fibroblasts, astrocytes, microglial cells, endothelial cells, smooth muscle cells, adipocytes, intrinsic renal cells, and others	Nucleated cells	Host defense; double role as a proinflammatory mediator by initiating a strong inflammatory response and an immunosuppressive mediator by limiting the extent and duration of inflammatory processes and by inhibiting the development of autoimmune diseases and tumorigenesis; epithelial apoptosis

SEF, Similar expression to FGFs; *STAT*, signal transducer and activator of transcription.

IL-4

IL-4 is produced by T_H2 cells, type 2 ILCs, basophils, mast cells, and eosinophils. There are 2 types of IL-4Rs (Fig 1).[5] IL-4 regulates allergic conditions and the protective immune response against helminths and other extracellular parasites.[74] IL-4 is the major stimulus of T_H2 cell development and induces IgE class-switching in B cells (Figs 2 and 3). It also suppresses type 1 immunity development, including T_H1 cells and M1 macrophages. IL-4 increases expression of class II MHC molecules in B cells, upregulates B-cell receptors, increases expression of CD23, prolongs the lifespan of T and B cells in culture, and mediates tissue adhesion and inflammation. IL-4 and IL-4Rα knockout (KO) mice have defects in T_H2 cell differentiation and reduced serum IgG_1 and IgE levels. There have been extensive clinical trials targeting IL-4 and IL-13 pathways, with more promising results on anti–IL-13 approaches for the treatment of asthma and atopic dermatitis.[75]

IL-7

IL-7 is also known as pre–B-cell growth factor or lymphopoietin 1. IL-7R is present on most T cells and on progenitors of B cells and bone marrow macrophages. It consists of IL-7Rα (CD127) and γc (CD132) chains (Fig 1).[76] IL-7 responses are determined by expression of IL-7Rα, which is shared with the TSLP receptor, because γc is ubiquitously expressed on lymphocytes. IL-7 critically acts cooperatively with signaling through the pre–T-cell receptor to coordinate proliferation, differentiation, and T-cell receptor α recombination of thymocytes.[77] IL-7 signaling contributes to survival, proliferation, and development

TABLE II. Disease association and therapeutic application of cytokines

Cytokine	Disease association	Therapeutic application
IL-1α and IL-1β	Rheumatoid arthritis, multiple sclerosis, systemic lupus erythematous, psoriasis, inflammatory bowel disease, Graves disease, diabetes, cryopyrin-associated periodic syndromes, cancer, bacterial and viral infections, atopic dermatitis, asthma, osteoarthritis, chronic obstructive pulmonary disease, Alzheimer disease, atherosclerosis, myocardial infarction	*Treatment*: Cryopyrin-associated periodic syndromes, gout *Drugs*: Human mAbs targeting only IL-1β (ILARIS/canakinumab), dimeric fusion protein consisting of human IL-1R (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) linked with Fc region of human IgG_1 that neutralizes IL-1 (IL-1 Trap/rilonacept) *Clinical trials*: Adult-onset Still disease, systemic juvenile idiopathic arthritis, Schnitzler syndrome, osteoarthritis, hereditary periodic fevers, atrial fibrillation, HIV, cardiovascular disease (see also IL-1Ra)
IL-1Ra (antagonist)	Rheumatoid arthritis, multiple sclerosis, systemic lupus erythematous, psoriasis, juvenile idiopathic arthritis, Still disease, type 1 diabetes, inflammatory bowel disease, atopic dermatitis, asthma	*Treatment*: Rheumatoid arthritis *Drugs*: Recombinant nonglycosylated human IL-1Ra (anakinra) *Clinical trials*: Type I diabetes, metabolic syndrome, hypersecretion, type 2 diabetes mellitus, HIV, neurologic disorders, heart failure, acute myocardial infarction, Kawasaki disease, cancer
IL-2	T cell–mediated autoimmune and inflammatory diseases, X-Linked severe combined immunodeficiency 1	*Treatment*: Cancer, leukemia, and infectious diseases; use in bone marrow transplantation and to prevent kidney transplantation rejection *Drugs*: Recombinant human IL-2 (Proleukin, Interking), recombinant protein combining IL-2 and diphtheria toxin (Denileukin Diftitox), humanized IL-2Rα chain blocking mAbs (daclizumab, basiliximab) *Clinical trials*: Cancer, chronic graft-versus-host disease, multiple sclerosis, type I diabetes, thrombocytopenia, ulcerative colitis, Sjögren syndrome, different autoimmune and inflammatory diseases
IL-3	Allergic asthma, cancer, lymphocytic and acute myeloid leukemias, inflammatory arthritis	*Drugs*: Fusion toxin composed of catalytic and translocation domains of diphtheria toxin (DT388) linked to IL-3 (DT388Il3), recombinant human IL-3 (IL-3) *Clinical trials*: Breast neoplasms, leukemia, myelodysplastic syndromes, blastic plasmacytoid DC neoplasm, HIV infections; cytopenias
IL-4	Allergic asthma, allergic rhinitis, diabetes mellitus, parasite infection, chronic lymphocytic leukemia	*Therapy*: Asthma *Drugs*: Soluble recombinant human IL-4 receptor (pitrakinra), humanized blocking mAbs specific for IL-4 (pascolizumab) *Clinical trials*: tuberculosis
IL-5	Asthma, atopic dermatitis, chronic obstructive pulmonary disease, eosinophilic gastrointestinal diseases, hypereosinophilic syndrome, Churg-Strauss syndrome and eosinophilic nasal polyposis	*Therapy*: Asthma *Drugs*: Humanized blocking mAbs specific for IL-5 (mepolizumab), mAbs targeting IL-5 receptor (MEDI-563/benralizumab), humanized mAbs (reslizumab) *Clinical trials*: Hypereosinophilic syndrome, COPD, atopic dermatitis, asthma
IL-6	Systemic lupus erythematosus, psoriasis, rheumatoid arthritis, juvenile idiopathic arthritis, B-cell malignancy, Castleman disease, pulmonary fibrosis, chronic inflammatory diseases, plasmacytoma/multiple myeloma, cardiac myxoma, asthma	*Treatment*: Rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman disease *Drugs*: Humanized mAbs targeting IL-6R (Actemra/tocilizumab) *Clinical trials*: Acute graft-versus-host disease, type 1 diabetes mellitus, dermatomyositis, schizophrenia, sclerosis, hemophagocytic lymphohistiocytosis, myocardial infarction, diabetic macular edema, arthritis, cardiovascular disease, primary Sjögren syndrome, leukemia
IL-7	Multiple sclerosis, type 1 diabetes, rheumatoid arthritis, primary biliary cirrhosis, inflammatory bowel disease, atopic dermatitis, inhalation allergy, sarcoidosis, graft-versus-host disease	*Drugs*: Human recombinant IL-7 (CYT107) *Clinical trials*: Cancer treatment, improving recovery after allogeneic stem cell transplantation, HIV therapy, sepsis, lymphopenia, cancer

(Continued)

TABLE II. *(Continued)*

Cytokine	Disease association	Therapeutic application
IL-8	Rheumatoid arthritis, psoriasis, bacterial and viral infections, chronic obstructive pulmonary disease, cystic fibrosis; cancer, acute myeloid leukemia, myelodysplastic syndromes, HIV infection	*Drugs*: Full human mAbs targeting IL-8 (HuMax-IL-8, ABX-IL-8) *Clinical trials*: Pustulosis palmoplantaris, cancer, chronic bronchitis and COPD
IL-9	Helminth infections, Hodgkin lymphoma, asthma and food allergy	*Drug*: Humanized mAbs specific for IL-9 (MEDI-528) *Tested in clinical trials*: Asthma treatment
IL-10	Systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, inflammatory bowel disease, allergic asthma, allergic rhinitis, atopic dermatitis, bee venom allergy, contact dermatitis, cancer	*Drugs*: Human recombinant IL-10 (Tenovil), fusion protein consisting of targeting antibody and IL-10 (Dekavil/F8-IL-10) *Clinical trials*: Rheumatoid arthritis
IL-11	Allergic asthma and cancer	*Drugs*: Recombinant human IL-11 (oprelvekin) *Clinical trials*: Chemotherapy-induced thrombocytopenia, leukemia, hemostatic disorders
IL-12 (p35/p40)	Bacterial infections, inflammatory bowel disease, psoriasis, cancer	*Treatment*: Psoriatic arthritis and severe plaque psoriasis *Approved drugs*: Anti–IL-12/23 human IgG_1 mAbs (ustekinumab), recombinant human IL-12 (NM-IL-12) *Clinical trials*: Lymphoma, wound infection, cancer, leukemia, HIV, infectious disease, multiple sclerosis, Behçet disease, acute radiation syndrome, CVID
IL-13	Asthma, allergic rhinitis, and fibrosis	*Drugs*: Humanized mAbs specific for IL-13 (lebrikizumab), soluble IL-13Rα2–Fc fusion protein (QAX576, IMA638), human anti–IL-13 mAbs (tralokinumab) *Clinical trials*: Asthma, atopic dermatitis, idiopathic pulmonary fibrosis, COPD
IL-14	Systemic lupus erythematosus, Sjögren syndrome, lymphoma	
IL-15	Rheumatoid arthritis, psoriasis, diabetes mellitus, autoimmune vasculitis, systemic lupus erythematosus, pemphigus vulgaris, multiple sclerosis, celiac disease, Behçet disease, asthma, sarcoidosis, inflammatory bowel diseases, inflammatory synovitis	*Drugs*: Recombinant human IL-15 (rhIL-15), fusion protein IL-15N72D:IL-15RαSu/Fc (ALT-803), human mAbs against IL-15 (AMG-714) *Clinical trials*: AML, cancer, HIV infection (as adjuvant), cancer, rheumatoid arthritis, celiac disease
IL-16	Atopic dermatitis, allergic asthma, Crohn disease, rheumatoid arthritis, HCV, tuberculosis, HIV, multiple sclerosis, cancer, multiple myeloma	
IL-17A	Rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, psoriasis, allergic asthma, atopic dermatitis, contact hypersensitivity, graft-versus-host-disease	*Treatment*: Severe plaque psoriasis *Drugs*: Human mAb binding to IL-17A (secukinumab/AIN457) *Clinical trials*: Psoriatic arthritis, rheumatoid arthritis, nail psoriasis, ankylosing spondylitis, chronic plaque-type psoriasis
IL-17B, C, D	Rheumatoid arthritis, allergic asthma, inflammatory cardiomyopathy, Wegener granuloma, multiple sclerosis, psoriasis	
IL-17F	Inflammatory bowel disease, psoriasis, allergic asthma, rheumatoid arthritis, Crohn disease	
IL-18	Bacterial and viral infections, rheumatoid arthritis, psoriasis, multiple sclerosis, type I diabetes, Crohn disease, Alzheimer disease, allergic rhinitis, atopic dermatitis, asthma	*Drugs*: Recombinant human IL-18 (SB-485232, Tadekinig alfa) *Clinical trials*: Cancer and lymphoma (in combination with other therapies), psoriasis, Still disease
IL-19	Psoriasis, asthma, atopic dermatitis, arthritis, cancer	
IL-20	Psoriasis, rheumatoid arthritis, obesity, atherosclerosis, ulcerative colitis, asthma, cancer, osteoporosis	
IL-21	Cancer, systemic lupus erythematous, rheumatoid arthritis, EAE, Behçet disease	*Drugs*: Recombinant human IL-21 (Denenicokin/BMS-982470), IL-21–specific mAbs (NNC0114-0006) *Clinical trials*: Cancer, lymphoma, leukemia, rheumatoid arthritis, diabetes mellitus (type 1), Crohn disease
IL-22	Psoriasis, inflammatory bowel disease, cancer	*Drugs*: Recombinant protein containing a human IL-22 dimer (F652), human mAbs specific for IL-22 (fezakinumab/ILV-094) *Clinical trials*: Acute graft-versus-host disease, atopic dermatitis, rheumatoid arthritis, psoriasis

(Continued)

TABLE II. *(Continued)*

Cytokine	Disease association	Therapeutic application
IL-23 (p19+p40)	Exacerbate organ-specific autoimmune inflammation, Crohn disease, and psoriasis	*Drugs*: Human mAbs directed against IL-12 and IL-23 (Ustekinumab), mAbs against IL-23 (LY 3074828, guselkumab, tildrakizumab) *Clinical trials*: Systemic lupus erythematosus, graft-versus-host disease, axial spondyloarthritis psoriasis, colitis, Crohn disease, type 1 diabetes mellitus, dermatitis, Behçet disease, CVID, multiple sclerosis
IL-24	Melanoma, psoriasis	
IL-25 (IL-17E)	Gastrointestinal disorders, chronic rhinosinusitis, atopic dermatitis, allergic asthma	
IL-26	Inflammatory bowel disease	
IL-27 (p28+EBI3)	Immune pathology caused by uncontrolled inflammatory response, Crohn disease or ulcerative colitis, asthma, and HIV	
IL-28A/B/IL29 (IFN-λ family)	Allergy (IgE-mediated food allergy, atopic dermatitis) and atopic asthma, autoimmune diseases, HBV, HCV, and cancer	*Drugs*: Pegylated interferon Lambda-1a (pegIFNλ), pegylated recombinant IL-29 (PEG-rIL-29) *Clinical trials*: Hepatitis C infection
IL-30 (p28 subunit of IL-27)		
IL-31	Atopic dermatitis, allergic contact dermatitis, prurigo nodularis, chronic spontaneous urticaria, nonatopic eczema, asthma, and other inflammatory disorders	*Drugs*: Anti–IL-31 mAbs (BMS-981164) *Tested in clinical trials*: Atopic dermatitis
IL-32	Autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, Crohn disease, chronic rhinosinusitis, atopic dermatitis, asthma, cancer	
IL-33	Autoimmune and cardiovascular diseases, asthma, rheumatoid arthritis, gastrointestinal tract and lung disorders, parasite infections	
IL-34	Synovitis, rheumatoid arthritis, Sjögren syndrome	
IL-35 (p35+EBI3)	Tumor pathogenesis, asthma, atopic dermatitis, allergic rhinitis and celiac disease	
IL-36	Psoriasis, asthma	
IL-37	Rheumatoid arthritis, systemic lupus erythematosus, atopic dermatitis	
IL-38	Systemic lupus erythematosus	
IFN-α, IFN-β	Viral infections, systemic lupus erythematosus, polymyositis, rheumatoid arthritis, multiple sclerosis, asthma	IFN-α *Treatment*: Hairy cell leukemia, malignant melanoma, AIDS-related Kaposi sarcoma, hepatitis C infections, multiple sclerosis, genital warts, hepatitis C with HIV coinfection, hepatitis B, general viral infections, myelogenous leukemia, cutaneous T-cell lymphoma, follicular non-Hodgkin lymphoma, renal cell carcinoma, *Drugs*: IFN-α-con-1 (Infergen), IFN-α-n3 leukocyte derived (Alferon-N), Pegylated IFN-α-2a (Pegasys), Recombinant IFN-α-2a (Roferon-A), Recombinant IFN-α-2b (Intron A), PEG recombinant IFN-α-2b (PEG Intron) *Clinical trials*: HIV infections, polycythemia vera, thrombocythemia, leukemia, myeloproliferative disorders, hepatocellular carcinoma, cancer, chronic myeloid leukemia, COPD, diabetes mellitus type 1 IFN-β *Treatment*: Clinically isolated syndrome, relapsing multiple sclerosis, early/relapsing multiple sclerosis *Drugs*: IFN-β-1a (Avonex, Rebiferon), IFN-β-1b (Betasteron) *Clinical trials*: Ulcerative colitis, asthma, respiratory disease syndrome, cancer, HTLV-I Infection
IFN-γ	Susceptibility to intracellular pathogen infection and tumor development, type 1 diabetes, rheumatoid arthritis, atopic dermatitis, EAE	*Treatment*: Chronic granulomatous disease, osteoporosis, autoimmune diseases (Crohn disease) *Drugs*: Humanized anti–IFN-γ mAbs (fontolizumab), Bioengineered IFN-γ1b (Actimmune) *Clinical trials*: HIV infection, Friedreich ataxia, glioblastoma, gliosarcoma, autosomal dominant osteopetrosis type 2, pulmonary fibrosis, sepsis, uveitis, inherited ophthalmic diseases, cancer

(Continued)

TABLE II. *(Continued)*

Cytokine	Disease association	Therapeutic application
TGF-β	Alzheimer disease, cardiovascular pathologies, cancer, allergic rhinitis, fibrosis	*Drugs*: Synthetic antisense oligodeoxynucleotide (trabedersen/AP12009), human mAbs against TGF-β1, TGF-β2, and TGF-β3 (fresolimumab/GC1008); acetic salt of a 14mer peptide from human TGF-β1 type III receptor (P144); TβR-I inhibitor (Galunisertib/LY2157299) *Clinical trials*: Anaplastic astrocytoma, glioblastoma, pancreatic neoplasms, melanoma, colorectal neoplasms, anaplastic astrocytoma, metastatic breast cancer, diffuse systemic sclerosis, primary focal segmental glomerulosclerosis, non–small cell lung cancer, primary brain tumors, skin fibrosis, hepatocellular carcinoma and non–small cell lung cancer (recurrent)
TNF-α	Psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile arthritis, ankylosing spondylitis, inflammatory bowel disease, Crohn disease, ulcerative colitis, systemic sclerosis, systemic lupus erythematosus, pulmonary diseases, allergic diseases (asthma, allergic rhinitis, and atopic dermatitis), insulin resistance, depression, cancer, vascular diseases, neurological diseases	*Treatment*: Crohn disease, ulcerative colitis, psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, Behçet disease, ulcerative colitis, moderate-to-severe chronic psoriasis, juvenile idiopathic arthritis, ankylosing spondylitis, moderate-to-severe plaque psoriasis, ulcerative colitis *Drugs*: Chimeric blocking mAbs specific for TNF-α (infliximab/INN), human anti–TNF-α mAbs (adalimumab/D2E7), humanized anti–TNF-α mAbs (certolizumab pegol), human anti–TNF-α mAbs (golimumab), soluble p75 TNF receptor–Fc fusion (etanercept) *Clinical trials*: Peripheral spondyloarthritis, osteoarthritis, hidradenitis suppurativa, uveitis, sarcoidosis, mucocutaneous lymph node syndrome, Kawasaki disease, leukemia and lymphoma, graft-versus-host disease

AML, Acute myeloid leukemia; *COPD*, chronic obstructive pulmonary disease; *CVID*, common variable immunodeficiency; *EAE*, experimental autoimmune encephalomyelitis; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HTLV-I*, human T-lymphotropic virus type I.

of naive and memory B and T cells, mature T cells, and NK cells. Studies of IL-7 and IL-7Rα KO mice have shown that IL-7 is important for homeostatic T- and B-cell development (see Table E2). IL-7R expression is a marker of ILCs.[5]

IL-9

IL-9 was first discovered in mice, where it was found to be a potent antigen-independent growth factor for T cells[78] and mast cells. T_H2 cells and ILC2s are the main sources of IL-9 production; mast cells (mainly within the airways of asthmatic subjects) 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. IL-9 has important roles in the pathogenesis of asthma models and in helminth infections. A new population of T cells, T_H9 cells, which produce IL-9 and IL-10, have been proposed to contribute to inflammation, mast cell accumulation, and activation (Figs 2 and 3).[26,79] Allergen-specific T_H1 and T_H2 responses are both enhanced by IL-9.[27,80]

IL-15

IL-15 is structurally homologous to IL-2 and was discovered to have the ability to induce T-cell, NK cell, and ILC proliferation, like IL-2.[81] IL-15R consists of the IL-15Rα chain, the IL-2Rβ chain, and γc (Fig 1).[76,82] IL-15 is produced by nonimmune (keratinocytes and skeletal muscle cells) and immune (monocytes and activated $CD4^+$ T cells) cells in response to signals that induce innate immunity.[82] 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 based on differences observed between phenotypes of IL-2 and IL-15 KO mice.

IL-21

IL-21 is produced by T cells, NKT cells, and the follicular helper subset of CD4 T cells. The receptor for IL-21 is expressed on various cells, indicating a broad spectrum of action. IL-21 affects B-cell functions by strongly inducing their proliferation, regulating antibody production, and preventing their apoptosis and differentiation into plasma cells.[29] Cytotoxic activity and proliferation of $CD8^+$ T cells, NK cells, and NKT cells increase on stimulation with IL-21.

THE IL-10 FAMILY

The IL-10 subfamily of cytokines comprises IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29.[83,84] Their binding to IL-10R2, IL-20R1, IL-20R2, IL-22R1, and IL-28R1 and distinct expression of these receptors in immune system and tissue cells characterize their functions (Fig 1).

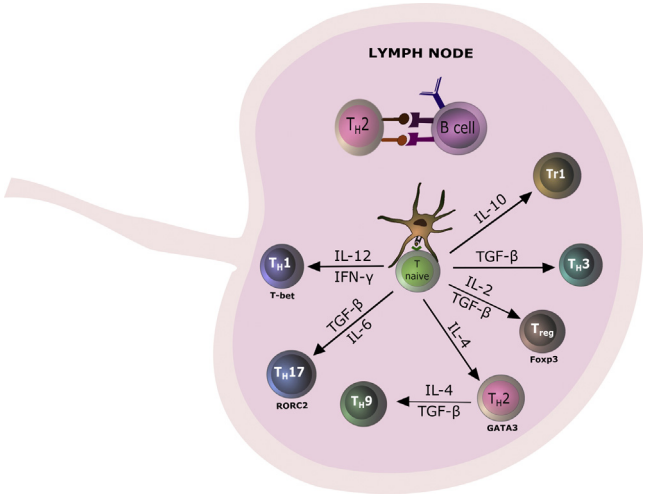

FIG 2. Differentiation of naive T cells to functional T-cell subsets. Differentiation of naive CD4 T cells into distinct phenotypes occurs on TCR activation driven by dendritic cells, which migrate into the lymph nodes after allergen uptake. IL-4 is important for differentiation of naive T cells into T_H2 cells, which can further differentiate into the T_H9 lineage. Development of T_H1 cells requires the presence of IFN-γ and IL-12. The transcription factors T-bet and GATA-3 play an important role in differentiation of T_H1 and T_H2 cell lineages, respectively. The combination of TGF-β and IL-6 facilitates T_H17 differentiation, which is regulated by the transcription factor RORC2, whereas Treg cell programming requires TGF-β and IL-2 and is controlled by FoxP3.

IL-10

IL-10 is an anti-inflammatory interleukin produced mainly by monocytes, T cells (mainly type 1 Treg cells), B cells (mainly Breg cells), a small fraction of NK cells, macrophages, and DCs. Recently demonstrated human Breg cells play a significant role in immune suppression and increase in AIT,[35,71] and their IL-10 production is regulated by B-cell linker protein.[85] Mast cells can also produce IL-10, which limits the rate of leukocyte infiltration, inflammation, and skin disorders, such as contact dermatitis; this also occurs after chronic UVB irradiation. The receptor complex for IL-10 is comprised of 2 chains: IL-10R1 and IL-10R2 (Fig 1). IL-10 directly affects APC functions by downregulating the expression of MHC class II and costimulatory molecules on the surfaces of macrophages and monocytes. IL-10 inhibits the expression of many proinflammatory cytokines, chemokines, and chemokine receptors. Clinically, it might mediate allergen tolerance in AIT and exposure to high doses of allergens, such as beekeepers and cat owners.[30,86,87] IL-10 directly affects T-cell activation by suppressing CD28, CD2, and signaling of the inducible T-cell costimulator through the tyrosine phosphatase Src homology domain 2–containing protein tyrosine phosphatase 1 (SHP-1). In contrast to its inhibitory effects on T cells, IL-10 promotes the survival, proliferation, and differentiation of human B cells and increases IgG_4 production.[35,71,88]

Several mouse models demonstrate the importance of IL-10 in regulation of the inflammatory response (see Table E2). IL-10 KO mice have normal lymphocyte and antibody responses but show reduced growth and anemia and spontaneous chronic colitis. In patients with colitis with IL-10/IL-10R deficiency in hematopoietic lineage cells, hematopoietic stem cell transplantation should be considered as a potentially curative therapeutic option.[89] In addition, coassociations between *IL10* polymorphisms, IL-10 production, helminth infection, and asthma/wheeze have been found, suggesting that polymorphisms related to protection against helminths during evolution might be associated with increased risk of allergic diseases.[90]

IL-19

IL-19 binds to a heterodimeric receptor comprising IL-20R1 and IL-20R2: this receptor complex also binds IL-20 and IL-24. IL-19 is expressed by LPS-stimulated monocytes, and low levels have been observed in B cells.[91] 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. IL-19 might promote T_H2 cell responses because it induces IL-4, IL-5, IL-10, and IL-13 expression by activated T cells.[84] Increased levels of IL-19 have been observed in asthmatic patients, whereas lower circulating levels and increased epidermal expression of IL-19 were observed in patients with psoriasis. An immunosuppressive role has been suggested for IL-19, IL-20, and IL-24 during *Staphylococcus aureus* infection because of their signaling through the IL-20 receptor.[92]

IL-20

The IL-20 subfamily of cytokines (ie, IL-19, IL-20, IL-22, IL-24, and IL-26) have been grouped together to form the IL-20 subfamily based on their use of common receptor subunits and similarities in their biological functions.[83] 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). IL-20 is mainly produced by LPS-stimulated monocytes and DCs but also by epithelial and endothelial cells and keratinocytes. IL-20 has important functions in the skin. Transgenic overexpression in mice caused skin abnormalities that include hyperkeratosis, a thickened epidermis, and a compact stratum corneum.[93] Together with IL-19, IL-20 appears to have a role in the pathogenesis of psoriasis: mRNA of these cytokines and their receptors was detected in psoriatic lesions but not in uninvolved skin from the same subjects.

IL-22

IL-22 is expressed by activated T_H22 cells, ILC3s, mast cells, and NK-22 cells.[94] The IL-10R2 chain, which is shared with other cytokine receptors, is ubiquitously expressed. In contrast, the IL-22R1 chain is not detected on immune cells but rather in the kidneys, small intestine, liver, colon, lung, and particularly the pancreas and skin. IL-22 induces genes that are involved in the antimicrobial defenses of keratinocytes. IL-22 is upregulated during bacterial infection, psoriasis, and atopic dermatitis.[95] Although IL-22 has been associated with inflammatory disorders, it might also have anti-inflammatory effects.[96,97] For example, IL-22 inhibits IFN-γ–induced secretion of the proinflammatory chemokines CCL5/RANTES and CXCL10/interferon-inducible protein 10 and antagonizes IFN-γ in lung inflammation.[98] $IL\text{-}13^+$ T cells display increased IL-22 levels in patients with atopic dermatitis, whereas IL-17 and IFN-γ coexpression with IL-22 becomes predominant in patients with psoriasis.[99] IL-22 and IFN-λ act synergistically for the induction of interferon-stimulated genes and control of rotavirus infection.[100]

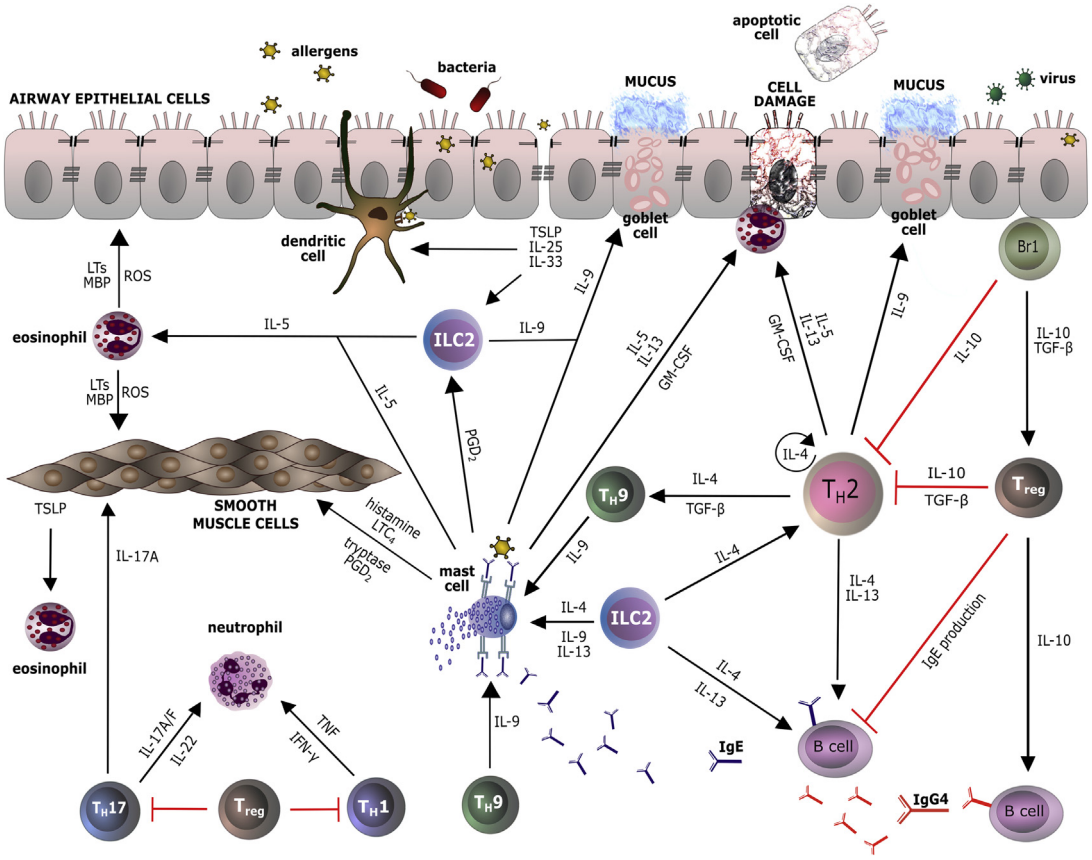

FIG 3. Cytokine and other mediator networks in allergic inflammation. Epithelial barrier impairment during inflammation can allow penetration of allergens through the tissues. Allergens with protease activity can cleave epithelial cell tight junction proteins and gain access to submucosal DCs. Once activated and loaded with antigens, DCs mature and migrate to local lymph nodes and present processed allergen peptides to naive T cells through MHC class II molecules. Naive T cells in the presence of IL-4 differentiate into T_H2 cells. The T_H2-type cytokines IL-4 and IL-13, which are produced not only by T_H2 cells but also by ILC2s, are involved in immunoglobulin class-switch recombination in B cells, which leads to IgE production. IgE binds to FcεRI on the surfaces of tissue-resident mast cells, sensitizing them. Subsequent release of mast cell–associated mediators, such as histamine, tryptase, prostaglandins, leukotrienes, and cytokines, induced goblet cell hyperplasia, smooth muscle contraction, vasodilation, increased vascular permeability, and intensified mucus production. During allergic inflammation, activated epithelial cells release TSLP, IL-25, and IL-33, which also contribute to the T_H2 response. Highly activated epithelial cells undergo apoptosis. T_H17 and T_H1 cells mediate neutrophil recruitment, whereas eosinophilia is induced by IL-5, IL-25, and IL-33. Immunoregulatory cytokines, such as IL-10 and TGF-β, released by Treg cells can suppress T_H2-type immune responses and control airway inflammation and remodeling. IL-10–producing B_R1 cells inhibit effector T cells. *LTs*, Leukotrienes; *LTC4*, leukotriene C_4; *MBP*, major basic protein; *PGD2*, prostaglandin D_2; *ROS*, reactive oxygen species.

IL-24

IL-24 is expressed by normal melanocytes, T cells, and monocytes[101] and binds to complexes comprising IL-22R1 and IL-20R2 or IL-20R1 and IL-20R2 (Fig 1).[102] IL-24 specifically inhibits tumor growth, and its antitumor activities require phosphorylation.[103] In a phase I clinical trial intratumoral injections of a nonreplicating adenovirus vector that carried *IL24* were well tolerated and induced apoptosis in large volumes of tumor tissue.[104] T cell–derived microvesicles induce mast cells to produce IL-24, which might have implications for allergic inflammations of the skin and lung.[105]

IL-26

IL-26 was discovered during the analysis of human T cells after transformation by *Herpesvirus saimiri*.[106] Interestingly, mice and rats do not have the *IL26* gene, whereas zebrafish, chickens, and frogs do, and its evolutionary conservation is limited. IL-26 expression seems to be restricted to memory T cells, NK cells, and T_H17 cells.[107] 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).[108] In contrast to 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.[93] There have been few studies on its physiologic function or role in disease processes because mice do not carry *IL26*. IL-26 is expressed by T_H17 cells and might have proinflammatory effects in disorders such as Crohn disease. A recent functional study suggested that T_H17 cells promote microbial killing and innate immune sensing of DNA through IL-26.[109]

IL-28A, IL-28B, and IL-29 (IFN-λ)

IL-28A, IL-28B, and IL-29 (alternatively termed IFN-λ2, IFN-λ3 and IFN-λ1, respectively) have homology with type I interferons, although the intron-exon structure of their genes more closely resembles that of the IL-10 family.[110] A new gene upstream of IL-28B was discovered in 2013, and it was designated *IFNL4*. This gene encodes IFN-λ4 and is similar to IFN-λ3.[111] 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, CRF2-12, or LICR) chain and an IL-10R2 chain (Fig 1). Expression of IL-28 and IL-29 is induced by exposure of cells to polyinosinic-polycytidylic acid or viral infection, indicating their antiviral activities. IL-28 and IL-29 inhibit replication of hepatitis B and C viruses, and therefore they might be used to treat patients infected with these viruses.[112] Interestingly, IL-28 and IL-29 might also promote the development of tolerogenic DCs.[113]

THE IL-12 FAMILY

IL-12, IL-23, IL-27, and IL-35 share receptor and ligand chains (Fig 1). Their functions differ because of 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

The bioactive form of IL-12 (IL-12p70), first described as NK-stimulating factor, is a heterodimer that consists of 2 subunits: a 35-kDa light chain (p35) and a 40-kDa heavy chain (p40).[114] It is produced by activated monocytes, macrophages, neutrophils, microglia, and DCs. In contrast, the p40 subunit, referred to as IL-12p40 and secreted in the absence of p35 as either monomer or homodimer by APCs, was shown to inhibit IL-12–dependent immune functions acting as an antagonist of IL-12 receptors.[115] Bioactive IL-12 mediates the development and maintenance of T_H1 cells by inducing IFN-γ production by T_H1 and NK cells. In addition, it plays an important role for the induction of ILC1s.[116] IL-12 indirectly activates the antimicrobial, antiparasitic, and antitumor activity of macrophages and promotes cytolytic activity of NK cells and lymphokine-activated killer cells.[117] Reduced IL-12 production impairs T_H1 responses and increases susceptibility to infection with intracellular pathogens. In neonatal DCs dectin-1 activation unlocks *IL12A* expression and reveals their T1-inducing potency.[118] IL-12 controls the homeostasis of Treg cells by eliminating them, as observed during the elimination of pathogen-specific Treg cells during *Mycobacterium tuberculosis* infection.[119]

IL-23

IL-23 includes the IL-12p40 subunit and a distinct IL-23p19 subunit (Fig 1). IL-23 is mainly produced by phagocytic cells, macrophages, and activated DCs from peripheral tissues, including the skin, intestinal mucosa, and lungs. Activated and memory T cells express high levels of IL-23R, along with NK and NKT cells, eosinophils, monocytes, macrophages, DCs, and epithelial cells.[120] IL-23 contributes to the development of T_H17 cells,[5] and a population of ILCs respond to IL-23 and might have a role in the pathogenesis of inflammatory bowel disease.[121] A recent study has shown a link of IL-23 to alopecia areata lesional cytokine profiles.[122]

IL-27

IL-27 is a heterodimeric cytokine consisting of p28 and EBI3 subunits. The p28 chain is related to IL-12p35, whereas the EBI3 chain is related to IL-12p40 and structurally resembles soluble IL-6R (Fig 1).[123] IL-27 is expressed predominantly by DCs and macrophages and endothelial cells. IL-27 promotes early commitment of naive T cells to the T_H1 cell lineage.[124] It directly antagonizes the development of T_H17 cell responses and limits the induction of inflammation by cells that produce IL-17 in the central nervous system.[125] IL-27 also limits the development of uveitis and scleritis by cells that produce IL-17 and induces FOXP3 expression by Treg cells.[126] Recent studies also suggested mechanisms that might play a role in immune privilege and immune tolerance.[127] $CD4^+$ T cells of asthmatic patients are resistant to IL-27–mediated inhibition. This can be linked to resistance of T_H2 cells by their IL-4– to IL-27–induced reprogramming toward T_H1 cells. IL-27 expression in bronchoalveolar lavage cells associates with type 2 immunity and asthma severity.[128] In addition, IL-27 stimulates the effector functions of human NK cells and increases their IL-18 responsiveness.[129] IL-27 induces CD39, which acts on DCs to suppress the T-cell response and autoimmunity.[130] IL-27 plays a role in antitumor immunity, as shown in patients with prostate cancer.[131]

IL-35

IL-35 is a heterodimeric cytokine consisting of EBI3 and the p35 subunit of IL-12 (Fig 1).[132] EBI3 is specifically expressed in mouse $FOXP3^+$ Treg cells, and the EBI3/p35 heterodimer is constitutively secreted by these cells.[133] The increased expression of EBI3 and IL12 p35 in mouse $FOXP3^+$ Treg cells compared with effector T cells and transcription analyses indicated that EBI3 expression is regulated by FOXP3.[133] IL-35 stimulation of mouse $CD4^+CD25^+$ Treg cells induced IL-10 production but did not influence FOXP3 expression. $CD4^+CD25^+$ T cells expanded in the presence of IL-35 were able to suppress the proliferation of $CD4^+CD25^-$ effector T cells. IL-35, but not EBI3 alone, inhibited differentiation of mouse $CD4^+$ T cells into T_H17 cells that produce IL-17. Furthermore, IL-35 reduced the incidence of arthritis, numbers of arthritic paws, and pathologic features in mice with collagen-induced arthritis in parallel to increased serum levels of IL-10 and IFN-γ and reduced induction of IL-17.

CYTOKINES OF TYPE 2 IMMUNE RESPONSE

Cytokines produced during the induction and function of T_H2 and ILC2 responses with the contribution of epithelial cells, DCs, ILCs, T cells, eosinophils, mast cells, and basophils include IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33, and TSLP. A default role for these cytokines can be suggested in immunity against helminth infections, with IgE production and eosinophilia, as well as decreased tissue injury, during severe type 1 inflammation (Fig 3). IL-4 and IL-9 have been highlighted at the "common γ chain cytokines" and IL-33 in the "IL-1 family" sections above.

IL-5

IL-5 was initially described as an eosinophil and B-cell growth factor; it is mainly produced by $CD4^+$ T_H2 cells, activated eosinophils, mast cells, $CD8^+$ Tc2 cells, γδ T cells, NK cells, NKT cells, and $CD4^-$c-$Kit^-CD3\varepsilon^-IL\text{-}2R\alpha^+$ 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 asthmatic patients.[134] 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. Anti–IL-5 therapy seems to be efficient in patients with eosinophilic asthma, eosinophilic esophagitis, and CRS.[75,135,136]

IL-13

IL-13 is expressed by activated T_H2 cells, mast cells, basophils, eosinophils, and NKT cells. Its receptors are IL-13Rα1 and IL-13Rα2, and signaling occurs through the IL-4R complex type II, which consists of IL-4Rα and IL-13Rα1 (Fig 1).[137] IL-13R chains are regulated during viral infection and inflammation.[138] 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 genes, which takes place in the IL-4 and IL-13 pathways, increases the risk of asthma by 16.8-fold; polymorphisms in only the *IL13* gene increase the incidence of asthma exacerbations in children and increase total IgE levels and eosinophil numbers in blood samples.[139] IL-13 KO mice produce less IL-4, IL-5, IL-10, and IgE and do not have goblet cell hyperplasia (see Table E2). They are unable to expel *N brasiliensis*, indicating the role of IL-13 in parasite defense. IL-13Rα1–deficient mice lack features of asthma and airway remodeling. IL-5 and IL-13 from the ILC2s play an important role in the setting of eosinophilic asthma. There were significantly greater numbers of sputum $IL\text{-}5^+IL\text{-}13^+$ ILC2s in patients with severe asthma whose airway eosinophilia was greater than 3%, despite normal blood eosinophil numbers.[140]

IL-25 (IL-17E)

Because of homology with IL-17 family members, IL-25 has also been named IL-17E. It is produced by polarized T_H2 cells,[141] mast cells, eosinophils, and basophils from atopic subjects. IL-25 induces production of T_H2-associated cytokines. IL-25 KO mice do not expel *N brasiliensis* efficiently because of subtle changes in the induction of T_H2-type cytokine responses and are very susceptible to experimental autoimmune encephalomyelitis. Transgenic expression of IL-25 leads to blood eosinophilia and increased levels of IgE, IgG_1, IL-5, and IL-13. IL-25 might be involved in asthma pathogenesis. It is expressed at high levels in the lungs of sensitized mice after allergen challenge, and transgenic mice that express IL-25 only in lungs have increased numbers of eosinophils and $CD4^+$ T cells on allergen-specific stimulation. Anti–IL-25 treatment reduced the number of polyps, mucosal edema and thickness, collagen deposition, and infiltration of inflammatory cells, such as eosinophils and neutrophils, in a mouse chronic rhinitis model, suggesting a role in the pathogenesis of CRS with nasal polyps.[142]

IL-31

IL-31 is expressed by activated $CD4^+$ T cells (mostly by T_H2 cells) and at lower levels by $CD8^+$ T cells. 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 is induced by IL-4 and promotes T_H2-driven inflammation.[143] IL-31 expression is increased in patients with atopic dermatitis, contact dermatitis, and prurigo nodularis. IL-31RA is a functional receptor expressed by a small subpopulation of $IL\text{-}31Ra^+/TRPV1^+/TRPA1^+$ neurons and is a critical neuroimmune link between T_H2 cells and sensory nerves for the generation of T cell–mediated itch.[144] Transgenic overexpression of IL-31 in mice results in a phenotype that resembles nonatopic dermatitis.[13] *IL31* mRNA is upregulated in the lungs after antigen challenge in a mouse model of airway inflammation.[13] In addition, serum IL-31 levels are increased in a subset of patients with mastocytosis and correlate with disease severity.[145]

TSLP

Cellular sources of TSLP include keratinocytes, airway epithelial cells, intestinal epithelial cells, thymic stromal cells, tonsillar crypt epithelial cells, mast cells, and basophils.[146] Structurally, TSLP resembles IL-7. TSLP is released in response to viral, bacterial, and parasitic pathogens; TLR engagement; and other cytokines, such as IL-1β, TNF-α, IL-4, and IL-13.[146] TSLP acts through a heterodimeric receptor, TSLP receptor (TSLPR), which consists of the IL-7Rα chain and a unique TSLPR chain resembling the common cytokine receptor γ chain.[147] Activation of TSLPR leads to signal transducer and activator of transcription 5 phosphorylation. TSLP acts on DCs, monocytes, $CD4^+$ T cells, mast cells, and B cells, promoting development of the T_H2 inflammatory response, often in cooperation with IL-25 and IL-33 and other cytokines.[146,148] TSLP has been reported to play a pivotal role in allergic asthma, with anti-TSLP (AMG157) antibody showing promising efficacy in reducing allergen-induced inflammation in primates and human subjects.[149,150] TSLP is also associated with atopic dermatitis.[151] Aside from its role in allergic inflammation, TSLP has been implicated to play a role in CRS with nasal polyps, idiopathic pulmonary fibrosis, primary spontaneous pneumothorax, breast cancer, pancreatic cancer, cervical cancer, and lung cancer. TSLP has been extensively reviewed elsewhere.[146,152,153]

INTERLEUKINS 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. 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-1α, IL-1β, IL-17, TNF-α, or TLRs.[154] The receptors for IL-8 are CXCR1 (IL-8RA) and CXCR2 (IL-8RB).[155] The major effector functions of IL-8 are activation and recruitment of neutrophils to the site of infection or injury. In addition to neutrophils, IL-8 also attracts NK cells, T cells, basophils, and GM-CSF– or IL-3–primed eosinophils.[156] Increased IL-8 concentrations were found in inflammatory sites in patients with diseases such as psoriasis, rheumatoid arthritis, respiratory syncytial virus infection, asthma, and chronic obstructive pulmonary diseases.[157]

IL-16

IL-16 was discovered as a T cell–specific chemoattractant.[158] Pro–IL-16, its 80-kDa precursor protein, is cleaved by caspase-3, resulting in a 60-kDa N-terminal fragment and a 14- to 17-kDa C-terminal fragment.[159] The N-terminal fragment regulates the cell cycle, whereas the C-terminal fragment forms homotetramers (56 kDa) that mediate cytokine functions. *IL16* 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 *IL16* mRNA. IL-16 mediates its biological activity through CD4. IL-16 inhibits T-cell proliferation, promotes T_H1-mediated responses, and reduces T_H2-mediated inflammation by activating the release of TNF-α, IL-1β, and IL-15 and concomitantly inhibiting IL-4 and IL-5 production.[160]

THE IL-17 FAMILY

IL-17A, also called IL-17 in some studies, is the founding member of this structurally distinct cytokine family. It binds as a homodimer or a heterodimer with IL-17F to its receptor, IL-17RA.[161] IL-17A is expressed by activated $CD4^+$ T_H17 cells (Fig 3),[23] but its expression has also been detected in $CD8^+$ T cells, γδ T cells, NK cells, and neutrophils.[161] 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.[162] RORC2 in human subjects acts as the main transcription factor.[24] 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 rheumatoid arthritis[163] and multiple sclerosis.[161] Similarly, they are upregulated in mouse models of collagen-induced arthritis and experimental autoimmune encephalitis.[161] Increased IL-17A levels have also been found in patients with psoriasis, inflammatory bowel disease, and allergic asthma and atopic dermatitis.[164] Diesel exhaust is one of the factors that induce IL-17 in asthmatic patients.[165] IL-17A is not inhibited by steroids in asthmatic patients, whereas 1α,25-dihydroxyvitamin D_3 shows an inhibitory role.[166] Steroid-resistant asthma was suggested to have IL-17A (high) and IFN-γ (high) endotypes.[167]

In contrast to its homologue 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. IL-17C induces production of proinflammatory cytokines and metalloproteases by certain cells[168] and has been associated with pathologic conditions, such as arthritic paws of mice with collagen-induced arthritis. IL-17D is highly expressed in skeletal muscle, brain, adipose tissue, heart, lung, and pancreas tissue.[169] 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.[170] IL-17F binds to the same receptor as IL-17A (IL-17RA), although with lower affinity.[171] IL-17A and IL-17F form heterodimers, as expected from their structural similarities. There are 2 isoforms of IL-17F expressed by activated T_H17 cells.[23] Like IL-17A, IL-17F acts on many cell types and induces similar proinflammatory cytokines and chemokines. Double-positive $IL\text{-}17^+IL\text{-}22^+$ cells with memory characteristics are observed in lung draining lymph nodes of patients with cystic fibrosis,[172] and IL-17A and neutrophils have a central role in fibrosis in the lungs of patients with hypersensitivity pneumonitis.[173] IL-17A seems to be more expressed in patients with psoriasis and intrinsic-type atopic dermatitis skin compared with those with extrinsic-type atopic dermatitis skin. Severe atopic dermatitis is characterized by selective expansion of circulating T_H2/T_C2 and T_H22/T_C22 cells, but not T_H17/T_C17 cells, within the skin-homing T-cell population.[174]

OTHER INTERLEUKINS

IL-3

IL-3, IL-5, and GM-CSF share a common receptor subunit β chain (CD131), and their functions partially overlap (Fig 1). IL-3 is expressed by T cells, macrophages, stromal cells, NK cells, mast cells, and eosinophils. On binding to IL-3, the β chain forms a heterodimer with the cytokine-specific α chain. IL-3 is a multilineage hematopoietic growth factor that functions in synergy with other cytokines during early stages of hematopoiesis. In combination with erythropoietin or GM-CSF and granulocyte colony-stimulating factor, 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 crosslinking.[175] 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. IL-3 is essential in basophil activation in patients with allergic asthma.[176]

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.[177] 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. IL-6 promotes T-cell proliferation, B-cell differentiation and survival, and plasma cell production of IgG, IgA, and IgM.[178] In addition, allergen-induced IL-6 promotes type 2 and type 17 airway inflammation.[179]

IL-11

IL-11 is expressed by stromal cells, including fibroblasts, epithelial cells, endothelial cells, osteoblasts, and several tumor cell lines. It binds a heterodimeric receptor consisting of IL-11Rα and gp130.[180] 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.[181] Recombinant IL-11 has been approved for the treatment of thrombocytopenia, a major dose-limiting hematologic complication of chemotherapy for cancer,[182] and recombinant human IL-11 is a protective factor in patients with severe sepsis with thrombocytopenia.[183]

IL-14

IL-14 was first described as a high-molecular-weight B-cell growth factor. Two transcripts are produced from opposite strands of the *IL14* gene, termed IL-14α and IL-14β.[184] IL-14 is produced by T cells and B- and T-lineage lymphoma cell lines.[185] IL-14 binds and signals through a 90-kDa receptor expressed on activated B cells to promote B-cell proliferation. This receptor is expressed especially on germinal center B cells and surface IgD^{low} human tonsil B cells, including B1 cells and activated B2 cells, and is expressed in patients with autoimmune thyroiditis.[186] Phenotypes of transgenic mice that overexpress IL-14α resemble features of systemic lupus erythematosus or Sjögren syndrome; older transgenic mice have B-cell malignancies ($CD5^+$ B-cell lymphoma) similar to these observed in patients with these disorders, and the mice have hypergammaglobulinemia with IgG, IgA, and IgM autoantibodies.[184]

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. 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.[187] Proteinase 3 cleaves IL-32α, resulting in formation of 2 peptides that upregulate production of proinflammatory cytokines by mouse and human monocytes.[187] IL-32 is highly expressed in synovial tissue samples from patients with rheumatoid arthritis, and expression levels are associated with disease severity.[187] IL-32 also regulates keratinocyte apoptosis and contributes to eczema formation in patients with atopic dermatitis.[188]

IL-32 is induced by IFN-γ, TNF-α, T_H1 cells, and rhinovirus in bronchial epithelial cells. It inhibits angiogenesis, and its serum levels are associated with a good treatment response in asthmatic patients.[189] Although IL-32 is not expressed by rodents, transgenic overexpression of IL-32 by endothelial and hematopoietic cells in mice intensified vascular inflammation and exacerbated sepsis.

IL-34

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.[190] The receptor for IL-34 is colony-stimulating factor 1 receptor, and it is required for the development of Langerhans cells and microglia.[191] IL-34 stimulates monocyte and macrophage proliferation and development. It is highly expressed in atopic dermatitis lesions.[192]

IFN-γ

Cells from the innate (eg, NK cells, NKT cells, macrophages, and myelomonocytic cells) and adaptive (eg, T_H1 cells, cytotoxic T lymphocytes, and B cells) immune systems produce IFN-γ. High IFN-γ levels 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 3).[193] In addition to its role in the development of a T_H1-type response and the B-cell isotype switch to IgG_{2a} (in mice), IFN-γ regulates MHC class I and II protein expression and antigen presentation. IFN-γ also inhibits cell growth and apoptosis and controls extension of the immune response by inducing activation-induced cell death of $CD4^+$ T cells.[20,22] IFN-γ plays a role in keratinocyte apoptosis in eczema formation,[22] and loss-of-function variants in *IFNGR1* are linked to atopic dermatitis complicated by eczema herpeticum.[194] In addition, steroid-resistant severe asthma is characterized by IL-17A (high) and IFN-γ (high) endotypes.[167]

IFN-α and IFN-β

All nucleated cells can produce and respond to IFN-αβ in the context of a viral infection, but plasmacytoid DCs are the most abundant source, producing up to 1000-fold more IFN-αβ (and IFN-λ) than other cell types.[195] After viral entry, pathogen-associated molecular patterns and danger and stress signals can lead to type I interferon production.[196] Cytosolic (eg, melanoma differentiation-associated protein 5 and retinoic acid–inducible gene 1) and endosomal (TLR3, TLR7, and TLR9) receptors can sense nucleic acids of viral origin and induce their production.[197] IFN-αβ bind both to a specific cell-surface receptor complex (IFNAR) on both the virus-infected cell and nearby uninfected cells. The receptor complex consists of 2 known subunits: IFNAR-1 and IFNAR-2. Their biological effects are mainly mediated by the transcriptional control of interferon-inducible genes (approximately 1000), but direct mechanisms acting on translation have also been described.[198]

Antiviral activity mediated by IFNAR requires induction of the enzyme 2′-5′-oligoadenylate synthetase, a double-stranded RNA–dependent protein kinase, as well as a myxovirus resistance protein. Early production of IFN-β is very important because it induces other cells (infected or noninfected) to make IFN-α, thus amplifying and maintaining the type I interferon response. IFN-α and IFN-β can directly influence immune cells through IFNAR and indirectly by inducing chemokines for recruitment of immune cells to the site of infection. Type I interferons induce secretion of a second wave of cytokines, such as IL-15, to regulate NK cell and memory CD8 T-cell numbers and activities.[199]

IFN-α and IFN-β are critical for DC stimulation and activation of naive T cells, B-cell development, and antibody production. Normally, self-nucleic acids do not activate adaptive immune responses, but their coupling to host antimicrobial components can activate TLR9 and induce type I interferon secretion by DCs, providing the initial scenario for boosting autoreactive clones in susceptible subjects.[200] Increased type I interferon levels are found in patients with several autoimmune diseases and have been associated with disease mechanisms.[201] In regard to allergic diseases, type I interferons inhibit type 2 responses through different mechanisms, such as IL-21 and IL-13Rα2 (a decoy receptor) upregulation.[138] Allergic patients produce less type I interferons in response to viruses.[202] Different mechanisms have been suggested to be related to dampened type I interferon responses in atopic subjects,[203] such as suppression by suppressor of cytokine signaling genes, which might play a role in decreased viral clearance in the epithelium of asthmatic patients.[203]

TGF-β

The 3 highly homologous isoforms of TGF-β belong to the large TGF-β superfamily. They are made up of a secretory peptide, the prodomain, also called latency-associated peptide, and the active C-terminal peptide. Before secretion, TGF-β dimerizes and forms, together with latency-associated peptide and the latent TGF-β–binding protein, a large complex that binds to the extracellular matrix.[204] TGF-β needs to be released and activated with proteolysis, pH drop, reactive oxygen species, or αV integrins to bind to its receptor.[204] The canonical signaling pathway for TGF-β uses the SMAD2/3 pathway, but after binding to TGF-βRI and TGF-βRII, a variety of other pathways are activated. TGF-β is produced by a variety of cells, such as epithelial cells, fibroblasts, and immune cells (eg, macrophages, eosinophils, and lymphocytes). TGF-β is one of the major cytokines for the suppressive function of Treg cells[205] and differentiation of proinflammatory T_H17 and T_H9 cells.[206] Most body cells express TGF-β receptors and can respond to TGF-β signaling. TGF-β plays a role in embryonic development, especially of the skeleton and cardiovascular system. It influences structural changes of tissues through induction of mesenchymal transition from epithelial and endothelial cells[207] by controlling extracellular matrix deposition,[208] apoptosis induction, and inhibition of proliferation. Inhibition of proliferation is also a major feature in the balancing influence of TGF-β on the immune system. TGF-β is part of the pathologic mechanisms behind autoimmune diseases,[209] Marfan syndrome and Duchenne muscle atrophy,[210] Alzheimer disease,[211] fibrotic disorders,[208] cancer,[212] allergic diseases, and osteoarthritis. Several studies suggest that TGF-β1 might play a role in remodeling in patients with several diseases, including eosinophilic esophagitis.[213,214] Because of its variety of functions, TGF-β often has a double-faced effect in patients with these diseases but still represents a promising therapeutic target.[215,216]

TNF-α

TNF-α was first described as TNF, a protein in sera of mice infected with BCG and treated with LPS, which caused hemorrhagic necrosis of different transplanted tumors *in vivo* and cytolysis of a mouse fibrosarcoma cell line *in vitro*.[217] TNF-α is an important pleiotropic cytokine involved in host defense, inflammation, and apoptosis. It plays a double role in regulation of immune responses, acting both as a proinflammatory mediator, initiating a strong inflammatory response, and an immunosuppressive mediator, inhibiting the development of autoimmune diseases and tumorigenesis, and exhibiting a vital role in maintenance of immune homeostasis by limiting the extent and duration of inflammatory processes. TNF-α plays an important role in host defense against viral, bacterial, fungal, and parasitic pathogens, in particular against intracellular bacterial infections, such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*. High systemic TNF-α levels can lead to septic shock. Local increases in TNF-α concentrations cause the 5 cardinal signs of inflammation: heat, swelling, redness, pain, and loss of function. TNF-α is involved in the development of allergic diseases, particularly asthma[218] and atopic dermatitis.[193]

FUTURE DIRECTIONS

Several new cytokines are likely to be categorized as interleukins within the several hundred secreted proteins that regulate communication among immune system cells and between the immune system and resident tissue cells. The growing list of interleukins requires a better classification strategy and improved understanding of their functions. Classification according to sequence homogeneity, structure, and common receptor chains is useful; however, most interleukins do not fit into any particular structural category. Bioinformatics data and information about their roles in the evolution of the immune system, as well as their nonimmune functions, in mammals should also be taken into consideration. Categories according to sequence homology and evolutionary relationship (IL-1, IL-10, and IL-17 families) and common receptor chains (γ chain cytokines), as well as subgrouping according to major functions (type 2 interleukins and chemokines), have been taken into consideration in this extensive review article.

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