Cytokines and Cytokine Receptors

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Cytokines play pivotal roles in controlling the development and function of a variety of immune and nonimmune cells. These include immune regulation, disease pathogenesis, and, increasingly, modulation and treatment of immune-mediated diseases. The term *cytokine* encompasses factors that are structurally or functionally unrelated. Included among cytokines are a number of different factors produced by lymphoid and nonlymphoid cells that mediate intercellular communication. The term *lymphokines* was originally used to denote products of lymphocytes,[1] whereas the term *interleukin* was introduced to emphasize the importance of these factors in communication between leukocytes.[2] Although the designation *interleukin* has remained in use, it is inaccurate in that some cases individual interleukins are made by cells other than leukocytes.

Because of the way they were discovered, the complex nomenclature and classification that have developed can be a barrier to understanding cytokines. Many were first identified by researchers in different disciplines, and they were named on the basis of their original observed functions, which may not necessarily reflect the full spectrum of an individual cytokine's actual biological functions.

Cohen et al.[3] coined the word *cytokine* to emphasize the point that these factors need not be made by one specific cell source. This was an important insight because many immunologically relevant cytokines are made by nonlymphoid cells. Cytokines are thus defined operationally as polypeptides secreted by leukocytes and other cells that act principally on hematopoietic cells, the effects of which include modulation of immune and inflammatory responses. However, there are clear exceptions to even this broad definition. Some definitions distinguish cytokines from hormones and growth factors, which act on nonhematopoietic cells.

Cytokines are typically characterized as factors made by more than one cell type that act locally, whereas hormones are secreted by specialized cells and act at a distance on a restricted set of target cells. Although many cytokines act locally in an autocrine or paracrine fashion, some do enter the bloodstream and can act in a typical endocrine fashion. Consequently, the boundary between cytokines and hormones is rather indistinct. In fact, classic hormones, such as growth hormone (GH), prolactin (PRL), and erythropoietin (EPO), and a more recently identified hormone, leptin, are all clearly cytokines, as evidenced by the structure of their receptors and their modes of signaling. Perhaps it is just simplest to accept that cell–cell communication and host defense went hand-in-hand during evolution, and so functional and structural similarities exist among families of molecules that act on the immune, hematopoietic, endocrine, and nervous systems.

KEY CONCEPTS

Cytokine Characteristics

- Cytokines have pleiotropic effects: they may have more than one receptor.
- Cytokines can be redundant—their receptors often share subunits.
- Cytokines can have specific and unique functions—their receptors typically have ligand-specific subunits as well.

CYTOKINE CLASSIFICATION

A major challenge in discussing cytokines is how best to classify them. One can legitimately group cytokines in different ways, but here, we classify cytokines on the basis of the type of receptor that they bind. Our scheme emphasizes the evolutionary relatedness of cytokines, growth factors, and hormones and highlights the similarities in signal transduction. The classification used is adapted from Vilcek[4] and includes the following receptors: the so-called type I (hematopoietin family) and type II (interferon family) cytokine receptors, tumor necrosis factor (TNF) family receptors, interleukin (IL)-1 receptor and the related Toll-like receptors (TLRs), IL-17 receptors, receptor tyrosine kinases, and the transforming growth factor-β (TGF-β) family receptor serine kinases (Table 9.1; Fig. 9.1). A sixth group, known as chemokines, form a separate family and bind seven transmembrane domain receptors (Chapter 10). This chapter reviews in detail only a selected set of cytokines with important immunological functions (Fig. 9.2).

TYPE I AND II CYTOKINE RECEPTORS (HEMATOPOIETIN FAMILY AND INTERFERON RECEPTORS)

Ligand and Receptor Structure

Cytokines (see Table 9.1) that bind the class of receptors, termed *type I* or *hematopoietic cytokine receptor superfamily,* include hormones, such as EPO, thrombopoietin (TPO), PRL, GH, and leptin; colony-stimulating factors (CSFs), such as granulocyte–colony-stimulating factors (G-CSFs), granulocyte macrophage–colony-stimulating factors (GM-CSFs); and IL-2–IL-7, IL-9, IL-11–IL-13, IL-15, IL-21, IL-23, IL-27, IL-31, and IL-35. Also included in this family are ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), and cardiotropin 1 (CT-1). Closely related are the interferons (IFN-α, -β, -τ, -ω, limitin) and IL-10-related cytokines,

TABLE 9.1 Cytokines Classified by Receptor Families

Receptor Family	Cytokine	Signaling	Source	Target	Action	Knock-out Phenotype
Type 1 (hemato-poietin)	GH	Janus kinase (JAK)2, signal transducer and activator of transcription 5b (STAT5b)	Two growth hormone (GH) genes, pituitary, placental	Diverse tissues	Growth, adipocyte differentiation	Dwarfism
	Prl	JAK2, STATa	Two *Prl* genes pituitary, uterus	Mammary epithelium	Growth, differentiation	Infertility, lactation defects
	Erythropoietin (EPO)	JAK2, STAT5	Kidney, liver	Erythroid precursors	Erythroid differentiation	Embryonic lethal, severe anemia
	Thrombopoietin (TPO)	JAK2, STAT5	Liver, kidney	Committed stem cells and megakaryocytes	Platelet	Severe thrombocytopenia
	Leptin	JAK2/STAT3	Adipocytes	Hypothalamus, thyroid	Satiety, controls metabolic rate	Obesity
	Granulocyte–colony-stimulating factor (G-CSF)	JAK2, STAT3	Many tissues, macrophages, endothelium, fibroblasts	Committed progenitors	Differentiation, activates mature granulocytes	Neutropenia
	Interleukin (IL)-6	JAK1, STAT3	Macrophages, fibroblasts, endothelium, epithelium, T cells, other	Liver, B cells, T cells, thymocytes myeloid cells, osteoclasts	Acute-phase reactants proliferation, differentiation, costimulation	Reduced immunoglobulin (Ig), especially IgA; T lymphopenia; impaired acute-phase response; and T-helper 17 (Th17) cells
	IL-11	JAK1, STAT3	Stromal cells, synoviocytes, osteoblasts	Hematopoietic stem cells, hepatocytes, macrophages, neurons	Proliferation	Female infertility
	IL-27	JAK1, STAT1, STAT3, STAT4, STAT5	Activated dendritic cells (DCs), macrophages, epithelial cells	T cells and natural killer (NK) cells, other cells	Enhancement of Th1 responses, and IL-10; inhibition of Th1, Th2, and Th17 responses	Fatal inflammatory disease with infection
	IL-31	JAK1, STAT3, STAT5	Th2 cells CD8 T cells	Monocytes, epithelial cells, keratinocytes, eosinophils basophils	Induces chemokines, PMN recruitment	
	Ciliary neurotropic factor (CNTF)[a]	JAK1, STAT3	Schwann cells	Neuronal	Survival	Progressive atrophy and loss of motor neurons
	Leukemia inhibitory factor (LIF)[a]	JAK1, STAT3	Uterus, macrophages, fibroblasts, endothelium, epithelium, T cells	Embryonic stem cells, neurons hematopoietic cells	Survival	Decreased hematopoietic progenitors, defective blastocyst implantation
	Oncostatin M (OSM)	JAK1, STAT3	Macrophages, fibroblasts, endothelium, epithelium	T cells, myeloid cells, liver, embryonic stem cells	Differentiation, acute-phase induction	
	Cardiotropin-1 (CT-1)	JAK1, STAT3	T cells, others, myocardium	Myocardium	Growth	
	Granulocyte macrophage–colony-stimulating factor (GM-CSF)	JAK1, STAT3	T cells, macrophages, endothelium, fibroblasts	Immature and committed myelomonocytic progenitors macrophages and granulocytes, DCs	Growth, differentiation survival, activation	Pulmonary alveolar proteinosis
	IL-3	JAK2, STAT5	T cells, macrophages, mast cells, natural killer T cells (NKT cells), eosinophils	Immature hematopoietic progenitors of multiple lineages	Growth, differentiation survival	No defects in basal hematopoiesis

TABLE 9.1 Cytokines Classified by Receptor Families—cont'd

Receptor Family	Cytokine	Signaling	Source	Target	Action	Knock-out Phenotype
	IL-5	JAK2, STAT5	Th2 T cells, activated eosinophils, NK cells, NKT cells	Eosinophil, B cells, basophils, mast cells	Proliferation, activation	Decreased eosinophilia, defective CD5, B1-cell development
	IL-2	JAK1, JAK3, STAT5	T cells, NK cells, NKT cells	T cells, B cells, NK cells, macrophages	Proliferation, cytotoxicity interferon-γ (IFN-γ) secretion, antibody production	Lymphoproliferation[a]
	IL-4[b]	JAK1, JAK3, STAT6	Th2 cells, mast cells, NKT cells, γ/δ T cells	T cells, B cells, macrophages	Proliferation, Th2 differentiation, IgG1 and IgE production, inhibition of cell-mediated immunity	Defective Th2 differentiation and IgE production, decreased allergic responses
	IL-7	JAK1, JAK3, STAT5	Bone marrow, thymic stromal cells, spleen DCs, keratinocytes, monocytes, macrophages	Thymocytes, T cells, B cells	Growth, differentiation, survival	Severe combined immunodeficiency (SCID)[a]
	IL-9	JAK1, JAK3, STAT5	Th2 and Th9 T cells, mast cells, eosinophils	T cells, B cells, mast cell precursors	Proliferation, Th1 inhibition	Not essential for Th2 pathology
	IL-15[b]	JAK1, JAK3, STAT5	Many cells	T cells, especially memory cells, NK and NKT cells	Proliferation, survival and activation	Absence of NK and memory cells
	IL-21	JAK1, JAK3, STAT3	T cells, Th17 cells, Tfh cells	T cells, B cells, and NK cells, DCs, macrophages, keratinocytes	Isotype switching, plasma cell differentiation, enhances CD8 and NK-cell responses, promotes Th17 cell differentiation	Acts in concert with IL-4 Decreased Th17 cells
	IL-13	JAK1, TYK2, STAT6	Activated T cells, NKT cells, mast cells, basophils	B cells, mast cells, macrophages, epithelial cells, smooth muscle cells	Costimulator of proliferation, IgE increased CD23 and class II, inhibits cytokine secretion and cell-mediated immunity	Defective Th2 responses and IgE production, decreased allergic responses
	IL-12	JAK2, TYK2, STAT4	Macrophages, DCs, B cells	T cells, NK cells	Th1 differentiation, proliferation, cytotoxicity	Defective Th1 differentiation, susceptibility to bacterial infections*
	IL-23	JAK2, TYK2, STAT3, STAT5	Macrophages, DCs	T cells, macrophages	IL-17 production	Reduced arthritis, inflammation
	IL-35	?	Tregs	T cells	Treg proliferation Suppresses proliferation and functions of Th17	Reduced Treg activity
	Thymic stromal lymphopoietin (TSLP)	JAK1, JAK2, STAT1 STAT3, STAT5	Epithelial cells, keratinocytes	DCs (human) B cells (mouse)	Th2 differentiation (human)	Shared receptor usage with IL-7R
Type II (interferon)	IFN-α/β	JAK1, TYK2, STAT1, STAT2	Plasmacytoid DCs, macrophages, fibroblasts, other	All, NK cells	Antiviral, antiproliferative increased major histocompatibility complex (MHC) class I activation	Susceptibility to viral infections[a]
	IFN-γ	JAK1, JAK2, STAT1	Th1 cells, NK cells	Macrophages, endothelium, NK cells	Activation, increased MHC class II expression, increased antigen presentation	Susceptibility to bacterial infections[a]
	IL-10	JAK1, TYK2, STAT3	Th2 cells, other cells	Macrophages	Decreased MHC class II expression, decreased antigen presentation	Exaggerated inflammatory response and autoimmune disease

Continued

TABLE 9.1 Cytokines Classified by Receptor Families—cont'd

Receptor Family	Cytokine	Signaling	Source	Target	Action	Knock-out Phenotype
	IL-19, -20, -22, -24, -26	STAT1, STAT3	T cells, monocytes, melanocytes, NKT cells	T cells, keratinocytes, epithelial cells	Induces production of inflammatory cytokines, Th2 responses, activation of epithelial cells	
	IL-28, -29, -30	STAT1, STAT2, STAT3, STAT4, STAT5	DCs, many cells	Many cells	Antiviral	
IL-1/TLR	IL-1α/β	IRAK (IL-1 receptor-associated kinase), MyD88, TRAF6 (TNF receptor–associated factor 6), nuclear factor (NF)-κB	Many cells, especially macrophages	Central nervous system, endothelial cells, liver, thymocytes, macrophages, T cells	Fever, anorexia, activation acute-phase reactants costimulation, activation, cytokine secretion, differentiation of Th17 cells	Reduced inflammation, cooperates with tumor necrosis factor (TNF) in host defense
	IL-18	IRAK, MyD88, TRAF6, NF-κB	Many cells, especially macrophages, keratinocytes, osteoblasts	T cells, NK cells, macrophages, epithelial cells		Increased susceptibility to infection, reduced arthritis
	IL-33			T cells, nuocytes (ILC2)	Enhanced Th2 responses	
	IL-36 IL-37		Skin			
	IL-38			Macrophages		
IL-17	IL-17A		Th17 cells, CD8 T cells, γ/δ T cells	Endothelium, many cells	Inflammation	Susceptibility to extracellular bacteria
	IL-17B, -C, -D		Many cells	Monocytes, epithelial cells	Inflammation, chondrogenesis	
	IL-17E (IL-25)	TRAF2	Mast cells, Th2 cells	Th2 cells	Enhanced Th2 responses	Increased susceptibility to helminths
	IL-17 F		Th17 cells, CD8 T cells, γ/δ T cells	Endothelium, many cells	Inflammation	
Transforming growth factor (TGF)-β receptor serine kinase family	TGF-β_1, -β_2, -β_3		T cells, macrophages, other	T cells, macrophages, other	Inhibits growth and activation, promotes Th17	
Receptor tyrosine kinases	Stem cell factor	Ras/Raf/ mitogen-activated protein kinase (MAPK), stromal cells	Bone marrow	Pluripotent stem cells	Activation, growth	Defective hematopoietic stem cell proliferation, melanocyte production and development
	CSF-1 (macrophage (M)-CSF)	Ras/Raf/MAPK	Macrophages, endothelium, fibroblast, other	Committed myelomonocytic progenitors	Differentiation, proliferation, survival	Monocytopenia, osteopetrosis, female infertility
	FMS-like tyrosine kinase 3 ligand (FLT-3) ligand	Ras/Raf/MAPK	Diverse tissues	Myeloid cells, especially DCs	Proliferation, differentiation	Reduced repopulating hematopoietic stem cells; reduced B-cell precursors
	IL-32	NF-κB, p38 MAPK	T cells, NK cells, monocytes, epithelia	Monocytes	Induces TNF, IL-1, IL-6, IL-8	
	IL-16		T and B cells, mast cells, eosinophils	CD4 T cells		
	IL-3	Extracellular signal–regulated kinase (ERK)	Many cells	Monocytes	Proliferation binds CSF-1 receptors	

In cases where STAT5a or STAT5b are designated, the cytokines appear to use either interchangeably.
[a]LIFR is shared by these cytokines.
[b]Note that two forms of the IL-4 and perhaps IL-15 receptor exist.

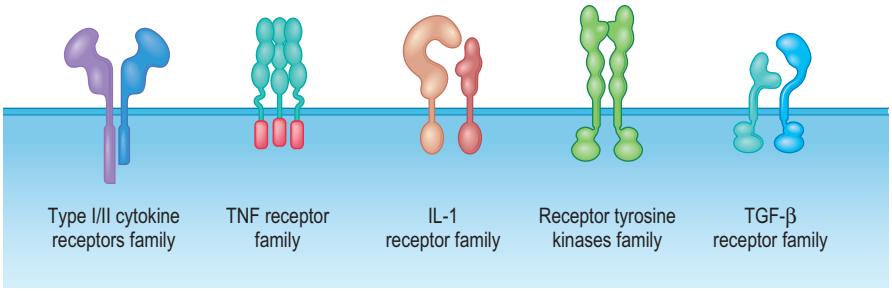

FIG 9.1 Schematic representation of prototypical receptors from five of the major cytokine receptor superfamilies.

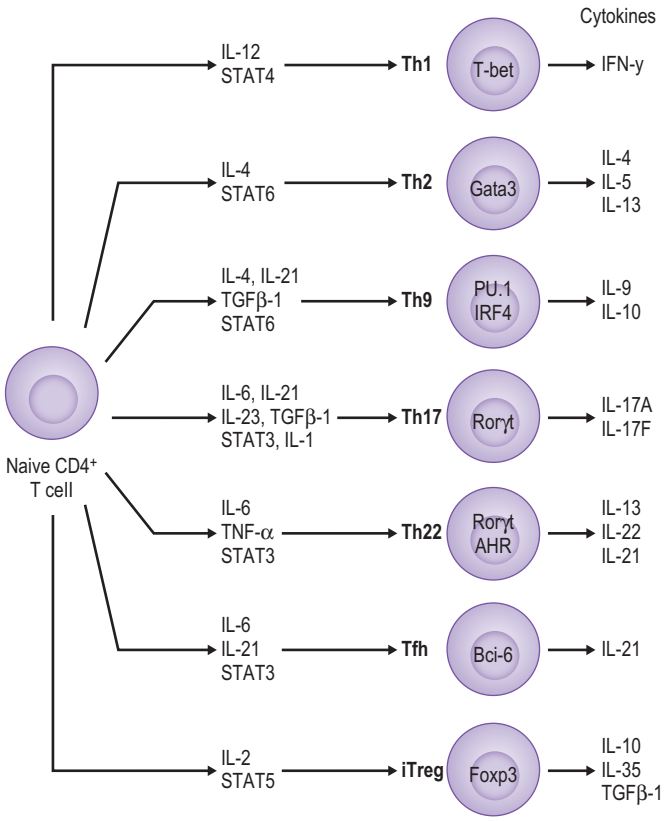

FIG 9.2 Differentiation of T-helper cell subtypes.

IL-19, IL-20, IL-22, IL-24, IL-26, and the IFN-related cytokines IL-28A (IFN-λ2), IL-28B (IFN-λ3), IL-29 (IFN-λ1), which bind type II receptors. The ligands and receptors in this superfamily are structurally similar and utilize related molecules for signal transduction.[5,6]

A central feature of type I cytokines is a similarity in their basic structure. Each contains four antiparallel α helices with two long and one short loop connections arranged in an up–up/down–down configuration. Because of this structure, these cytokines have also been referred to as the *α-helical bundle cytokine family.*

Structurally, the receptors in the type I family have conserved cysteine residues, a conserved Trp–Ser–X–Trp–Ser motif (where X indicates any amino acid), and fibronectin-like repeats in their extracellular domains. These receptors have a single transmembrane domain and divergent cytoplasmic domains. Within the cytoplasmic portion of these receptors, two segments of homology can be discerned, termed *Box 1* and *Box 2 motifs.* The membrane proximal domain binds Janus kinases (JAKs; see below). Some of the cytokine receptors are homodimers, such as the receptors for EPO, TPO, PRL, and possibly leptin, whereas other receptors for type I cytokines are heterodimers, containing two distinct receptor subunits. On the basis of this characteristic, the type I family of receptors can be divided into subfamilies. Each member of the subfamily uses a shared receptor subunit in conjunction with a ligand-specific subunit. For example, the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 all use a common cytokine γ chain, γc (see Table 9.1), whereas a common β chain, βc, is shared by IL-3, IL-5, and GM-CSF. Similarly, gp130 is a shared subunit for IL-6 family cytokines (IL-6, IL-11, IL-27, IL-35, CNTF, LIF, OSM, and CT-1). IL-12 and IL-23 also share a receptor subunit, as do members of the IL-10 family.

Other levels of shared receptor usage also exist. For example, the receptors for LIF, CNTF, OSM, and CT-1 all share the LIF receptor subunit, IL-31 and OSM also share one receptor chain, whereas IL-2 and IL-15 utilize the same β and γ c chains. Conversely, IL-4 can bind two different receptor complexes. The classic IL-4 receptor is composed of the IL-4Rα chain and the γc chain. Additionally, IL-4 can also bind the IL-13 receptor, which comprises a heterodimer of the IL-4Rα chain and the IL-13Rα chain. IL-13 only utilizes the IL-13 receptor complex for signaling.

The utilization of common receptor subunits explains the phenomenon of shared biological activities (cytokine redundancy) between cytokines that belong to the same subfamily. Within a subfamily, actions distinct for each cytokine can be attributed, at least in part, to the ligand-specific subunits. The pleiotropic effects of a single cytokine can be accounted for by the existence of more than one receptor for that cytokine.

Family Members and Their Actions

Homodimeric Receptors

Many of the cytokines that use homodimeric receptors are classic hormones. These include EPO GH, PRL, and leptin. EPO is required for erythrocyte growth and development and is widely used to treat anemia. Similarly, TPO is required for megakaryocyte development and may have a use in the treatment of thrombocytopenia. G-CSF not only regulates the production of neutrophils through its action on committed progenitor cells but also supports the survival of mature neutrophils, enhancing their functional capacity. G-CSF is widely used clinically to treat patients with granulocytopenia. As one would predict, G-CSF–deficient mice have marked neutropenia, and mutations of the G-CSF receptor (G-CSFR) result in severe congenital neutropenia in humans.

Cytokine Receptors Utilizing gp130

gp130 is a receptor component for IL-6, IL-11, IL-27, and IL-35 as well as LIF, OSM, CNTF, and CT-1.[7] Targeted disruption of the gp130 gene is lethal in early embryogenesis, causing defects in myocardial, hematological, and placental development. LIF binds to gp130 in association with the LIF receptor (LIFR), as do the cytokines OSM, CNTF, and CT-1. Deletion of the *LIFR* gene is also embryonically lethal, creating defects in placental architecture and developmental abnormalities in neural tissue and bone. Targeted disruptions of LIF lead to failure of blastocyst implantation. Another critical role of LIF is the maintenance of stem cell pluripotency in culture.

Interleukin-6. The IL-6 receptor (IL-6R) consists of a soluble IL-6 binding protein (α chain) (CD126) and membrane bound gp130. IL-6 has a wide array of biological actions on both lymphoid and nonlymphoid cells with the consequences of signaling by the membrane bound and soluble receptors being distinct.[8] IL-6 is important in host defense, and IL-6–deficient mice are susceptible to infection with *Candida* and *Listeria.* IL-6 is a growth and differentiation factor for B cells, inducing the production of immunoglobulin (Ig), including IgE. $IL6^{-/-}$ mice have normal numbers of B cells with reduced Ig response to immunization and reduced IgA production. IL-6 also promotes T-cell growth and differentiation. Consequently, $IL6^{-/-}$ mice have reduced numbers of thymocytes and peripheral T cells. IL-6 is important for T-helper 17 (Th17) cell differentiation and the cytotoxic T-cell response to viruses. IL-6 functions synergistically with IL-3 in hematopoiesis, and IL-6–deficient mice have reduced numbers of progenitor cells.

IL-6 is a major inducer of fever, inflammation, and the synthesis of acute-phase proteins (*e.g.,* fibrinogen, serum amyloid A, haptoglobin, C-reactive protein [CRP], etc.) in the liver. The elevation of the erythrocyte sedimentation rate (ESR) in inflammatory disease largely reflects the accelerated synthesis of these proteins, and IL-6–deficient mice are defective in this response. IL-6 reduces synthesis of albumin and transferrin in the liver and initiates hepatocyte regeneration. IL-6 induces adrenocorticotrophic hormone and anterior pituitary hormones, such PRL, GH, and luteinizing hormone (LH). IL-6 also plays a role in osteoporosis by affecting osteoclast function. IL-6–deficient mice are protected from bone loss following estrogen depletion.

Levels of IL-6 in serum are low in the absence of inflammation but rapidly increase in response to bacterial and viral infections, inflammation, or trauma. Patients with rheumatoid arthritis (RA), cardiac myxoma, Castleman disease, and other autoimmune diseases have high serum levels of IL-6. This cytokine may also contribute to malignancies, such as multiple myeloma.

IL-6 is produced by many cells, but its expression in mononuclear phagocytes has been well documented. Stimulation of monocytes with IL-1, TNF, or lipopolysaccharide (LPS) stimulates the expression of IL-6, whereas IL-4 and IL-13 inhibit its production. The *IL6* gene contains binding sites for nuclear factor-κB (NF-κB), nuclear factor for IL-6 (NF-IL-6, or CCAAT element-binding protein), activator protein-1 (AP-1), cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), and the glucocorticoid receptor.

Not surprisingly, much effort has been made to develop biological IL-6/IL-6R antagonists. Tocilizumab, an anti–IL-6 receptor antibody approved for treatment of RA, juvenile idiopathic arthritis, and other diseases and another anti–IL-6R monoclonal antibody (mAb), sarilumab, is in development. Anti–IL-6 mAbs (olokizumab, siltuximab, and clazakizumab) are also being developed for similar indications.

Interleukin-11. IL-11 and its receptor are widely expressed. IL-11 stimulates stem cells, megakaryocytes, myeloid precursors, and erythroid precursors, as well as promoting B-cell differentiation. It also acts on nonhematopoietic cells, including bone and liver cells. IL-11 is induced by proinflammatory cytokines (IL-1, TNF) and by TGF-β.

Interleukin-27. IL-27 is composed of two subunits designated EBI3 and p28 and signals through gp130 and WSX-1/TCCR (T-cell cytokine receptor). The receptor is expressed on naïve CD4 T cells. IL-27 promotes Th1 differentiation but also has essential antiinflammatory properties, inhibiting Th17 differentiation and enhancing IL-10 production.[9]

Cytokine Receptors Utilizing the β_c Chain

IL-3, IL-5, and GM-CSF bind to a ligand-specific α subunit associated with the common βc receptor subunit (common β subunit). Mice, but not humans, have a second β chain, βIL3. This species-specific redundancy may explain why gene targeting of βc in the mouse did not result in loss of IL-3 responses, although βc-null mice did have reduced GM-CSF and IL-5 responses.

Interleukin-3. IL-3 synergizes with other cytokines to stimulate the growth of immature progenitor cells of all lineages and is termed *multilineage colony-stimulating factor*. It promotes survival of macrophages, mast cells, and megakaryocytes. IL-3 is produced mainly by lymphoid cells, but also by mast cells and eosinophils. IL-3–deficient mice have no obvious defect in hematopoiesis, suggesting that the major role of IL-3 *in vivo* may be in the response to stress.

Interleukin-5. IL-5 is unusual in that it is a disulfide-linked homodimer, with each component containing three α-helical bundles. It promotes the growth, differentiation, and activation of eosinophils and so is very important in pathogenesis of allergic disease. $IL5^{-/-}$ mice fail to develop eosinophilia in response to parasitic or aeroallergen challenge and exhibit minimal signs of inflammation and damage to lungs. IL-5 deficiency does not affect the worm burden of infected mice, indicating that eosinophilia may not play an essential role in the host defense against helminths *per se.* Both IL-5 and IL-5R knock-out mice have decreased numbers of $CD5^+$ B cells (B-1 cells) and concomitant low serum IgM and IgG3 levels. IL-5 is produced by activated helper T cells of the Th2 phenotype (see below), mast cells, and eosinophils in an autocrine manner. Mepolizumab and reslizumab are anti–IL-5 mAbs that have been approved for the treatment of severe eosinophilic asthma disease.

Granulocyte macrophage–colony-stimulating factor. GM-CSF acts on hematopoietic precursors to support myelomonocytic differentiation. It activates mature neutrophils and macrophages, increasing their microbicidal activity and inducing the production of proinflammatory cytokines. Along with IL-4 and IL-13, GM-CSF is a major stimulatory cytokine for the *in vitro* production of dendritic cells (DCs). GM-CSF induces proliferation and activation of eosinophils and upregulates adhesion molecules on fibroblasts and endothelial cells. Deletion of the GM-CSF gene (*Csf2*) in mice, however, does not affect steady-state hematopoiesis. Instead, these animals develop alveolar proteinosis and lymphoid hyperplasia. $\beta c^{-/-}$ mice also develop alveolar proteinosis, characterized by the accumulation of surfactant in the lungs. A

similar defect may be responsible for disease in a subset of humans with this abnormality.

The production of GM-CSF can be induced by proinflammatory cytokines and LPS. GM-CSF is made by activated lymphocytes and other stimulated cells and is an important driver of immune pathology in murine models of autoimmunity.[10,11] GM-CSF is not ordinarily detectable in blood except under pathological conditions, such as asthma. GM-CSF has been used clinically to treat chemotherapy-induced neutropenia, especially in the context of certain infections (*e.g.,* fungal), and has been tested in myelodysplastic syndrome and aplastic anemia. Mavrilimumab is an anti–GM-CSF antibody being studied in rheumatoid arthritis.[12]

Cytokine Receptors Utilizing the γc Chain

The cytokines IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 all bind to receptors that share a common γc receptor subunit. The γc subunit and the ligand-specific subunits are expressed predominantly on lymphocytes, although they can be found on other hematopoietic cells as well. Mutation of the γc gene is responsible for X-linked severe combined immunodeficiency (SCID), characterized by a lack of T cells and natural killer (NK) cells, and poorly functioning B cells (T^-B^+ SCID) (Chapter 35).[13] The lack of γc abrogates signaling by all cytokines that utilize this subunit (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21). The lack of IL-7 and IL-15 signaling is largely responsible for the lack of T and NK cells, respectively.

Interleukin-2. The IL-2 receptor consists of three subunits, α, β, and γc. The latter two are members of the type I cytokine receptor family. NK cells constitutively express these latter two subunits and respond to high doses of IL-2, whereas in T cells the IL-2Rα subunit is induced upon activation, creating a high-affinity receptor for IL-2. IL-2Rα is also inducible in activated monocytes and B cells. IL-2Rα, however, is not a member of the type I cytokine receptor family. Rather, it resembles members of the complement family and IL-15R (see below).

IL-2, one of the first cytokines to be intensively studied, is produced principally by activated T cells. It is a prototypical autocrine T-cell growth factor and is required for *in vitro* T-cell proliferation. It is an important factor in determining the magnitude of T-cell and NK-cell responses *in vivo,* although other factors also contribute. It is thus redundant to some degree for this function. It augments the cytolytic activity of T and NK cells and enhances IFN-γ secretion. IL-2 is also important in programming CD8 memory T cells, which undergo secondary expansion in viral infections.[9] IL-2 is a growth factor for B cells and induces class switching. It also activates macrophages.

IL-2–deficient mice develop massive enlargement of peripheral lymphoid organs, hemolytic anemia, inflammatory bowel disease (IBD), and infiltrative granulopoiesis. In addition, the mice have high levels of IgG1 and IgE. They succumb to widespread autoimmune and lymphoproliferative disease, which points to the nonredundant roles of IL-2 in promoting tolerance and preventing autoimmunity.[14] A similar phenotype is seen in humans with IL-2Rα mutations.

Regulatory T cells (Tregs) in both mice and humans express high levels of IL-2Rα. Maintenance of peripheral Treg numbers is dependent on IL-2.[15] In addition, IL-2 inhibits Th17 and T-follicular helper (Tfh) cell differentiation.[16,17]

IL-2 is produced by activated T cells but also myeloid cells, including DCs. The *IL2* gene has been extensively characterized and contains binding sites for nuclear factor of activated T-cells (NFATs), AP-1, and NF-κB. IL-2 production is also regulated by stabilization of its messenger RNA (mRNA).

IL-2 is approved by the US Food and Drug Administration (FDA) for the treatment of renal cancer; however, its clinical utility is limited by its toxicity, two important manifestations being hepatic dysfunction and the so-called capillary or vascular leak syndrome. However, the anti–IL-2Rα mAbs daclizumab and basiliximab are used to prevent rejection of allotransplants and, more recently, have been found to be effective in the treatment of multiple sclerosis (MS).[18] Polymorphisms of IL-2Rα are also associated with MS.

Interleukin-4. Two classes of IL-4R appear to exist. The first consists of the IL-4Rα subunit in conjunction with γc. It is expressed on hematopoietic cells.[19] The second, which is more widely expressed, is a "type II" receptor. It consists of the IL-4Rα subunit in associated with IL-13R α chain. Two IL-13R subunits have been cloned, so the exact composition of the type II IL-4R remains uncertain. The existence of two receptors helps explain why IL-4 has diverse actions on both hematopoietic and non-hematopoietic cells. The loss of IL-4Rα would be predicted to block the actions of both IL-4 and IL-13, which could explain why gene targeting of IL-4Rα leads to a more severe phenotype than that observed in IL-4–deficient mice. Polymorphisms of IL-4Rα have been reported to be associated with a propensity to atopy.[20]

In general, IL-4 promotes allergic responses and inhibits cell-mediated immune responses. Among the most important roles of IL-4 is its ability to promote differentiation of naïve CD4 T cells into a subset that produces IL-4 and IL-5,[21] denoted as Th2 subset, as opposed to Th1 cells, which produce IFN-γ (Chapter 16). In conjunction with CD40 activation, IL-4 also promotes B-cell proliferation and class switching, particularly to IgG1 and IgE in mice and to IgG4 and IgE in humans. Mice deficient in IL-4 have normal B lymphopoiesis but marked reductions in IgG1 and IgE production in response to parasites. These mice have residual Th2 responses because IL-13, which also binds IL-4Rα, can partially compensate for the defect.

IL-4 upregulates the expression of surface IgM, major histocompatibility complex (MHC) class II, and CD23 on B cells. In conjunction with GM-CSF, it is a growth factor for mast cells and basophils, as well as a potent inducer of DC differentiation. IL-4 inhibits macrophage activation and the production of proinflammatory cytokines. It antagonizes the effects of IFN-γ, blocks cytokine-induced proliferation of synoviocytes, downregulates the expression of adhesion molecules, and antagonizes the induction of some acute-phase reactants in hepatocytes by IL-6.

IL-4 is made by the Th2 subset of CD4 T cells, $NK1.1^+$ $CD4^+$ T cells, basophils, and mast cells. A number of transcription factors appear to be important in regulating IL-4 production, including NFAT, NF-IL6, C/EBP, c-MAF, and GATA-3. The *IL4* gene has multiple signal transducer and activator of transcription 6 (STAT6) binding sites, consistent with the fact that IL-4 regulates its own expression. Epigenetic control and chromatin remodeling are also important aspects.[22]

Clinically, IL-4 has been tested in the treatment of malignancies and some autoimmune disorders. The ability of IL-4 to generate DCs is being exploited in the use of tumor vaccines. Conceivably, soluble IL-4R might also be useful in the treatment of allergic disease. Dupilumab is an anti-IL-4/13R mAb being studied in severe atopic dermatitis.[23]

Interleukin-7. The IL-7 receptor consists of the IL-7Rα chain (CD127) in association with γc. It is expressed on both immature and mature thymocytes. Humans with loss-of-function (LOF) mutations of IL-7Rα have T^-B^+ SCID but, unlike in individuals with γc mutations, display normal NK-cell development (Chapter 35). Gain-of-function (GOF) mutations of the IL-7Rα chain result in constitutive JAK1 signaling and cell transformation and give rise to T-cell acute lymphoblastic leukemia (Chapter 78).

IL-7Rα expression is tightly regulated during thymocyte development (Chapter 8). IL-7 plays an important role in both developing thymocytes and mature T cells. Its receptor is expressed in double-negative thymocytes, downregulated in double-positive cells, and then reexpressed in single-positive thymocytes and mature peripheral T cells. This may be a reflection of its anti-apoptotic effects, which are attributable to the induction of Bcl-2 family members. IL-7 promotes the growth of thymocytes, as well as the expression and rearrangement of T-cell receptor (TCR) genes and the expression of *RAG1* and *RAG2* (Chapter 4). IL-7Rα is expressed on cutaneous T-cell lymphomas, which also produce this cytokine; thus the autocrine response to IL-7 may contribute to the growth of these tumors.

IL-7– and IL-7R–deficient mice exhibit impairments in both T- and B-cell development. Postnatal B-cell development in $Il7^{-/-}$ mice is blocked at the transition to pre–B cells and is arrested even earlier in $Il7ra^{-/-}$ mice. Why these abnormalities do not occur in humans with IL-7Rα mutations is not clear.

IL-7 is produced by a wide variety of cells, including marrow and perhaps thymic stromal cells, as well as in the kidney, spleen, and epithelial cells and keratinocytes. This is consistent with its role in the maintenance of function in both immature and mature lymphocytes.

Clinically, IL-7 may be useful to restore immune function in some congenital immunodeficiencies, after bone marrow transplantation, and in human immunodeficiency virus (HIV) infection. Polymorphisms of the *IL7R* gene are associated with MS.

Interleukin-9. IL-9 has some of the same properties as IL-4. It synergizes with stem cell factor to promote the growth and differentiation of mast cells and regulate mast cell function. IL-9 potentiates IgE production induced by IL-4 in B cells. Although first identified as a T-cell growth factor, a physiological role in T-cell development has not been established. IL-9 is produced by activated Th2 cells, mast cells, and eosinophils. Recently, a new subset of Th cells, termed *Th9,* has been proposed. These cells have been shown to not only secrete IL-9 but also to enhance inflammatory responses. Interestingly, IL-9 inhibits Th1 cytokine production. Some lymphoid tumors also produce IL-9, where it may serve as an autocrine growth factor. A subset of innate lymphoid cells, ILC2 (Chapter 3), also produces IL-9, which is thought to contribute to the pathogenesis of allergy and asthma.

Interleukin-15. The IL-15 receptor consists of the IL-2Rβ and γc subunits in association with a unique ligand-specific subunit, IL-15Rα, which is homologous to IL-2Rα. These receptor proteins contain protein-binding motifs termed "sushi domains." In both humans and mice, these receptors and their cognate ligands are physically linked in the genome. Given their shared receptor usage, there are many similarities in the actions of IL-2 and IL-15, particularly in terms of the effects on lymphoid cells. Like IL-2, IL-15 induces proliferation and cytokine production in T and NK cells. However, despite the similarities between these two ligands/receptors, there are some important differences. In T cells, IL-15 is less efficient than IL-2 in inducing effector memory T-cell differentiation or sensitivity to apoptosis.[24] IL-15Rα is more widely expressed than IL-2Rα, IL-2Rβ, and γc. IL-15Rα is expressed by lymphoid cells, DCs, fibroblasts, and epithelial, liver, intestine, and other cells and is thought to present IL-15 in *trans* to cells expressing IL-15β and γ chains. IL-15– and IL-15Rα–knock-out mice are defective in NK-cell production and in the generation of memory T cells, explaining the absence of NK development in patients with γc mutations.

IL-15 mRNA is expressed broadly in hematopoietic and nonhematopoietic cells but is not typically produced by T cells. (human T-lymphotropic virus 1 [HTLV-1]–transformed T cells are an exception in that they produce abundant IL-15.) Following the pattern seen in IL-7 and IL-9, there are multiple triplet repeats of adenosine, uradine, guanosine (AUGs) in the 5′ untranslated portion of the IL-15 message that interfere with translation. Thus IL-15 is controlled by translational regulation. IL-15 protein is also controlled at the level of secretion of the protein, but this is incompletely understood. High levels of IL-15 protein have been reported in synovial fluids from patients with RA, alveolar macrophages from patients with sarcoidosis, and peripheral blood mononuclear cells from patients with ulcerative colitis.

Interleukin-21. IL-21 is a T-cell–derived cytokine that works in concert with other γc cytokines. It synergizes with IL-7 and IL-15 to expand and activate CD8 T cells. IL-21 also augments the activity of NK cells. IL-21, along with IL-6, drives differentiation of Tfh. Tfh cells are found preferentially in B-cell follicles, where, under the control of the transcription factor BCL6, they regulate B-cell development, activation, and class switching. Tfh cells are also a source of IL-21.[25] IL-21 appears to have some anticancer properties, and it has been tested in the treatment of melanoma.[26,27]

Other Heterodimeric Receptors

Interleukin-12. IL-12 is a heterodimer composed of two disulfide-linked polypeptide chains, p35 and p40, derived from two distinct genes.[28,29] IL-12 p35 shares homology with other cytokines, such as IL-6, whereas p40 resembles the IL-6 receptor. Thus IL-12 can be viewed as being synthesized as a ligand–receptor complex. IL-12R consists of two chains, and because the ligand already comprises the α subunit, the two chains of the IL-12R are denoted IL-12Rβ_1 and β_2. Expression of high-affinity IL-12R is very restricted, being found predominantly on T and NK cells. IL-12Rβ_1 and β_2 are highly inducible upon T-cell activation, and IL-4 inhibits IL-12Rβ_2 expression. This is important because IL-12Rβ_2 is required for IL-12 signaling and the activation of the STAT4. NK cells constitutively express IL-12Rβ_1 and IL-12Rβ_2.

IL-12 plays a pivotal role in promoting cell-mediated immune responses. Humans with *IL12R* mutations, as well as mice with IL-12 and IL-12R deficiency, have very blunted immune responses and are highly susceptible to infections by intracellular pathogens. An important function of IL-12 is that it promotes the differentiation of uncommitted Th cells to the Th1 subset (*i.e.,* T cells that produce LT-α and INF-γ). Th1 differentiation is markedly impaired in IL-12– and IL-12R–deficient mice. A major action of IL-12 is its ability to induce the production of IFN-γ, doing so synergistically in combination with IL-2 or IL-18. Consequently, many of the actions of IL-12 are blocked in IFN-γ or IFN-γR knock-out mice. IL-12 also induces proliferation and cytolytic activity of T and NK cells.

DCs and macrophages are the major producers of IL-12 in response to various pathogens, occupancy of TLRs, and CD40. The *IL12p40* gene is complex and contains NF-κB sites, IFN response elements (IREs), and ETS-binding sites. As with other cytokine genes, nucleosome remodeling is important in the regulation.[30]

Because of its profound effects on cell-mediated immunity, IL-12 has been used in the treatment of malignancies and infectious diseases. However, its utility has been limited because of significant toxicity. IL-12 may also have use in vaccines as an adjuvant. Conversely, antagonizing the actions of IL-12 has been found to be useful in Th1-mediated diseases, including IBD (Chapter 75). Ustekinumab inhibits both IL-12 and IL-23 and is approved for psoriasis and psoriatic arthritis.

Interleukin-23. IL-23 is another heterodimeric type I cytokine. It is composed of two disulfide-linked polypeptide chains, p19 and IL-12 p40. The IL-23 receptor also shares the IL-12Rβ_1 chain paired to the IL-23R. The IL-23R complex is expressed on T cells and ILCs and regulates production of IL-17 (Th17, see below). As such, IL-23 is thought to be important in host defense against extracellular bacteria and the pathogenesis of autoimmune and autoinflammatory disorders. IL-23 is produced primarily by DCs in response to TLR agonists. IL23R polymorphisms are associated with IBD, ankylosing spondylitis, and other autoimmune diseases. Tildrakizumab and guselkumab inhibit IL-23 but not IL-12.

Interleukin-35. IL-35 is a dimer consisting of IL-12 p35 and EB13. It is preferentially produced by Tregs. Tregs are also the main cellular target of IL-35, where it induces proliferation and production of IL-10. A synthetic form of IL-35, obtained by covalently linking EBI3 to IL-12p35, can reduce the incidence of arthritis in mouse models.[26]

Interleukin-13. IL-13 has many of the same effects as IL-4 and shares a receptor subunit(s) with IL-4. IL-13–deficient mice have reduced levels of IL-4, IL-5, and IL-10, with lower IgE levels and eosinophils. In mice deficient for both IL-4 and IL-13, these Th2 responses are abolished, and the ability to clear parasites is severely impaired. These double-knock-out mice default to Th1 responses, with concomitant production of INF-γ, IgG2a, and IgG2b. It thus appears that IL-4 and IL-13 cooperate in promoting Th2 responses, having both overlapping and additive roles. Anti–IL-13 mAbs in clinical trials include lebrikizumab and tralokinumab for severe asthma.[31,32]

Interleukin-31. IL-31 signals through the heterodimeric receptor IL-31Rα and oncostatin M receptor (OSMR). It is produced by activated Th2 cells. Overexpression of IL-31 results in atopic dermatitis, but surprisingly, IL-31Rα–deficient mice showed an increased Th2 response.[33,34]

Thymic stromal lymphopoietin. Thymic stromal lymphopoietin (TSLP) is an IL-7–like cytokine expressed by epithelial cells and keratinocytes. Its receptor comprises TSLP receptor (TSLPR) and IL-7Rα, which is expressed primarily on monocytes and myeloid-derived DCs, as well as on B cells. TSLP-treated human DCs promote Th2 differentiation.[35] A major means by which TSLP exerts its effect is through promotion of basophil hematopoiesis.[36] Elevated TSLP levels have been found in humans and animal models of airway inflammatory disease and atopic dermatitis. In the mouse, TSLP contributes to prenatal B-cell development.

Interferons

Type I Interferons

Interferon-α/β. The type I IFNs include IFN-α, IFN-β, and IFN-ω. IFN-β and IFN-ω are encoded by single genes, whereas IFN-α includes at least 14 separate genes, each encoding structurally distinct forms. These intronless genes are all clustered on the short arm of chromosome 9 and appear to have diverged from a common ancestor more than 100 million years ago. Each of these molecules binds to the same IFN-α/β receptor, and their actions are similar. The receptor is a heterodimer composed of two subunits termed *IFNAR1* and *IFNAR2.* These subunits have limited similarity to type I cytokine receptors, although they lack the WSXWS motif.

A major effect of type I IFNs is their antiviral action.[37] Discovered in 1957, they act on all cells to inhibit viral replication as well as cellular proliferation. It is unclear why there are so many type I genes. Given that their relative potencies differ, it is possible that these genes evolved in response to various viral pathogens. Alternatively, IFN gene duplication may affect the magnitude of antiviral responses. A major mechanism is the inhibition of protein translation. Type I IFNs also upregulate MHC class I and can block the ability of IFN-γ to upregulate MHC class II expression.[38] IFN-α/β increase the cytolytic activity of NK cells. IFNARI knock-out mice are extremely susceptible to infections, even though lymphoid development is normal.

IFNs are produced ubiquitously. Recognition of extracellular and intracellular foreign DNA, produced in viral infection, is a major inducer of their transcriptional regulation. Type I IFN is also induced by intracellular bacterial pathogens and LPS. Immunoregulatory effects of IFN-α/β are being increasingly recognized, and it is notable that a subset of DCs produces very high levels.[39,40] IFN genes are bound by multiple transcription factors, including NF-κB, interferon regulatory factor 3 (IRF-3), IRF-7, and STAT1.

Type I IFN is used clinically in the treatment of certain infections (*e.g.,* viral hepatitis). Because of its antiproliferative action, it is also used in the treatment of certain malignancies, particularly hairy cell leukemia. IFN-β is used in the treatment of MS.

Newer IFN-like cytokines, including IL-28A, IL-28B, and IL-29 (also designated IFN-λ1, -λ2, and -λ3), have been identified. They bind to a receptor designated IL-28R. The exact *in vivo* functions of these IFN-like cytokines are poorly understood, although they probably contribute to antiviral responses.

Interferon-γ. IFN-γ is a major activator of macrophages, enhancing their ability to kill microorganisms by augmenting their cytolytic machinery. IFN-γ exerts this effect by causing the cell to increase its production of reactive oxygen intermediates, including hydrogen peroxide, nitric oxide, and indoleamine dioxygenase. It also upregulates MHC class II expression. IFN-γ acts on CD4 T cells to promote Th1 differentiation while inhibiting the generation of Th2 cells. It promotes the maturation of CD8 T cells to cytotoxic cells. IFN-γ augments NK-cell cytolytic activity and regulates B-cell class switching. Endothelial cells and neutrophils are also activated by IFN-γ. Like IFN-α/β, IFN-γ also contributes to antiviral defenses.

The IFN-γ receptor is a heterodimer composed of two subunits, IFN-γRα and IFN-γRβ. When one IFN-γ homodimer binds, a complex of two α and two β receptors is created.[41] Mice with a disrupted IFN-γR develop normally and have normal lymphoid development but are highly susceptible to viral and bacterial infections, especially those by intracellular microbes. They have diminished macrophage MHC class II expression, decreased NK function, and reduced serum IgG2a concentrations. Humans with mutations of IFNGR subunits (OMIM #209950) are also susceptible to mycobacterial and *Salmonella* infections.

IFN-γ is produced by Th1 and NK cells. Transcription factors, including STAT4, T-BET, and EOMES, play an important roles in IFN-γ gene regulation.[22] IFN-γ has been used to treat patients with immunodeficiencies (*e.g.,* chronic granulomatous disease [CGD]) and in certain patients with disseminated mycobacterial

infections.[22] A monoclonal anti-IFN-γ antibody, fontolizumab, is being studied in the treatment of autoimmune diseases.

Interleukin-10 and related cytokines. The major function of IL-10 is to serve as an antiinflammatory and immunosuppressive cytokine. Unlike other cytokines in this family, it is a disulfide-linked dimer. A single IL-10R has been cloned, but the receptor may have additional components. IL-10R is expressed on macrophages, mast cells, and most other hematopoietic cells. It is also inducible in nonhematopoietic cells by stimuli, such as LPS.

IL-10 strongly inhibits the production of proinflammatory cytokines. It inhibits macrophage antigen presentation and decreases expression of MHC class II, adhesion molecules, and the costimulatory molecules CD80 (B7.1) and CD86 (B7.2). The importance of IL-10 as an endogenous inhibitor of cell-mediated immunity is emphasized by the finding that IL-10–deficient mice develop autoimmune disease, which manifests with severe IBD and exaggerated inflammatory responses. Humans with mutations of the *IL10* and *IL10R* genes suffer from IBD.

IL-10 is made by T cells, B cells, macrophages, keratinocytes, bronchial epithelial cells, and other cells. LPS and TNF are inducers of IL-10. IL-10 is readily detected in the blood of patients with septic shock and other inflammatory and immune disorders. Because of its antiinflammatory properties, IL-10 has been used experimentally in the treatment of some Th1-mediated autoimmune diseases. IL-10 is elevated in patients with systemic lupus erythematosus (SLE), and there is a correlation between levels of IL-10 and autoantibody production.

There are viral homologues of IL-10 that may blunt the immune response to these pathogens. IL-10 also contributes to the immunosuppression seen in lepromatous leprosy or parasitic infestations. Other IL-10–related cytokines include IL-19, IL-20, IL-22, IL-24, and IL-26, but their biological actions are incompletely understood.[42]

Signaling

Neither type I nor type II receptors exhibit intrinsic enzymatic activity. However, the conserved membrane proximal segment of each of these receptors serves as the site at which these receptors bind JAKs (see Table 9.1). These JAKs play a pivotal role in signaling via this family of cytokine receptors.[5]

Janus Kinases

Four mammalian JAKs, JAK1, JAK2, JAK3, and TYK2, have been identified. JAKs are structurally unique, consisting of a C-terminal catalytically active kinase domain that is preceded by a segment termed the *pseudokinase domain*. The latter gives JAKs their name and has regulatory functions. A key feature of the JAKs is their association with cytokine receptors, which appears to be mediated by the N-terminus.

Ligand binding to type I and II receptors induces the aggregation of receptor subunits, which brings JAKs in close proximity and allows them to phosphorylate and activate each other. After activation, the JAKs phosphorylate receptor subunits on tyrosine residues, which allow the recruitment of proteins with SRC homology-2 (SH2) or phosphotyrosine-binding (PTB) domains. These proteins can also be phosphorylated by JAKs. Phosphorylation results in the activation of a number of biochemical pathways. Importantly, phosphorylation of cytokine receptors generates docking sites for a class of SH2-containing transcription factors termed *STATs* (see below) (Fig. 9.3).

The pivotal function of the JAKs is vividly illustrated by mice or humans that are deficient in these kinases. Consistent with the association of JAK3 with the common gamma chain, γc, mutations of JAK3 cause autosomal recessive T^-B^+ SCID (Chapter 35).[43] *Jak3*$^{-/-}$ also exhibit SCID. Indeed, mutation of either γc or JAK3 leads to the same functional defects. These findings led to the notion that JAK inhibitors might represent a new class of immunomodulatory drugs. Multiple JAK inhibitors have been approved or are in late phase clinical development (Chapter 87).

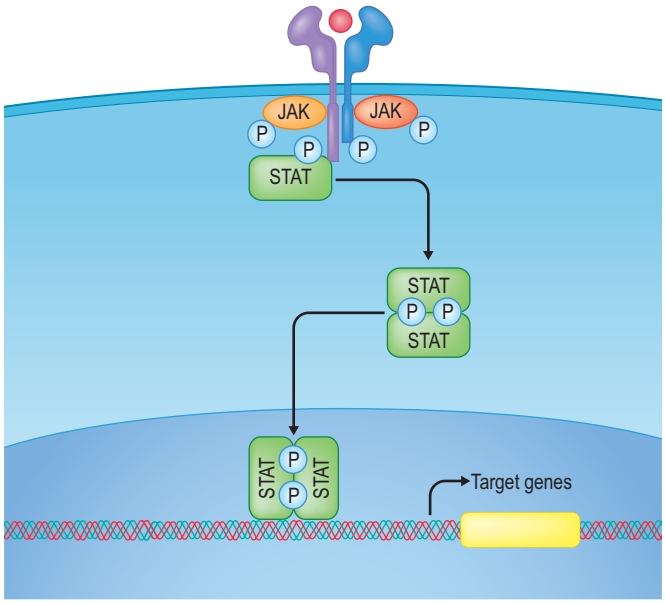

FIG 9.3 The roles of Janus kinases (JAKs) and signal transducer and activator of transcription factors (STATs) in signal transduction by type I and II cytokine receptors.

Gene targeting of *Jak1* and *Jak2* results in diverse abnormalities. *Jak1*$^{-/-}$ mice not only die perinatally as a result of neurological defects but also have a SCID phenotype similar to *Jak3*$^{-/-}$ mice. This is explained by the fact that γc-containing cytokine receptors utilize JAK1 in association with their ligand-specific receptor subunit. Other cytokines that are dependent on JAK1 include those that use gp130 cytokine receptors (IL-6, LIF, OSM, CNTF, and IL-11) and type II receptors (IL-10, IFN-γ, and IFN-α/β). Gene-targeting of *Jak2* was embryonically lethal, principally because JAK2 is essential for erythropoietin function, and the mice fail to form blood. In addition, JAK2 is necessary for signaling of other cytokines, including IL-3.

The importance of the JAKs is also substantiated by mutations in many leukemias and lymphomas. Mutation in the pseudokinase domain of *JAK* underlies most cases of polycythemia vera. Loss of function mutations of *TYK2* are associated with immunodeficiency.

Signal Transducer and Activator of Transcription (STAT)

Members of the STAT family of DNA-binding proteins serve a key role in transducing signals from cytokine receptors on the cell surface to the nucleus, where they regulate gene transcription. STATs are latent, cytosolic transcription factors that have SH2 domains (phosphotyrosine-binding modules) that allow them to be recruited to phosphorylated cytokine receptors (see Fig. 9.3). Different STATs bind to specific cytokine receptors (see Table 9.1). STATs are themselves tyrosine phosphorylated by JAKs, and this promotes their dimerization. STATs translocate to the nucleus, bind DNA, and regulate transcription.

There are seven mammalian STATs: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. *Stat* knock-out mice document the essential and specific functions of these transcription factors in transmitting cytokine signals. *Stat1*$^{-/-}$ mice develop normally but have extreme susceptibility to viral and some bacterial infections, consistent with the defects seen in *Ifng*$^{-/-}$ and *Ifngr*$^{-/-}$ mice. Humans with loss of function mutations of *STAT1* have increased susceptibility to *Salmonella* and mycobacterial infections, whereas GOF mutations of *STAT1* cause chronic mucocutaneous candidiasis (CMC). Gene targeting of *Stat3* leads to early embryonic lethality, the lethality being related, in part, to interference with Lif function. Conditional knock-outs of *Stat3* in myeloid cells display exaggerated inflammatory responses as a result of failure of IL-10 signaling. STAT3 is also essential for Th17 cells, and mutations of *STAT3* underlie the primary immunodeficiency Hyper-IgE syndrome (HIES, or Job's syndrome) associated with impaired IL-17 production. Polymorphisms of *STAT3* are associated with IBD (Chapter 75). STAT4 is activated by IL-12. *Stat4*$^{-/-}$ mice develop normally but have defective Th1 differentiation and IFNγ production combined with augmented Th2 development.

STAT6 is activated by IL-4. *Stat6*$^{-/-}$ mice have defective Th2 development with defective IgE responses following infection with parasites. Lack of STAT6 dramatically attenuates allergic and asthmatic disease in animal models of these diseases. IL-13 also activates STAT6, and its responses are abrogated in *Stat6*$^{-/-}$ mice.

STAT5A and STAT5B are highly homologous, but nonetheless have different functions. *Stat5a*$^{-/-}$ mice have impaired mammary gland development and failure of lactation, whereas *Stat5b*$^{-/-}$ mice have defective sexually dimorphic growth and growth hormone–dependent regulation of liver gene expression. *Stat5a/5b* doubly deficient mice manifest increased perinatal lethality, decreased size, female infertility, and impaired lymphocyte development.

Stat5$^{-/-}$ mice develop lymphoproliferative disease reminiscent of IL-2- and IL-2R–deficient mice, related to loss of Tregs with expansion of Tfh and Th17 cells.

Patients with *STAT5B* mutations have short stature and immune dysregulation.

CLINICAL RELEVANCE

Type I and II Cytokine Receptors

- Mutations of genes encoding interleukin (IL)-7R, γc, and Janus kinase 3 (JAK3) cause severe combined immunodeficiency (SCID).
- TYK2 and signal transducer and activator of transcription 3 (STAT3) mutations cause hyper-IgE syndrome (HIES).
- STAT1 mutations cause autosomal dominant chronic mucocutaneous candidiasis (CMC) with increased susceptibility to mycobacterial and viral infections.
- Mutations of genes encoding IL-12, IL-12R, and interferon-γ receptor (IFN-γR) are associated with susceptibility to intracellular infections.
- Polymorphisms of IL-2R and IL-7R are associated with multiple sclerosis (MS).
- Polymorphisms of IL-23R are associated with inflammatory bowel disease (IBD).
- Polymorphisms of STAT4 are associated with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).
- Erythropoietin (EPO), granulocyte–colony-stimulating factor (G-CSF), and thrombopoietin (TPO) are used to treat cytopenias.
- Anticytokine and/or cytokine receptor monoclonal antibodies (mAbs) are used to prevent transplant rejection and treat several autoimmune and inflammatory diseases.

Attenuation of Type-I and Type-II Cytokine Signaling

Perhaps as important as the triggers that initiate signal transduction are the mechanisms for extinguishing the response.[44] There are several families of proteins involved in downregulating cytokine signaling. Among these are phosphatases, cytokine-inducible inhibitor molecules, and transcriptional repressors. The phosphatase SHP-1 interacts with cytokine receptors and downregulates signaling. Mice with the naturally occurring "moth-eaten" mutation in *SHP-1* lack a functional SHP-1 protein and die at an early age as a result of autoimmune disease.

Another family of proteins that attenuate cytokine signaling is the suppressors of cytokine signaling (SOCS), which are alternatively termed JAB, SSI, and CSIS. These are SH2-containing proteins that bind to either cytokine receptors or to JAKs and inhibit signaling. There are at least eight members of this family. Largely as a result of systemic hyperresponsiveness to IFN-γ, *Socs-1*$^{-/-}$ mice die within a few weeks of birth. SOCS-2 has been recently shown to regulate Th2 differentiation and allergic responses. Another family member, SOCS-3, is important in controlling Th17 differentiation.[45-47]

KEY CONCEPTS

Properties of the Tumor Necrosis Factor (TNF) Receptor Superfamily

- Activation of a TNF receptor can lead to a wide range of effects, from proliferation to apoptosis.
- Transduction of signals through TNF receptor–associated factors (TRAFs) leads to the enhancement of survival.
- Signaling through death domains leads to the induction of apoptosis.

THE TNF CYTOKINE AND RECEPTOR SUPERFAMILY

This large family of structurally related ligands, receptors, and inhibitory decoy receptors has various roles both within and outside the immune system. The first two members of this family to be discovered were TNF and lymphotoxin-α (LTα; formerly named TNF-β). These molecules are secreted principally by activated myeloid and T cells. They have similar proinflammatory functions and belong to a large family of related molecules that includes CD30 ligand, CD40 ligand, FAS ligand, and TNF-related apoptosis inducing ligand (TRAIL). Indeed, the TNF cytokine family now contains 18 ligands and 29 receptors, each of which exhibits marked differences in tissue expression, ligand specificity, receptor binding, and biological function (Fig. 9.4) This section describes general aspects of TNF and TNF receptor (TNFR) biology, with examples from three of the best-studied TNF-family members. More complete listings of TNF-family cytokines and their receptors can be found in Table 9.2 and Table 9.3.

Ligand and Receptor Structure

Much of our understanding of the structural and functional characteristics of the TNF ligand and receptor superfamilies has come from the analysis of TNF (TNFSF2), LTα (TNFSF1), FASL (TNFSF6), and their receptors. Among these, TNF and LTα are closely related homotrimeric proteins (32% identity). Human TNF is synthesized as a 233-amino acid glycoprotein. It contains a long (76 residue) amino-terminal sequence that anchors it to the cell membrane as a 25-kilodalton (kDa) type II membrane protein. A secreted 17-kDa form of TNF is generated through

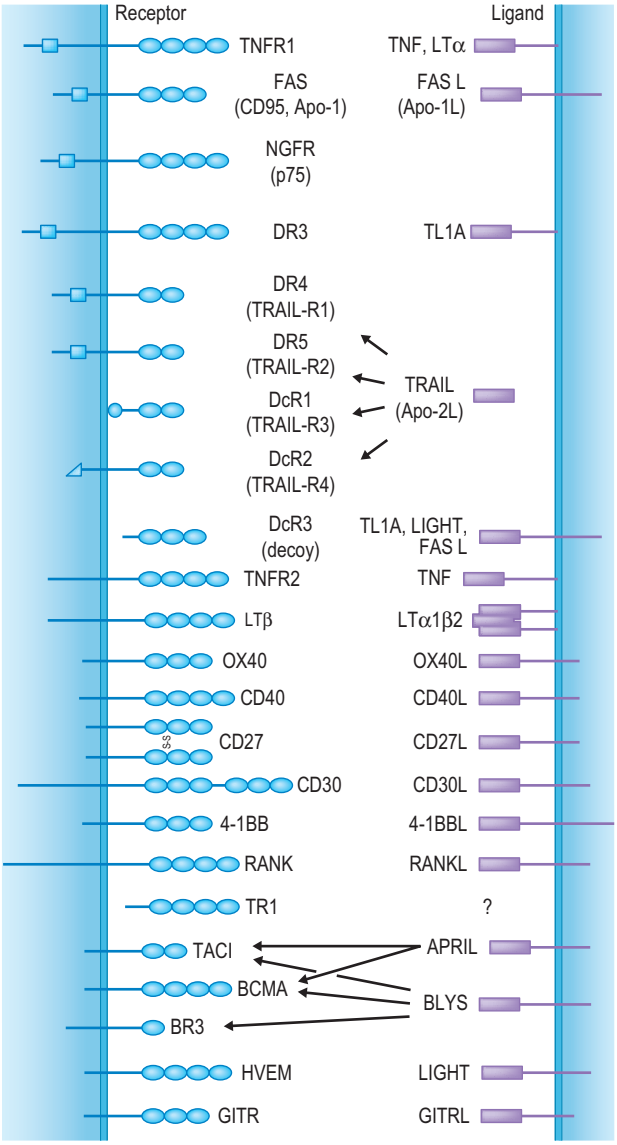

FIG 9.4 Schematic representation of members of the tumor necrosis factor (TNF) ligand and receptor superfamily.

the enzymatic cleavage of membrane-bound TNF by a metalloproteinase termed TNF-α–converting enzyme (TACE). Both soluble and membrane forms of TNF are thought to be homotrimers held together by noncovalent interactions through a trimerization domain. Both membrane-bound and soluble forms of TNF are biologically active. They have different affinities for the two TNF receptors and thus can exhibit different biological properties (see below).

LTα differs from TNF in that it is synthesized as a secreted glycoprotein. Human LTα is synthesized as a 205-amino acid glycoprotein that in native form exists as a 25-kDa homotrimer. It can bind both TNF receptors with affinities comparable to those of TNF and has similar biological effects. A membrane-bound form of LT has been identified that consists of a heterotrimeric complex containing one LTα subunit noncovalently linked to two molecules of an LTα-related type II membrane protein termed LTβ. The $LT\alpha_1\beta_2$ heterotrimer, also known as *mLT,* is not cleaved by TACE and is thought to exist exclusively as a membrane-bound complex. mLT does not bind either of the two TNF receptors, but rather exerts its effects on another member of the TNF receptor superfamily, the lymphotoxin β receptor (LTβR). TNF and the two LT subunits are encoded by closely linked single-copy genes situated in the MHC class III locus, at chromosome 6p21.3 in humans (Chapter 5).

The two receptors for TNF (and LTα) are type-I transmembrane glycoproteins. They are designated TNFR1 (TNFRSF1A) and TNFR2 (TNFRSF1B). (TNFR1 is also known as p60 in humans and p55 in mice, and TNFR2 is known as p80 in humans and p75 in mice.) These receptors are characterized by cysteine-rich repeats of about 40 amino acids in their aminoterminal extracellular domains. Each extracellular domain consists of three or four cysteine-rich regions containing 4–6 cysteines involved in intrachain disulfide bonds. The cytoplasmic domains of these receptors have no obvious similarity to any known kinase and are thought to lack intrinsic enzymatic activity. Signal transduction is, therefore, achieved by the recruitment and activation of adaptor proteins that recognize specific sequences in the cytoplasmic domains of these receptors. Recruitment of adaptor molecules activates a number of characteristic signaling pathways that can lead to a remarkably diverse set of cellular responses. These include differentiation, activation, release of inflammatory mediators, and apoptosis.

Family Members and Their Actions

Tumor Necrosis Factor, Lymphotoxin-α, and Receptors

TNF is a major physiological mediator of inflammation. It is one of the first cytokines made in response to TLR4 stimulation by bacterial (LPS) and other TLR ligands.[48] IFN-γ also induces TNF and augments its effects. TNF has been shown to induce fever, activate the coagulation system, induce hypoglycemia, depress cardiac contractility, reduce vascular resistance, induce cachexia, and activate the acute-phase response in the liver. Thus TNF is the major mediator of septic shock. TNF also upregulates MHC class I and class II expression, activates phagocytes, and induces mononuclear phagocytes to produce cytokines, such as IL-1, IL-6, chemokines, and TNF itself. Activation by TNF causes increased adhesion of cells to the endothelium and can be cytotoxic, particularly to tumor cells. TNF-deficient mice are resistant to septic shock induced by high doses of LPS but have increased susceptibility to bacterial infection. The dual role of TNF in controlling bacterial replication and in septic shock emphasizes the point that although the goal of an immune response is to eliminate invading microorganisms, the response itself can be injurious to normal host tissues. Septic shock is an extreme example of this. Although the primary source of TNF is the mononuclear phagocyte, it is also produced by T cells, NK cells, and mast cells. LTα shares many of the same biological effects as TNF, mainly because of its ability to bind the same receptors. However, LTβR plays a unique role in the development of secondary lymph nodes.

Fas Ligand and Its Receptor Fas/APO-1/CD95

Fas (Apo-1/CD95/TNFRSF6) is a type I integral membrane protein structurally related to TNFR1. Fas can trimerize and transduce proapoptotic signals upon binding of its ligand, FasL. Similar to TNF, the physiological ligand for Fas (CD95L or FasL)

Text continued on p. 143

TABLE 9.2 TNF Superfamily Cytokines

Symbol	Common Name	Aliases	Binds to Receptor(s)	OMIM ID	Key Functions	Phenotype Associated With Over Expression	Phenotype Associated With Deficiency	Human Genetic Disease Associations
TNFSF1	Lymphotoxin alpha (Ltα)	LT, TNFB, TNFSF1	TNFR2 (1B), TNFR1 (1A), HVEM (14)	153440	Lymphoid organ formation		Absence of LN and PP, defective GC formation	
TNFSF2	Tumor necrosis factor (TNF)	TNFα, TNFSF2, CACHECTIN	TNFR2 (1B), TNFR1 (1A)	191160	Inflammation	Wasting syndrome, arthritis	Defective GC formation, resistance to endotoxic shock and experimental arthritis	TNF2 (G-308A) promotor polymorphism associated with increased susceptibility to septic shock. Asthma and RA severity
TNFSF3	Lymphotoxin beta (LTβ)	p33, TNFC, TNFSF3	As a $\beta_2\alpha_1$ heterotrimer with LTα binds to LTβ receptor (3)	600978	Lymphoid organ formation	Ectopic lymphoid organ formation		
TNFSF4	OX40 Ligand	GP34, OX4OL, TXGP1, CD134L, OX-40 L	OX40 (4)	603594	CD4 T-cell expansion, survival, and Th2 development	Increased Th2 responses	Th2 deficiency, blockade improves EAE	Associated with SLE in GWAS
TNFSF5	CD40 Ligand	IGM, IMD3, TRAP, gp39, CD154, CD40L, HIGM1, T-BAM,	CD40 (5)	300386	Costimulation and differentiation of B cells and APC	Constitutive expression in B cells or keratinocytes leads to SLE-like syndrome	Immunodeficiency due to defective Ig class switching and germinal center formation	X-linked hyper-IGM syndrome associated with CD40L loss of function mutations
TNFSF6	Fas Ligand	FASL, CD178, CD95L, APT1LG1	Fas (6), DcR3 (6B)	134638	Mediator of CD4(+) T-cell apoptosis as a result of restimulation and apoptosis in other cell types		Lymphadenopathy and systemic autoimmunity	Autoimmune lymphoproliferative syndrome (ALPS) type Ib
TNFSF7	CD27 Ligand	CD70, CD27L, CD27LG	CD27 (7)	602840	T-cell costimulation	T-cell hyperactivation eventually leading to immunodeficiency (HIV-like)		
TNFSF8	CD30 Ligand	CD153, CD30L, CD30LG	CD30 (8)	603875				

Continued

TABLE 9.2 **TNF Superfamily Cytokines—cont'd**

Symbol	Common Name	Aliases	Binds to Receptor(s)	OMIM ID	Key Functions	Phenotype Associated With Over Expression	Phenotype Associated With Deficiency	Human Genetic Disease Associations
TNFSF9	4-1-BB Ligand	4-1BB-L	4-1BB (9)	606182	T-cell costimulation			
TNFSF10	TRAIL (TNF-like apoptosis inducing ligand)	TL2, APO2L, TRAIL, Apo-2 L	DR4 (10A), DR5 (10B), DcR1 (10 C), DcR2 (10D)	603598	Dendritic cell apoptosis, NK-cell mediated tumor cell killing		Defective NK-mediated tumor eradication	
TNFSF11	RANK-L	ODF, OPGL, sOdf, RANKL, TRANCE, hRANKL2	RANK (11A)	602642	Mediates osteoclast formation and bone remodeling. Stimulation of APC			
TNFSF12	TWEAK	APO3L	TWEAK-R (12A)	602695	Potential role in inflammation and lymphocyte function			
TNFSF13	APRIL	APRIL, TALL2, TWE-PRIL	TACI (13B), BCMA (17)	604472	Promotes T-independent type-2 responses through interactions with TACI	Overexpression in T cells produces prolonged T-cell survival and enhanced TI-2 responses		
TNFSF13B	BlyS, BAFF	BAFF, BLYS, TALL1, THANK, ZTNF4	TACI (3B), BAFF-R (13 C), BCMA (17)	603969	Promotes B-cell maturation, plasmablast survival	SLE-like systemic autoimmunity and arthritis		
TNFSF14	LIGHT	LTg, TR2, HVEML, LIGHT	HVEM (14), LT-βR (3), DcR3 (6B)	604520	CD8 T-cell and APC costimulation	inflammation, T-cell hyperactivation, Th1 bias	Defective CD8 T-cell costimulation	
TNFSF15	TL1A	TL1, VEGI	DR3 (25)	604052	Ligand for DR3 (TNFRSF25) on lymphocytes	T-cell activation, IL-13 dependent small intestinal hyperplasia and inflammation	Reduced immunopathology in T-cell-dependent autoimmune diseases	Common variant associated with inflammatory bowel disease through GWAS
TNFSF18	GITR Ligand	TL6, AITRL, GITRL, hGITRL	GITR (18)	603898	T-cell costimulation, $CD25^{+}$regulatory T cells			
ED1	Ectodermal dysplasia 1, anhidrotic (EDA1)	EDA, HED, EDA1, XHED, XLHED	EDAR	305100	Tooth, hair, and sweat gland formation			X-linked ectodermal dysplasia

TABLE 9.3 TNF Superfamily Receptors (Receptors in Italics Have a C-Terminal Death Domain)

Symbol	Common Name(s)	Aliases	Binds to Ligand(s)	OMIM ID	Key Functions	Phenotype Associated With Deficiency	Human Genetic Diseases
TNFRSF1A	Tumor necrosis factor receptor 1 (TNF-R1)	FPF, p55, p60, TBP1, TNF-R, TNFAR, TNFR1, p55-R, CD120a, TNFR55, TNFR60, TNF-R-I, TNF-R55, MGC19588	TNF-α (2), Lt α (1)	191190	Mediates TNF-induced inflammation (and apoptosis in some cells)	Resistance to TNF-induced arthritis models, resistant to endotoxic shock, increased sensitivity to bacterial pathogens	Periodic fever syndrome (TRAPS) associated with heterozygous extracellular mutations.
TNFRSF1B	Tumor necrosis factor receptor 2 (TNF-R2)	p75, TBPII, TNFBR, TNFR2, CD120b, TNFR80, TNF-R75, p75TNFR, TNF-R-II	TNF-α (2), Lt α (1)	191191	May enhance proapoptotic effect of TNFR1	Still susceptible to TNF-induced arthritis models, defective CD8T-cell apoptosis after restimulation, increased sensitivity to bacterial pathogens	
TNFRSF3	Lymphotoxin β receptor	LTBR, CD18, TNFCR, TNFR-RP, TNFRSF3, TNFR2-RP, LT-BETA-R, TNF-R-III	LIGHT (14), LTβ (3)	600979	Lymphoid organ formation	No LN, PP, defective GC formation	
TNFRSF4	OX40	OX40, ACT35, CD134, TXGP1L	OX40L (4)	600315	T-cell costimulation	Defective CD4 T-cell responses	
TNFRSF5	CD40	p50, Bp50, CD40, CDW40, MGC9013	CD40L (5)	109535	Costimulation and differentiation of B cells and antigen-presenting cells (APCs)	Defective immunoglobulin (Ig) class switching and germinal center formation	Autosomal hyper-IgM syndrome associated with loss-of function mutations Locus associated with rheumatoid arthritis (RA) through GWAS
TNFRSF6	*Fas, CD95*	FAS, APT1, CD95, APO-1	FasL (6)	134637	Apoptosis of restimulated CD4 T cells, B cells, ?others	Defective apoptosis of restimulated CD4 T cells	Autoimmune lymphoproliferative syndrome (ALPS) associated with heterozygous dominant-interfering mutations
TNFRSF6B	Decoy receptor 3	M68, TR6, DCR3, DJ583P15.1.1	FasL (6), TL1A (15), LIGHT (14)	603361	Soluble decoy receptor for FasL, LIGHT, and TL1A May have a role in tumor immune evasion		Associated with inflammatory bowel disease (IBD) in GWAS
TNFRSF7	CD27	T14, CD27, S152, Tp55, MGC20393	CD27L (7)	186711	T-cell costimulation	Defective T-cell responses	
TNFRSF8	CD30	CD30, KI-1, D1S166E	CD30L (8)	153243	?Inhibition of CD8 T-cell effector function		
TNFRSF9	4-1BB, CD137	ILA, 4-1BB, CD137, CDw137, MGC2172	4-1BBL (9)	602250	T-cell costimulation	Defective CD8 T-cell responses	Locus associated with ulcerative colitis in GWAS
TNFRSF10A	*Death Receptor 4 (DR4)*	DR4, APO2, MGC9365, TRAILR1, TRAILR-1	TRAIL (10)	603611	Mediator of dendritic cell and tumor cell apoptosis		
TNFRFRSF10B	*Death Receptor 5 (DR5)*	DR5, KILLER, TRICK2, TRICKB, ZTNFR9, TRAILR2, TRICK2A, TRICK2B, TRAIL-R2, KILLER/DR5	TRAIL (10)	603612	Mediator of dendritic cell (DC) and tumor cell apoptosis		
TNFRSF10C	Decoy receptor 1	LIT, DCR1, TRID, TRAILR3	TRAIL (10)	603613	GPI-linked decoy receptor, interferes with TRAIL function		

Continued

TABLE 9.3 TNF Superfamily Receptors (Receptors in Italics Have a C-Terminal Death Domain—cont'd

Symbol	Common Name(s)	Aliases	Binds to Ligand(s)	OMIM ID	Key Functions	Phenotype Associated With Deficiency	Human Genetic Diseases
TNFRSF10D	Decoy receptor 2	DCR2, TRUNDD, TRAILR4	TRAIL (10)	603614	Transmembrane decoy receptor, interferes with TRAIL function		
TNFRSF11A	(Receptor activator of NF-κ B) RANK	OFE, ODFR, PDB2, RANK, TRANCER	RANKL (11)	603499	Mediates DC costimulation and osteoclast maturation and activation	Osteopetrosis caused by osteoclast deficiency, no lymph nodes, impaired B-cell development	
TNFRSF11B	Osteoprotegerin (OPG)	OPG, TR1, OCIF, MGC29565	TRAIL (10), RANKL (11)	602643	Soluble decoy receptor for RANK	Osteoporosis, arterial calcification	
TNFRSF12A	TWEAK-receptor	FN14, TWEAKR	TWEAK (12)	605914			
TNFRSF13B	TACI	TACI	APRIL (13), BAFF (13B)	604907	May inhibit some of the pro-survival effects of BAFF-R	Decreased TI-2 B-cell responses, but B-cell hyperplasia and autoimmunity	Loss-of-function mutations associated with familial common variable immune deficiency (CVID)
TNFRSF13C	BAFF receptor (BAFF-R)	BAFF/BLyS receptor 3	BAFF (13B)	606269		Impaired survival of immature transitional B cells	
TNFRSF14	Herpes virus entry mediator (HVEM)	TR2, ATAR, HVEA, HVEM, LIGHTR	LIGHT (14), herpes viruses	602746			Locus associated with RA and ulcerative colitis in GWAS
TNFRSF16	NGF-R	TNFRSF16, p75(NTR)	NGF (not a TNF family member)	162010	Nerve growth factor (NGF) receptor - evolutionary outlier as NGF not classic TNF family molecule	Defective sensory neuron innervation; impaired heat sensitivity	
TNFRSF17	B-cell maturation antigen (BCMA)	BCM	APRIL (13), BAFF (13B)	109545		Apparently no B-cell phenotype	
TNFRSF18	Glucocorticoid-induced TNF receptor (GITR)	AITR, GITR, GITR-D	GITRL (18)	603905	T-cell costimulation, marker for $CD4^+CD25^+$ regulatory T cells (Tregs), modulates Treg function	T-cell hyperactivation	
TNFRSF19	Toxicity and JNK inducer (TAJ)	TROY, TRADE, TAJ-alpha		606122	Similar to ectodysplasin A receptor (EDAR), expressed in skin and brain		
TNFRSF19L	RELT	FLJ14993			Possible T-cell costimulator		
TNFRSF21	*Death Receptor 6 (DR6)*	BM-018		605732	Negative regulator B- and T-cell responses	Enhanced T- and B-cell activation	
TNFRSF25	*Death Receptor 3 (DR3)*	*DR3, TR3, DDR3, LARD, APO-3, TRAMP, WSL-1, WSL-LR*	*TL1A (15)*	*603366*		Impaired thymic negative selection. Reduced immunopathology and T-cell accumulation at site of autoimmune disease	
EDAR	*Ectodysplasin 1, anhidrotic receptor*	DL, ED3, ED5, ED1R, EDA3, EDA-A1R	E1	604095	Tooth, hair, sweat gland formation	Abnormal tooth, hair, and sweat gland formation	Ectodermal dysplasia
XEDAR	XEDAR: ectodysplasin A2 isoform receptor	EDAA2R, EDA-A2R	EDA-A2	300276			

LN, lymph node; PP, Peyer patch; GC, germinal center.
Locuslink ID: Gene "homepage" curated by NCBI. Go To and type the locuslink ID in the search window.OMIM: ID in the Online Mendelian Inheritance in Man Database. Go to and type in the OMIM ID in the search window.

is synthesized as a type II membrane protein and is expressed on activated B cells, T cells, and NK cells. Fas-induced apoptosis can play an essential role in the termination of T-cell responses, particularly in the peripheral immune system. Fas can also play a key role in the induction of cell death by cytotoxic T cells (CTLs) and NK cells (Chapter 17), where it functions in conjunction with perforin. Nonapoptotic functions of FasL include lymphocyte costimulation and T-cell differentiation into short-lived effector memory cells.[49,50]

CD40 Ligand and CD40

CD40 is expressed by a variety of cell types, including B cells, DCs, monocytes, macrophages, and endothelial cells. It plays a major costimulatory role in B-cell differentiation and recombination and promotes survival through the induction of BCL-2 family members. Studies of both CD40-deficient mice and patients with hyper-IgM syndrome (Chapter 34) reveal that its function extends beyond the humoral immune response, with CD40 signaling also playing a role in cell-mediated immunity. CD40 ligand (CD154) is a 39-kDa protein expressed by activated CD4 T cells that can bind to and activate CD40 by cell–cell contact.

CD40L on T cells triggers antigen-presenting cell (APC) activation, including upregulation of the CD28 ligands B7-1 and B7-2. This indirectly boosts costimulation of the T-cell response. Because of its critical role in mediating T-cell help for B-cell class switching and autoantibody formation, blocking CD40L/CD40 interactions has been a therapeutic goal in autoimmune diseases. Clinical trials of a blocking anti-CD40L antibody in SLE showed promising results but were halted because of thrombotic events, likely resulting from the off-target effects of these antibodies on CD40L expressed on platelets.[51] More recently, antagonistic antibodies against CD40 with possible applications to treat transplantation and autoimmune diseases have been developed.[52]

Other TNF-Family Cytokines

Other members of the TNFR family play various roles in the development and function of the immune system. OX-40, CD27, CD30, and 4-1BB can mediate costimulation of T-cell activation. The TNF family ligand BAFF (BlyS/TALL1/TNFSF13B) promotes B-cell maturation and antibody secretion and can bind three distinct receptors, TACI (TNFRSF13B), BADD-R (TNFRSF13C), and BCMA (TNFRSF17).

Signaling

The TNF receptor superfamily can be divided into three subfamilies on the basis of the types of intracellular signaling molecules recruited (*e.g.,* FAS-associated death domain [FADD], TNF receptor-associated death domain [TRADD], or TNF receptor–associated factor [TRAF]) (Fig. 9.5).[53] The cytoplasmic domains of several receptors, including death receptor 3 (DR3), DR4, DR5, TNFR1, and FAS contain a conserved ≈80-amino acid motif termed the death domain (DD). This element is required for recruitment of DD-containing adaptor molecules that are involved in the initiation of apoptotic cell death (Chapter 13). For this reason, these receptors have been termed "death receptors." The function of a number of death receptors can be regulated by decoy receptors. These are cell surface molecules that bind ligand but lack functional intracellular domains. Other TNF receptor superfamily receptors that lack death domains (*e.g.,* CD27, CD30, CD40, HVEM, TNFR2, LT-βR, OX-40, and 4-1BB) associate with different types of adapter molecules, most notably members of the TRAF family.

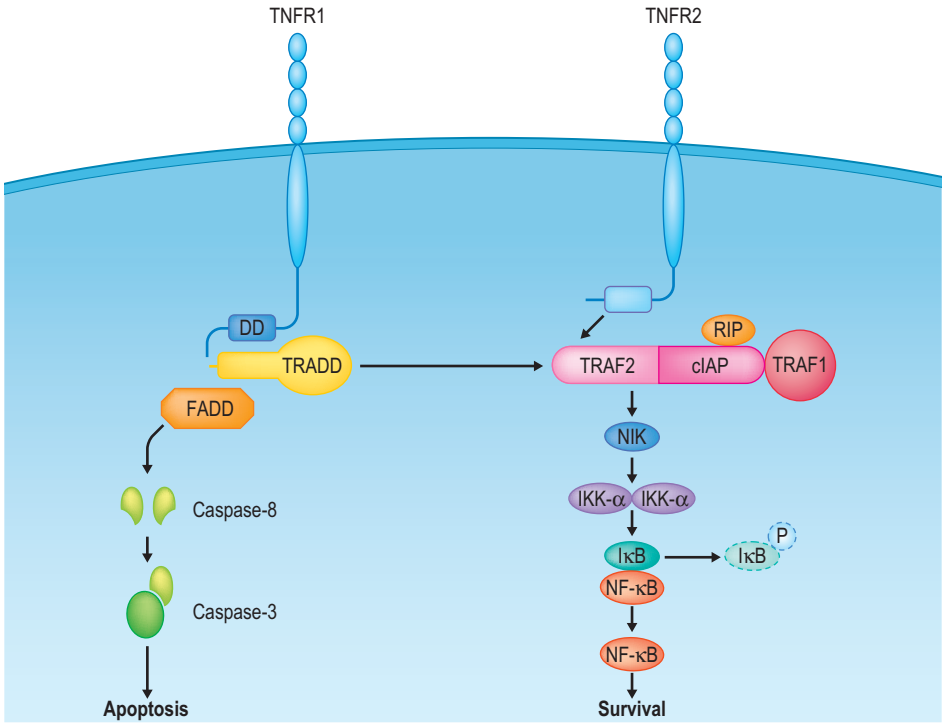

FIG 9.5 The role of the death domain (DD)– and death effector domain (DED)–containing molecules (e.g., Caspase-8) in signaling by tumor necrosis factor receptor 1 (TNFR1) and TNFR2.

Death Domains: TNF Receptor-Associated Death Domain and FAS-Associated Death Domain

The primary molecule transducing signals for TNFR1 is TRADD, which is directly recruited to TNFR1 after activation by TNF. This DD motif is found in both adaptor molecules, such as TRADD, and the cytoplasmic domains of the receptor itself (Fig. 9.6).

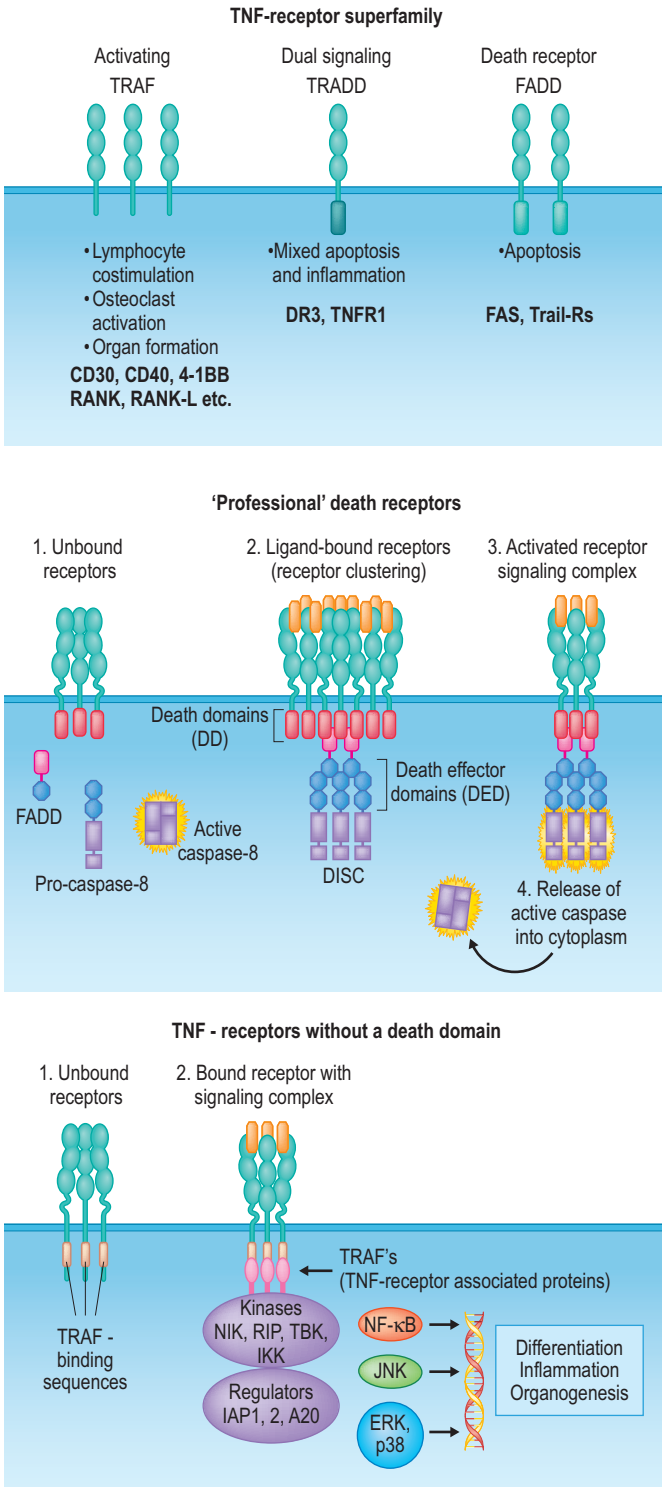

FIG 9.6 Signaling by tumor necrosis factor (TNF) family cytokines and their receptors.

The binding of TRADD to TNFR1 leads to the recruitment and activation of numerous associated signaling molecules. TNF-induced apoptosis is generally thought to be achieved by the interaction of TRADD with FADD (also known as MORT1), a ≈27-kDa protein that oligomerizes with TRADD through the DDs contained in both molecules. In turn, recruitment of FADD coordinately activates several members of the caspase family.[54]

Caspase-8, which is generally considered to be the apical caspase in the TNF and FAS pathways, is recruited to FADD in the activated complex and activated through increased local concentration. Cleaved caspase-8 can subsequently activate downstream caspases, notably caspase-3, which play a more proximal role in apoptosis. TRADD also has a TRAF-binding motif that leads to the recruitment of TRAF1 and -2 and the subsequent TRAF-dependent activation of proinflammatory signaling mediated by activation of NF-κB and mitogen-activated protein kinase (MAPK) pathways.

Although cell death in tumor cells can be induced by TNF, the most common result of TNFR1 ligation in primary immune cells is inflammation and sometimes protection from TNF-induced apoptosis. Recent evidence suggests that activation of proapoptotic and proinflammatory signaling by TNFR1 is not simultaneous but proceeds by sequential steps.

Unlike TNFR1, FAS can directly recruit FADD to its cytoplasmic DD, leading to the rapid formation of a death-inducing signaling complex (DISC), which contains FADD/MORT1 and caspase-8, thereby permitting activation of downstream caspases. FADD is recruited through interactions between charged residues in the DDs of FAS and FADD. Caspase-8 recruitment is accomplished through a structurally related domain termed the death-effector domain (DED). FADD DED contains two hydrophobic patches not present in the DD, which are vital for binding to the DEDs in the prodomain of caspase-8 and for apoptotic activity.[54]

Rather than DDs, the cytoplasmic domains of many receptors in the TNFR superfamily, including TNFR2, CD30, and CD40, contain short peptide consensus sequences that enable recruitment of a different family of adaptors, the TRAF proteins. A separate consensus sequence has been identified for TRAF6 versus other TRAF proteins, and other mechanisms probably operate to maintain the specificity of TRAF recruitment. Structural studies have revealed a mushroom-like structure for the TRAF proteins, with a trimer of the three TRAF subunits stabilized by a stalk-like coiled-coil domain.

TRAF proteins activate NF-κB and MAPK pathways through recruitment and activation of protein complexes that stimulate these signaling cascades. The exact mechanisms by which this occurs are not yet clear, but recent studies have called attention to the ability of TRAF proteins to catalyze ubiquitination of target signaling complexes, which can function as an activating step. TRAF6, which mediates NF-κB activation by a number of TNF-family receptors, associates with a protein complex that mediates K63-linked ubiquitination and activation of the inhibitor of κB kinase (IKK) complex, which consists of two catalytic subunits, IKKα and IKKβ, and a regulatory protein IKKγ or nuclear factor κB (NF-κB) essential modulator (NEMO).[55] Rather than causing degradation of IKK, K63-linked ubiquitination activates the kinase, leading to phosphorylation and degradation of IκB (inhibitor of NF-κB) and the release of active NF-κB subunits. Active NF-κB subunits translocate to the nucleus, where they regulate the expression of a wide variety of genes involved in the inflammatory response.

Some TNF-family receptors use other mechanisms to activate NF-κB. LTβ receptor activates the IKK complex via the serine–threonine kinase NIK, which was initially identified through its ability to associate with TRAF2. A naturally occurring mouse mutation termed *alymphoplasia* (*aly*) is the result of a point mutation of NIK. *Aly/aly* mice lack lymph nodes and Peyer patches and also exhibit disorganized splenic and thymic structures. This mutation, and the phenotype of LTβR knock-out mice, revealed the critical role of this receptor in normal lymph node development and the formation of "tertiary" lymphoid tissue in inflammation.

When a single TNF-family ligand, such as TNF, binds both a death receptor (TNFR1) and a non–death receptor (TNFR2), a number of mechanisms regulate receptor signaling and the cellular outcome. Rather than functioning in cell death, the physiological function of TNFR2 may be as a costimulator of lymphocyte proliferation.[56]

CLINICAL RELEVANCE

Tumor Necrosis Factor Receptor (TNFR) Superfamily Cytokines and Receptors and Disease

- Dominant mutations of in the gene encoding TNFR1 are associated with autosomal dominant periodic fever syndromes, known as TNFR1-associated periodic syndromes (TRAPS).
- Loss-of-function mutations in the gene encoding CD40L are associated with X-linked hyper-IgM syndrome (X-HIM).
- Dominant interfering mutations in *TNFRSF6,* encoding the Fas receptor are associated with autoimmune lymphoproliferative syndrome (ALPS).
- Rheumatoid arthritis (RA) often responds to therapeutic use of TNF antagonists.

Clinical Relevance

Mutations affecting the TNFR1 protein are associated with periodic fever syndromes (Chapter 60). Patients with the TNFR1-associated periodic syndrome (TRAPS) have missense mutations in exons encoding the extracellular regions of TNFR1 that affect normal TNFR1 function, prompting the designation. The mutated TNFR1 in TRAPS accumulates intracellularly and signals in a TNF-independent fashion to amplify inflammatory responses through the wild-type TNFR1.[57] Both TNF blockade with etanercept and IL-1 blockade have efficacy in reducing symptoms in TRAPS.[58]

The *in vivo* role of Fas signaling in the regulation of the immune system was confirmed when the naturally arising lpr and gld mouse strains were found to harbor homozygous mutations of Fas and Fas ligand, respectively. Both these mouse strains are characterized by lymphadenopathy and splenomegaly resulting from the accumulation of unusual $CD4^-CD8^-$ T cells, as well as the production of autoantibodies. Heterozygous dominant negative mutations in the gene encoding Fas cause the autoimmune lymphoproliferative syndrome (ALPS) (Chapter 35).

The gene encoding CD40 ligand is defective in X-linked hyper-IgM syndrome (X-HIM), a rare inherited disorder in which affected male children generate only IgM antibodies, many of which are autoantibodies (Chapter 34). Patients with X-HIM frequently suffer opportunistic infections, usually bacterial, and have an increased susceptibility to cancer. The physiological role of the B cell–activating factor (BAFF) receptor in mouse B-cell development is illustrated by BAFF-R mutations in the A/WySnJ mouse, which lacks peripheral B cells. TACI knock-out mice have hyperactive B cells, but in humans, dominant negative TACI mutations have been found in patients with common variable immunodeficiency affecting B-cell numbers and function (Chapter 34), which argues that in humans TACI serves as a positive modulator of B cells.

KEY CONCEPTS

Properties of the Interleukin-1 Receptor/Toll-Like Receptor (IL-1R/TLR) Family

- IL-1 plays a key role in fever and acute-phase responses.
- IL-18 augments T-helper 1 (Th1) cell differentiation.
- TLRs modulate proinflammatory signals in response to bacterial proteins.

INTERLEUKIN-1/TOLL-LIKE RECEPTOR FAMILY

Ligand and Receptor Structure

The IL-1/TLR family of receptors comprises at least 11 members, including the IL-1RI, IL-1RII, IL-1R-associated protein (IL-1RAcP), IL-18R, IL-18RAcP, IL-1Rrp2, IL-1RAPL, IL-33R(T1/ST2), TIGGIR, SIGGIR, and the mammalian TLRs.[59] The ligands for these receptors include IL-1, IL-18, IL-33, and IL-1 F5–IL-36 α, β, and γ; IL-36RA; IL-33 and IL-37; and IL-38.[60]

Family Members and Their Actions

Interleukin-1

There are two cell surface receptors for IL-1, type I (IL-1R1) and type II (IL-1R2). Both these bind ligand (see Fig. 9.4), but only IL-1R1 transduces signals. The extracellular domain of IL-1R1 has three Ig-like domains and a 200-amino acid cytoplasmic domain. Upon ligand binding, IL-1R1 associates with IL-1R accessory protein (IL-1RAcP), which is critical for the initiation of signaling. The IL-1R2 cytoplasmic domain is extremely short and has been suggested to be a "decoy" receptor, competing with IL-1RI for ligand binding and attenuating signaling. Both IL-1Rs are susceptible to proteolytic cleavage near the membrane surface. Thus they can be found as soluble proteins that can "buffer" IL-1 signaling. These soluble receptors are readily detectable in the circulation.

There are three members of the IL-1 gene family: two agonists, IL-1α and IL-1β, and one antagonist, IL-1 receptor antagonist (IL-1Ra). Both IL-1α and IL-1β are synthesized as precursor proteins. IL-1α and IL-1β are structurally similar and have similar actions, but they are regulated differently. IL-1α is processed by a calpain-like converting enzyme, but granzyme B and neutrophils and mast cell proteases can also cleave the precursor. The proform of IL-1α has biological activity, but cleavage results in increased biological activity. IL-1β is regulated at the levels of mRNA stabilization and translation, and it requires proteolytic activation. Pro–IL-1β remains in the cytoplasm until it is cleaved by proteases, such as caspase-1. It is then transported out of the cell.

The cleavage of IL-1β occurs in a multiprotein complex called the *inflammasome.* The key components of the inflammasome are caspase-1 and a recognition/assembly component nucleotide-binding oligomerization domain (NOD)–like receptor (NLR). Another protein called ASC (a simple adapter protein containing both pyrin and CARD domains) is required to facilitate assembly. NLR proteins are intracellular pattern-recognition receptors that contain three domains: *(i)* a segment with multiple leucine-rich repeats, whose

role is to recognize the trigger for activation (whether directly or indirectly remains unclear); *(ii)* a portion called a NACHT domain, which leads to adenosine triphosphate (ATP)–dependent dimerization of the NLR after trigger recognition; and *(iii)* a protein–protein interaction domain, most commonly either a pyrin or a CARD domain, which recruits caspase-1.

The NLRP3 inflammasome is the best studied. Recognition of the trigger by NLRP3 causes its dimerization, recruitment of ASC via interaction of the pyrin domains of NLRP3 and ASC, and subsequent recruitment of caspase-1 via the CARD domains present in both ASC and caspase-1. Dimerization of caspase-1 upon inflammasome assembly allows for autoactivation by cleavage of the proform to generate active enzyme. The NLRP3 inflammasome can be activated by ATP, components of gram-positive bacterial cell walls, intracytoplasmic DNA, molecules resulting from tissue damage, uric acid crystals, alum, silica, asbestos, and amyloid-β among others. Cigarette smoke and cholesterol crystals also activate caspase-1.[61]

Similar to IL-1α, IL-1β can be cleaved and activated by other proteases, including neutrophil elastase, cathepsin, and proteinase-3 (PR-3). Mast cell proteases, as well as caspase-8, have also been shown to cleave IL-1β precursor. The mechanism of release of IL-1 and related family members from cells is somewhat mysterious because they lack a classic signal peptide and do not enter the secretory pathway. Although there is some evidence that IL-1β can be cleaved and released from cells without cell death, a large body of evidence suggests that IL-1 family proteins are released from cells upon lysis. Because of this, and the large numbers of cellular insults that result in release of IL-1 and related proteins and trigger inflammation, it has been proposed that they function as "alarmins" and act as sentinels of cellular damage.

The principal functions of IL-1 include the induction of acute-phase protein synthesis, cachexia, and fever. In fact, it was the first endogenous pyrogen to be identified. It induces the production of IL-6 and chemokines, promotes hematopoiesis, stimulates adhesion of vascular leukocytes to the endothelium, and has procoagulant effects. Importantly, IL-1 is a critical differentiation factor for Th17 cells, which underscores the role of this cytokine in inflammation and inflammatory diseases. Interestingly, it has recently been shown to activate ILC2, inducing proliferation and cytokine expression.[62] Unlike Fas and some of the other TNF-family cytokines, IL-1 does not directly induce cell death. Mononuclear phagocytes are the main, but not exclusive, source of IL-1. IL-1RI$^{-/-}$ and IL-1β$^{-/-}$ mice have blunted fever responses to some (but not all) stimuli. This indicates that despite the impressive actions of IL-1, it is evidently redundant to some extent in febrile responses.

Interleukin-18

A major action of IL-18, which is constitutively expressed by most cell types, is the induction of IFN-γ, and NK cells activation, a function it typically performs synergistically with IL-12. These functions are important for its antitumor activity. It has also been shown to promote angiogenesis and tumor progression.[63] IL-18 can induce IL-4 and IL-13 production, indicating a somewhat broader range of action. IL-18 precursor can be cleaved by the NRLP3 inflammasome as well as the NRLC4. IL-18–binding protein interacts with IL-18 and prevents association with IL-18R. IL-18R was first designated IL-1Rrp (IL-1R–related protein) before being recognized as the receptor for IL-18. The receptor is expressed predominantly on T cells, B cells, and NK cells. It associates with an accessory protein, IL-18RAcP.

Interleukin-33

IL-33 (previously known as IL-1 F11) appears to be a cytokine that acts by binding to a specific extracellular receptor, namely, the IL-1R –related protein ST2, also known as IL-33R. It also acts as a transcriptional repressor by associating with chromatin. Because of this dual effect and because of the expression of ST2 on different cell types, IL-33 acts on both immune and nonimmune cells. It acts on T and B cells, promoting Th2-associated cytokines, including IL-4, IL-5, and IL-13.[64] IL-33 acts on mast cells, promoting degranulation, an effect also shown on basophils and granulocytes in general, but also enhancing cell survival. Upon cleavage by mast cell proteases, IL-33 can also activate ILC2, inducing cytokines production and eosinophils recruitment.[65,66] Interestingly, IL-33–treated basophils have been shown to suppress arthritic inflammation. IL-33 can also act on endothelial and epithelial cells to induce angiogenesis and production of other cytokines and chemokines.

Interleukin-36

The three members of the IL-36 subfamily, IL-36α, β, and γ, are encoded by separate genes. They bind to a receptor composed of IL-36R and IL-1RacP. These cytokines are mostly expressed in skin. IL-36α transgenic mice exhibit skin inflammation, and these IL-36 cytokines can play a role in psoriasis.[67] IL-36 receptor antagonist (IL-36Rα, also known as IL-1 F5) acts as an antagonist for the three IL-36 family cytokines. *IL36RA* mutations are associated with generalized pustular psoriasis. Keratinocytes from patients with deficiency of IL-36 receptor antagonist (DITRA) have elevated levels of multiple inflammatory cytokines in lesional skin. They are highly expressed in skin and airway and may be involved in skin diseases, such as psoriasis (Chapter 64).

Interleukin-37

IL-37 (also known as IL-1 F7) exists in several splice variants of which IL-1F 7b has been the most studied. IL-37 binds to IL-18Rα chain, although with a lower affinity than IL-18. It uses TIR8 (also known as SIGIRR) as second chain of the receptor. Despite binding to the same receptor and its capacity to complex with IL-18Acp, IL-37 does not seem to act as a receptor antagonist for IL-18. IL-37 translocates to the nucleus and binds Smad3, enabling regulation of gene transcription. Cleavage of IL-37 appears to be dependent on caspase-1 and -4. Its antiinflammatory activity is dependent on ASC or NLRP3. IL-37 negatively regulates excessive inflammatory responses. Macrophages expressing IL-37 no longer secrete proinflammatory cytokines, and IL-37 transgenic mice are resistant to LPS-induced shock.[68]

Interleukin-38

IL-38 (IL-1 F10) has a 43% homology with IL-36Rα and, similarly, has an antiinflammatory activity. It is released by apoptotic cells to limit macrophage activation. Polymorphic IL-38 genes have been associated with increased susceptibility for autoimmune and autoinflammatory diseases (*e.g.,* RA, spondyloarthritis, and psoriatic arthritis).

Other Members of the Interleukin-1 Family

The remaining members of the IL-1 and IL-1R families are the receptor homologues APL and TIGIRR. These receptors have limited tissue distribution, with TIGIRR found almost exclusively in the brain and APL in the brain and a small number of other tissues.[69] Little is known of about the function of TIGIRR or

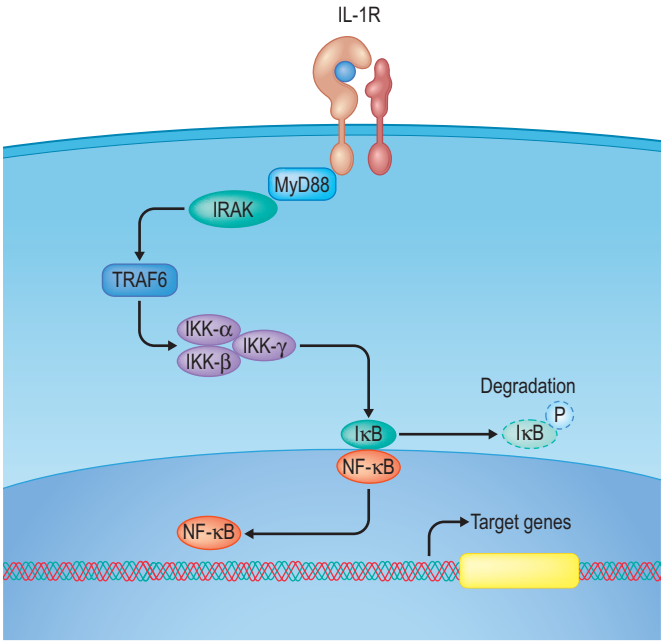

FIG 9.7 Mechanism of signal transduction by interleukin-1 receptor (IL-1R) and related receptors.

about APL in any organ other than the brain. Most insight into APL has come from the finding that deletions or mutations of this gene cause mental retardation.

Signaling

Ligand binding to IL-1R, IL-18R, and TLRs results in NF-κB activation (Fig. 9.7). These receptors all associate with the adapter protein MyD88 (Chapter 3). MyD88 has a C-terminal TIR domain and an N-terminal DD. MyD88 allows the recruitment of IL-1 receptor-associated kinase (IRAK), which also has an N-terminal DD. IRAK, in turn, permits the recruitment and activation of a member of the TRAF family, TRAF6. This leads to the activation of the serine kinases TAB2 and TAK1 (TGF-β–associated kinase-1), as well as that of the inhibitor of the κB kinases IKKα and IKKβ. With IKKγ or NEMO, these kinases phosphorylate IκB, which leads to its degradation within proteasomes, freeing bound NF-κB for nuclear translocation. Mice deficient in MyD88, IRAK, or TRAF6 have diminished responses to IL-1R/TLR family ligands. Other adapter molecules, including Mal and TRIF, are involved in TLR signaling.

CLINICAL RELEVANCE

Diseases Associated With the Interleukin-1 (IL-1) Family of Cytokines

- Mutations in genes involved in the formation of the inflammasome complexes result in increased secretion of IL-1 and other IL-1 family members.
- Mutations in the gene coding for IL-1 receptor antagonist cause a systemic autoinflammatory disease.

Clinical Relevance

The actions of IL-1 are tempered by the actions of a critical natural cytokine antagonist, IL-1Ra, which is encoded by the *IL1RN* gene. Mutations in *IL1RN* can cause a systemic autoinflammatory disease, which is denoted deficiency of IL-1Ra or DIRA.[70] Mutations in *NLRP3* contribute to several hereditary periodic fever syndromes (Chapter 60), including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID; in Europe called chronic infantile, neurological, cutaneous, and articular [CINCA] syndrome). NLRP3 is also called *cryopyrin;* thus these disorders have been collectively referred to as *cryopyrinopathies.*[71] Mutations in the alternative inflammasome component NRLC4 have also been showed to result in autoinflammation caused by excessive IL-18 production and, ultimately, macrophage activation syndrome.[72]

INTERLEUKIN-17 RECEPTORS

Although their precise functions are incompletely understood, IL-17 and related cytokines are major inducers of inflammation and serve to recruit inflammatory cells.

Ligand and Receptor Structure

The IL-17 receptor family is incompletely understood but comprises at least five receptors: IL-17AR and IL-17BR (IL-17RH1), IL-17RL (receptor like), IL-17RD, and IL-17RE, which are ubiquitously expressed.[73,74] These receptors have a single transmembrane domain and exceptionally large cytoplasmic tails. The ligands in the IL-17 family include IL-17A–F. The precise interactions between ligands and receptors have not been defined. A viral IL-17 homologue, designated HVS-13, is present in the *Herpesvirus saimiri* genome. Structurally, the IL-17 family contains cysteine knots. In this respect, these cytokines are related to other, better-known cytokines, such as nerve growth factor.

IL-17 (IL-17A) is located on human chromosome 6 (mouse chromosome 1) and is produced by activated CD4, γ/δ and CD8 T cells. Recent findings have suggested that CD4 T cells that preferentially produce IL-17 (Th17 cells) represent a distinct lineage of effector Th cells (Chapter 16). These cells can be differentiated via varied sets of stimuli that include IL-1β, IL-6, IL-21, and TGF-β. IL-23 appears to have a critical role in regulating the biological activity of these cells. IL-17F is located adjacent to IL-17. Although it seems to be regulated in a similar manner, it may be more widely expressed than IL-17. Less well studied are IL-17B, IL-17C, and IL-17D. All of these are thought to be expressed in a variety of nonhematopoietic tissues, although IL-17D is reported to be produced by CD4 T cells.

IL-17A and IL-17F evoke inflammation, largely by inducing the production of chemokines, G-CSF, and GM-CSF, and this leads to the subsequent recruitment of polymorphonuclear leukocytes. IL-17 also induces production of matrix metalloproteinase (MMP) by epithelial cells, which may be an important aspect of the proinflammatory effects. IL-17 family cytokines appear to be important in host defense against *Klebsiella pneumoniae* and *Mycobacterium tuberculosis.* Abundant data also point to the pathogenic roles of IL-17A in models of immune-mediated disease and in human autoimmune disorders. IL-17E, which is also known as IL-25, is produced by Th2 cells and mast cells. It evokes an inflammatory response characterized by overproduction of Th2 cytokines, mucus production, epithelial cell hyperplasia, and eosinophilia. This cytokine is essential for the elimination of helminthic parasites.[75]

Signaling

Engagement of the IL-17 receptor activates MAPKs, the PI3 kinase pathway and NF-κB. Signaling via IL-25 is reported to be dependent on the adapter molecule TRAF6. IL-17 acts

synergistically with TNF.[76] The IL-17R associates with an adapter molecule, called *Act,* through the SEFIR domains, which are part of both the receptor and the adaptor.

CLINICAL RELEVANCE

Therapeutic Application of Interleukin-17 (IL-17) Blockade

Monoclonal antibodies (mAbs) neutralizing IL-17 or antagonizing the IL-17 receptor are effective in treating psoriasis and psoriatic arthritis.

Clinical Relevance

Many human diseases and animal models of autoimmune disease have been associated with increased levels of IL-17. The inflammatory effects of IL-23 and IL-17 also appear to be associated with malignant transformation. Targeting IL-17 ligands and receptors could thus be a useful strategy. However, IL-17A and IL-17F are essential for mucocutaneous immunity against *Candida albicans,* and IL-17 deficiency results in chronic mucocutaneous candidiasis.[77]

CYTOKINES ACTIVATING RECEPTOR TYROSINE KINASES

Ligand and Receptor Structure

Many growth factors, such as insulin and epidermal growth factor, utilize receptor tyrosine kinases (RTKs). Some, but not all, of these factors can be classified as cytokines. These include CSF-1 (colony-stimulating factor 1 or M-CSF), stem cell factor (SCF, c-KIT ligand, or steel factor), platelet-derived growth factor (PDGF), and FMS-like tyrosine kinase 3 ligand (FLT3-L). All of these have important hematological effects and tend to be included in discussions of cytokines. The structure of SCF and CSF-1 is similar to that of the cytokines that bind type I receptors, as they too form four α-helical bundles, even though their receptors are entirely distinct. The similarities in their three-dimensional structures point to a common evolutionary ancestor. The receptors in this subfamily typically have five Ig-like loops in their ligand-binding extracellular domains. The cytoplasmic domain contains a tyrosine kinase catalytic domain interrupted by an "insert region" that does not share homology with other tyrosine kinases. This segment is used to recruit various signaling molecules.

Family Members and Their Actions

Stem Cell Factor

Bone marrow stromal cells can synthesize SCF (c-KIT ligand or Steel factor) as either a secreted or a transmembrane protein. SCF is required to make stem cells responsive to other CSFs. SCF is widely expressed during embryogenesis and is also detectable in blood circulation in normal adults. It has effects on germ cells, melanocytes, and hematopoietic precursors and has important effects on the differentiation of mast cells as well. Naturally occurring mouse mutations of SCF (Steel) or its receptor (W) have been recognized for many years. These mice have defects in hematopoiesis and fertility, lack mast cells, and have absent coat pigmentation.

Colony-Stimulating Factor 1

CSF-1, also known as monocyte–macrophage–CSF or macrophage-CSF (M-CSF), is a hematopoietic growth factor that supports the survival and differentiation of monocytic cells. It is produced by a wide variety of cells, including monocytes, smooth muscle cells, endothelial cells, and fibroblasts. M-CSF–deficient mice manifest monocytopenia and osteopetrosis. IL-34 is a new cytokine that binds to the CSF-1 receptor.

FMS-like tyrosine kinase 3 ligand (FLT3-L) synergizes with other cytokines, including SCF, in inducing proliferation of hematopoietic precursors. FLT3-L is an important regulator of DCs.

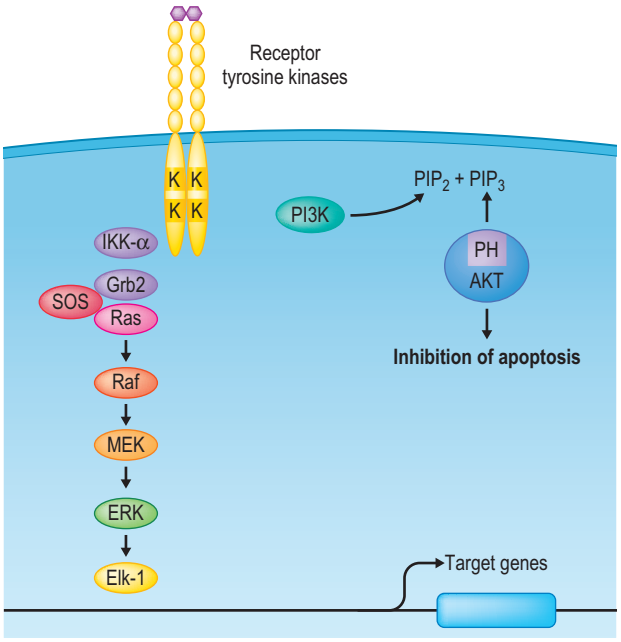

FIG 9.8 Mechanism of signal transduction by receptor tyrosine kinases.

Signaling

The first step in signaling by the RTKs is ligand-induced receptor dimerization (Fig. 9.8). Dimerization brings the two kinase domains into proximity and results in the activation of phosphotransferase activity. This leads to autophosphorylation of the receptor subunits on the tyrosine residues, which are then bound by a variety of signaling molecules, initiating signal transduction. During this important step, the signaling and adapter molecules recognize phosphotyrosine residues on the RTKs by virtue of either their SH2 domains or their PTB domains.

A major pathway activated by RTKs is the RAS/RAF/ERK pathway. RAS is a small G protein with intrinsic low guanosine diphosphate/guanosine triphosphate (GDP/GTP) exchange activity. In RTK signal transduction, two adapter proteins, GRB2 and SHC, have important functions in RAS activation. In some cases, GRB2 binds directly to phosphotyrosine residues on the cytoplasmic tail of the receptor via its SH2 domain. Alternatively, SHC can bind first and then recruit GRB2. In addition to an SH2 domain, GRB2 has two SH3 domains that bind proline-rich segments of the guanine nucleotide exchange factor son of sevenless (SOS) protein, recruiting it to the membrane and allowing it to activate RAS. Activated RAS binds and activates the serine/threonine kinase RAF, which, in turn, phosphorylates the dual-specificity kinase MEK. Activated MEK phosphorylates and activates ERK (extracellular signal–regulated kinase), which then translocates to the nucleus, where it phosphorylates and

modulates the activity of various transcription factors, including ELK-1. Accordingly, mutations of RAS that lead to the constitutive activation of the ERK pathway have been found in a wide variety of human cancers.

Another important pathway activated by RTKs is the phosphatidylinositol 3′-OH kinase (PI3-kinase) pathway.[78] PI3-kinase catalyzes the formation of phosphatidylinositol-3,4,5-trisphosphate (PtdIns[3,4,5]P3) and PtdIns(3,4)P2. These phospholipids are recognized by proteins with pleckstrin homology (PH) domains. One such protein is protein kinase B (PKB or AKT), which has been implicated in the regulation of apoptosis. The PI3-kinase pathway is inhibited by the lipid phosphatase PTEN, which dephosphorylates PI3-kinase–generated phosphatidylinositides. Deletion of PTEN has been found in numerous tumor types, demonstrating a role for this protein as a tumor suppressor.

GOF mutations of c-kit result in a disorder termed *systemic mastocytosis* (Chapter 23). Mutations resulting in a fusion between the *PDGFRA* and *FIP1L1* genes underlie hypereosinophilic syndrome.[79,80]

KEY CONCEPT

Properties of the Transforming Growth Factor-β (TGF-β) Receptor Family

- TGF-β receptors play a key role in lymphoid homeostasis, with pro- and antiinflammatory actions.
- TGF-β promotes the differentiation of regulatory T cells and T-helper 17 (Th17) cells.
- TGF-β receptors transduce signals through SMAD proteins.
- TGF-β receptor function is dysregulated in many forms of human cancer.

TRANSFORMING GROWTH FACTOR-β LIGAND AND RECEPTOR FAMILIES

TGF-βs are a family of over 40 cytokines that inhibit cellular proliferation and can induce apoptosis of a variety of cell types. TGF-βs are involved in a number of biological processes, including tissue remodeling, wound repair, development, and hematopoiesis. Mutations of the elements in this pathway also contribute to malignant transformation. The mammalian ligands that belong to this family include TGF-β_1, -β_2, and -β_3, bone morphogenic proteins (BMPs), activins, inhibins, and müllerian-inhibiting substance. Despite their name, TGF-βs inhibit the growth of many other cells and, in combination with other cytokines and growth factors, may induce growth instead. TGF-βs also induce collagen and fibronectin production by fibroblasts, which are thought to be responsible, at least in part, for diseases characterized by fibrosis (*e.g.,* systemic sclerosis and pulmonary fibrosis). Functionally, TGF-β inhibits many aspects of lymphocyte function, including T-cell proliferation and CTL maturation. Transgenic mouse studies have been performed by using dominant negative forms of the TGF-β receptor. These mice exhibit massive expansion of lymphoid organs and develop T-cell lymphoproliferative disorders.[46]

Ligand and Receptor Structure

TGF-βs are expressed as biologically inactive disulfide-linked dimers that are cleaved to form active dimers. On translocation into the endoplasmic reticulum, the N-terminal leader peptide is cleaved, and the mature protein is subsequently generated by a second cleavage event that releases an N-terminal proregion. The proregion can remain associated with the biologically active C-terminal region, inhibiting its activity.

The biological effects of TGF-βs and their related ligands are mediated by two classes of receptor, designated type I (RI) and type II (RII).[81] A third group of receptors, denoted type III, also exists (*e.g.,* TGF-β RIII in the case of TGF-β). This latter group does not actively participate in signal transduction but is thought to function to present ligands to the functional receptors. Similar to the RTKs described previously, the cytoplasmic domains of TGF-β receptors possess intrinsic kinase activity. However, TGF-βRI and TGF-βRII encode serine/threonine kinases. The signaling cascade appears to be initiated by the binding of TGF-β to the type II receptor, inducing the assembly of a ternary complex containing TGF-β, TGF-βRII, and TGF-βRI.

TGF-β Family Members and Their Actions

The three known human TGF-βs—TGF-β_1, TGF-β_2, and TGF-β_3—all have expressed molecular weights of 25 kDa. These three isoforms of TGF-β are closely related and have very similar biological functions. TGF-β_1, the most abundant form, is the only isoform found in platelets. T cells and monocytes mainly synthesize TGF-β_1, a critical function of which is to antagonize lymphocyte responses.

Approximately half of TGF-$\beta_1^{-/-}$ mice survive until birth, and 3–4 weeks later, they typically succumb to an overwhelming autoimmune state characterized by lymphoid and mononuclear infiltration of heart, lung, and other tissues, and by autoantibody production. These studies, along with selective inhibition of TGF-β function in T cells, indicate that TGF-β plays a crucial role in T-cell homeostasis and the prevention of spontaneous T-cell differentiation. TGF-β_1 induces FoxP3, promotes adaptive Treg-cell differentiation, and inhibits IFN-γ production. Conversely, TGF-β_1 with IL-6 induces IL-17, a proinflammatory cytokine. Thus TGF-β_1 has both proinflammatory and antiinflammatory activities.

TGF-β_2 is the most abundant TGF-β isoform in body fluids, whereas TGF-β_3 is the least abundant of the three. TGF-β_2– and TGF-β_3–null mice exhibit defects distinct from those observed in TGF-β knock-out mice, particularly in bone and internal organ formation. Their deficiency is embryonically lethal, demonstrating that although the three isoforms functional similarly *in vitro,* they play distinct roles *in vivo.*

The human type II receptor is an 80-kDa glycoprotein that is the principal receptor for TGF-β. Upon binding of its ligand to RII, the type I receptor is recruited into the complex and activated through phosphorylation of its GS domain. The principal type I receptor in the TGF-β pathway is the ≈55-kDa activin-like kinase-5 (ALK-5). ALK-1 can also be recruited into the complex and can transduce TGF-β–mediated signals.

Signaling

Ligand binding to the type II receptor allows the recruitment of the type I receptor[81] (Fig. 9.9). Although the receptor subunits have some affinity for one another, the complex of the receptor subunits bound to ligand is more stable. The type II receptor is thought to be a constitutively active kinase. Upon ligand binding, the type II receptor phosphorylates the type I receptor. The type I receptor is structurally distinct from the type II receptor in having a glycine- and serine-rich sequence juxtamembrane domain that precedes the kinase domain, which is referred to as the *GS domain.* It is this site that is phosphorylated by the

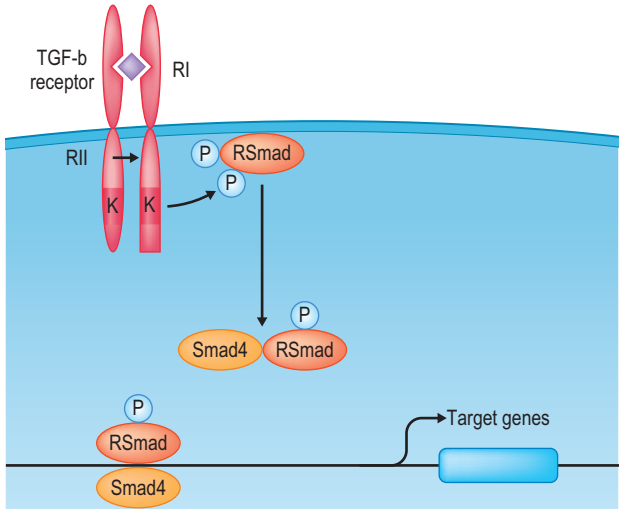

FIG 9.9 SMADs and signaling by transforming growth factor-β (TGF-β) superfamily receptor serine kinases.

type II receptor. In turn, the type I receptor is responsible for phosphorylating key signaling intermediates. It is not clear whether activation of the type I receptor results from enhancement of its kinase activity, the appearance of substrate-binding sites, or a combination of the two.

SMADs

The primary substrates activated by the type I receptors are SMADs, a group of related proteins that have been highly conserved throughout evolution and play a critical role in TGF-β signal transduction.[82] Eight mammalian SMADs have been identified. All exhibit a high degree of specificity for conserved motifs in the cytoplasmic tail of type I receptors. These proteins do not contain any previously known structural or enzymatic motifs. However, they have two homology domains, termed the MH1 and MH2 domains, at the N- and C-termini, respectively, which are separated by a central linker domain. The extreme C-terminus of some SMADs is a critical site of phosphorylation, as described below. SMADs have been subdivided into three classes based on functional distinctions.

R-SMADs. The receptor-regulated SMADs (R-SMADs) directly interact with, and are phosphorylated by, the type I receptor. These include SMAD1, -2, -3, -5, and -8. SMAD2 and SMAD3 are phosphorylated in response to TGF-β, whereas SMAD1, -5, and -8 are primarily activated in response to BMP activation. R-SMADs bind to the GS domain of type I receptor and are phosphorylated at a conserved SSXS motif in their C terminus. The interaction of R-SMADs with TGF-β receptors can also be regulated by another molecule termed SARA (SMAD anchor for receptor activation). SARA binds unphosphorylated SMAD2 and SMAD3. By virtue of its FYVE domain, SARA can bind phospholipids and localize SMADs to the plasma membrane, facilitating receptor binding. Phosphorylation of SMADs also permits dissociation from SARA.

Once phosphorylated, R-SMADs dissociate from the activated type I receptor and associate with SMAD4 in the cytoplasm. This is followed by nuclear translocation of the heteromeric SMAD complex, the binding to cognate DNA motifs in the promoters of TGF-β–responsive genes, and the concomitant induction of transcription. The SMAD MH1 motif mediates sequence-specific DNA binding, whereas the MH2 domain contains the transcriptional activation domain.

SMAD2-null mice lack anterior/posterior specification and fail to develop mesoderm. SMAD3-deficient mice have limb malformations and defective immune function. SMAD3-null mice exhibit defective TGF-β responses. However, these mice also display accelerated wound healing compared with normal mice, which seems to contradict the role of SMAD3 as a positive regulator of TGF-β in enhancing wound healing.

Upon recruitment to their cognate activated type I receptor, R-SMADs are phosphorylated on C-terminal serine residues, triggering homodimerization of R-SMADs or heterodimerization with another class of SMAD, the common SMAD or C-SMAD (see below).

C-SMADs. SMAD4 is the only known C-SMAD in vertebrates. It is thought to function as the central and essential downstream mediator of other SMADs in all TGF-β/BMP pathways. The SMAD MH2 domain is important for both receptor interaction and SMAD dimerization. SMAD4 lacks the SSXS element conserved in the R-SMADs and thus is not phosphorylated, rendering it unable to bind type I receptors directly. SMAD4-deficient mice die early in embryogenesis and exhibit severe defects in gastrulation.

I-SMADs. The third subfamily of SMADs is the inhibitory SMADs, or I-SMADs. In mammals, SMAD6 and SMAD7 are the I-SMADs. SMAD6 utilizes an alternative mechanism and is thought to function by competing with SMAD4 for binding to an R-SMAD. Studies with SMAD6-deficient mice indicate a role in the development and homeostasis of the cardiovascular system. SMAD7 is induced by TGF-β and binds to TGF-β receptors inhibiting the phosphorylation of R-SMADs, thus serving as a classic feedback inhibitor.

Consistent with their key functions in development, gene targeting of SMAD molecules has been shown to produce severe phenotypic abnormalities.

SMAD pathways. Although a canonical SMAD DNA-binding element (SBE) has been described (AGAC), comparison of the TGF-β responsiveness of synthetic promoters to natural promoters has revealed that SMADs can only partially account for the gene-regulatory effects of TGF-β signaling. SMADs also interact with a variety of other transcription factors, transcriptional coactivators, and transcriptional corepressors to regulate transcription of a select subset of complex promoters in a coordinated manner. For example, FAST-1 (forkhead activin signal transducer), a winged helix forkhead transcription factor, associates with the SMAD2/SMAD4 complex. SMADs also bind to c-JUN/c-FOS, and AP-1 sites frequently overlap with SBE sites in the naturally occurring promoters of TGF-β–responsive genes. SMADs can also bind ATF2, the vitamin D receptor, and other transcription factors and can recruit the coactivators CBP/p300. Additionally, the SKI and SNON corepressors can interact with SMADs and antagonize TGF-β signaling.

Other TGF-β–Activated Pathways

Other signaling pathways are known to mediate TGF-β signals. In particular, a number of members of the MAPK family are activated in response to TGF-β. TGF-β induces ERK, JNK, and p38 MAPK activity. Inhibition of several of these pathways inhibits TGF-β–mediated transcriptional activation. In addition, a MAPK family member, TAK1, has been implicated in TGF-β signaling. TAK1 is activated in response to ligand binding and has been

shown to associate with another molecule, TAB1 (TAK1-associated binding protein), which activates TAK1 kinase activity. Together, they have been reported to activate the MAPK pathway(s), leading to activation of p38/MPK2 and c-JUN N-terminal kinase (JNK), with evidence that this may take place via MKK6 and MKK4, respectively.

Clinical Relevance

Although the relevance of TGF-β to clinical immunology remains unclear, defects in the TGF-β pathway have been identified in a range of human cancers. SMAD4 is deleted in half of all human pancreatic carcinomas. Mutations in SMAD2 have been identified in patients with colon cancer, and somatic mutations in TGF-β receptors have been identified in colon and gastric cancers. Loss of SMAD3 is associated with leukemia. In addition, oncogenic RAS has been shown to repress SMAD signaling by negatively regulating SMAD2 and SMAD3.

OTHER CYTOKINES

Interleukin-14

Several new cytokines have been identified, but their functions are less clear compared with those discussed above. IL-14 was identified as a high-molecular-weight B-cell growth factor produced by T cells and some B-cell tumors. The precise nature of this putative cytokine is still unclear.

Interleukin-16

IL-16 was formerly termed *lymphocyte chemoattractant factor* because of its ability to recruit CD4 T cells.[83] It is unrelated to other cytokines, and its only known receptor is the CD4 molecule. It was originally identified as a product of CD8 T cells, but its message is widely expressed. CD4 T cells, eosinophils, and mast cells can all secrete IL-16. It is present in bronchoalveolar lavage (BAL) fluids from patients with asthma and those with sarcoidosis. It has also been detected in blister fluid from bullous pemphigoid lesions. The physiological function of IL-16 has yet to be clarified.

Interleukin-32

IL-32 is one of the newest cytokines, and it, too, is structurally distinct.[84] It is inducible by the combination of IL-12 and IL-18. IL-32 induces the expression of various cytokines, including TNF, IL-1, IL-6, and chemokines. It can synergize with muramyl dipeptides. IL-32 signals via NF-κB and p38. IL-32 is present in the rheumatoid synovium, and injection of IL-32 induces inflammation and recruitment of inflammatory cells.[85]

THERAPEUTIC TARGETING OF CYTOKINES AND CYTOKINE RECEPTORS

Because of their important activities in numerous diseases outlined in this chapter, cytokines and their receptors have been actively studied as therapeutic targets or as therapeutic agents (Table 9.4; Chapter 89). IFNs were the first cytokines to be considered as antiviral agents. Currently, type I IFNs are used to treat a wide array of disease from viral hepatitis (IFN-α and IFN-λ) to MS (IFN-β). IL-2 is currently marketed (as aldesleukin) for the treatment of renal cancer and melanoma. TNF was investigated after its discovery as an antitumor agent, but its inflammatory properties made it a highly successful target for the treatment of autoimmune and inflammatory diseases.

With the advent of molecular biology techniques and mAb engineering, targeting of these molecules has become a highly successful strategy to modulate the immune response (Chapter 89). IL-2 is not only a therapeutic protein but also a target. Daclizumab and basiliximab are mAbs directed against the IL-2Rα chain and have been approved for use in transplantation, MS, uveitis, and ulcerative colitis. IL-6, one of the most important proinflammatory cytokines, has also been targeted and several anti–IL-6 antibodies are now under development. Tocilizumab, which targets the IL-6R, has been approved for the treatment of several autoimmune diseases ranging from RA to ankylosing spondylitis.

The effective targeting of the p40 subunit of IL-12/IL-23 with the human mAb ustekinumab has resulted in effective treatment of some forms of psoriasis, psoriatic arthritis, and Crohn disease. However, ustekinumab is not effective in MS.

Many studies have implicated TNF in the pathogenesis of the chronic inflammatory diseases, such as RA and Crohn disease. Levels of TNF are highly elevated in the synovial fluid and the serum of patients with RA, as well as in the gastrointestinal mucosa of patients with Crohn disease. This suggests that the proinflammatory effects of TNF might underpin the severe inflammatory symptoms observed in these diseases. Of particular relevance to RA, TNF both inhibits the synthesis of cartilage components, such as proteoglycan, and stimulates bone resorption. These findings prompted the development of specific TNF inhibitors that have demonstrated great promise in the treatment of RA and Crohn disease. The two best-characterized of these inhibitors are monoclonal anti-TNF antibodies (infliximab, adalimumab, and golimumab) and chimeric TNFR2-Fc protein (etanercept). Clinical studies of these compounds have demonstrated that they can induce striking improvement in patients with RA (see Table 9.4). The side effects of TNF antagonism include increased incidence of infection, particularly with *M. tuberculosis,* and a possible increased incidence of cancer.[86] Other TNF-family cytokines have been targeted for therapeutic purposes. Targeting of RANKL with denosumab has been used for the treatment of osteoporosis as well as the bone resorption and hypercalcemia that results from bone metastases in cancer.

Because of the importance of IL-1 in the pathogenesis of fever, it would be expected that agents that inhibit IL-1 would be therapeutically useful. Indeed, IL-1Ra (anakinra), the naturally produced antagonist, has been studied in a variety of settings. It has been found to be somewhat efficacious in the treatment of RA. Anakinra, canakinumab, an anti–IL-1 antibody, as well as rilonacept, a fusion protein containing the extracellular portions of the two IL-1R components IL-1R and AcP, have been more successful in autoinflammatory disorders, particularly those related to overactivity of inflammasome components, such as the cryopyrinopathies. Canakinumab has also been successful in the treatment of more common autoinflammatory conditions, such as juvenile-onset idiopathic arthritis, as well as in the treatment of gout and type II diabetes.[87-89] Similarly, the human mAb canakinumab has entered the clinical arena with overlapping applications, and others are in various stages of clinical development. One of the most exciting new antireceptor antibodies is belimumab, which targets BAFF, a B-cell stimulatory TNF family member. Belimumab is the first licensed drug for the treatment for SLE in more than 50 years, and its mechanism of action is believed to be interference with B-cell survival, differentiation, and autoantibody formation.[90]

Beyond their beneficial effects to patients, the clinical effect of specific cytokine blockade with these agents is the ultimate

TABLE 9.4 Recombinant Cytokines and Biological Agents Currently in Clinical Use or Being Tested for Clinical Application

Name	Target	Phase	Indications
Daclizumab	Interleukin (IL)-2Rα	FDA approved	Transplantation, multiple sclerosis
Basiliximab	IL-2Rα	FDA approved	Transplantation uveitis, ulcerative colitis,
Benralizumab	IL-5R	II	Asthma, chronic obstructive pulmonary disease (COPD)
Reslizumab	IL-5R	II/III	Asthma, inflammation of skin and gastrointestinal tract
Mepolizumab	IL-5	FDA approved	Asthma, nasal polyp
Tocilizumab	IL-6R	FDA approved	Rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), Castleman disease, ankylosing spondylitis
Clazakizumab	IL-6	II	RA, psoriatic arthritis
Siltuximab	IL-6	FDA Approved	Castleman disease
Sarilumab	IL-6R	FDA approved	RA Uveitis
Olokizumab	IL-6	III	RA Crohn disease
Sirukinumab	IL-6	III	RA, systemic lupus erythematosus (SLE)
ALX-0061	IL-6		RA, SLE
Oprelvekin	IL-11R	II	Thrombocytopenia, von Willebrand disease
Ustekinumab	IL-12/23 p40	FDA approved	Psoriasis, psoriatic arthritis, Crohn disease, sarcoidosis, palmoplantar pustulosis
Briakinumab	IL-12/23 p40	III	Psoriasis, Crohn disease
Lebrikizumab	IL-13	II	Asthma
Tralokimumab	IL-13	II	Asthma, COPD
Anrukinzumab	IL-13	II	Ulcerative colitis
TNX-650	IL-13	I/II	Hodgkin lymphoma
Brodalumab	IL-17	FDA approved	RA, psoriasis
Ikzekizumab	IL-17	FDA approved	RA, psoriatic arthritis
Bimekizumab	IL-17	II	Psoriatic arthritis, rheumatoid arthritis
BCD-085	IL-17	II	Ankylosing spondylitis; plaque psoriasis
Secukinumab	IL-17	FDA approved	Psoriasis, psoriatic arthritis, ankylosing spondylitis, RA, Crohn disease, multiple sclerosis (MS), xerophthalmia
NNC-114-0005	IL-21	II	Type I diabetes, SLE
Tildrakizumab	IL-23	III	Plaque psoriasis
Risankizumab	IL-23	III	Plaque psoriasis
Guselkumab	IL-23	II	Plaque psoriasis
Anakinra	IL-1	FDA approved	Autoinflammatory syndromes, RA
IL-Trap/Rilonacpet	IL-1	FDA approved	Autoinflammatory syndromes, RA, gout, JIA
Canakinumab	IL-1β	FDA approved	Autoinflammatory syndromes, RA
MABp1	IL-1α	I/II/III	Cancer, cachexia, atherosclerosis, plaque psoriasis, acne vulgaris, type II diabetes
Gevokizumab	IL-1β	III	RA, type I and type II diabetes, giant cell arteritis, Behçet disease, uveitis
NI-0501	Interferon (IFN)-γ	II/III	Hemophagocytic lymphohistiocytosis
Anifrolumab	IFN-β	III	SLE
Etanercept	TNFα	FDA approved	RA, juvenile-onset rheumatoid arthritis (JRA), psoriatic arthritis, plaque psoriasis, ankylosing spondylitis
Infliximab	TNFα	FDA approved	RA, psoriasis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis
Adalimumab	TNFα	FDA approved	RA, plaque psoriasis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, JIA
Golimumab	TNFα	FDA approved	RA, ankylosing spondylitis, psoriatic arthritis
Ozoralizumab	TNFα	II	RA
Pegsunercept	TNFα	FDA approved	RA, JRA, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis
Certolizumab	TNFα	FDA approved	RA, JRA, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis
Belimumab	BAFF/BLyS	FDA approved	SLE
Brentuximab vedotin	TNFRSF8 (CD30)	FDA approved	Lymphoma
Denosumab	RANKL	FDA approved	Osteoporosis, RA, hypercalcemia of malignancy, cancer

FDA, US Food and Drug Administration.
Source: Pipeline (Drug pipeline information database by Citeline, Inc.)

test of the pathogenic role of the targeted cytokine. Bringing cytokine blockade into the clinics has helped unravel the complex web of interactions between cytokines in human autoimmune and inflammatory conditions.

ON THE HORIZON

- Although the number of cytokines already seems vast, it is likely that more will be discovered in the future.
- As continued improvement in the imaging of cells and macromolecular complexes improves, it is likely that we will obtain new insights into how cytokines actually signal.
- Improved understanding of regulators like the suppressors of cytokine signaling (SOCS) proteins should offer new therapeutic opportunities.
- Additional therapeutic options for the future may include the use synthetic cytokines and the creation of bispecific antibodies to target more than one cytokine or cytokine receptor at the same time.

CONCLUSIONS AND SUMMARY

Cytokines encompass a wide range of molecules that are essential for communication between cells of the immune system and other nonimmune cells. Although the number of cytokines already seems vast, it is likely that more will be discovered in the future. Considerable progress has been made in defining the *in vivo* functions of various cytokines. Equally impressive have been advances in our understanding how dysregulation of cytokines and cytokine signaling contribute to human disease. Cytokine and anticytokine therapies are being successfully used in the clinic. It is likely that their use will increase with advances in the understanding of the immunobiology of these cytokines.

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MULTIPLE-CHOICE QUESTIONS

1. The phenomenon of shared biological activities (cytokine redundancy) between cytokines that belong to the same subfamily reflects which of the following biological properties of type 1 family cytokines?
   A. The cytoplasmic portions of the type I family receptors all contain membrane proximal domains that bind Janus kinases (JAKs).
   B. Type I family cytokines act on all cells to inhibit viral replication, as well as cellular proliferation.
   C. Heterodimeric type I cytokine receptors often use a shared receptor submit in conjunction with a ligand specific subunit.
   D. There can be more than one receptor for each cytokine.

2. Which of the following cytokines promotes allergic responses and inhibits cell-mediated immune responses?
   A. Interleukin-1 (IL-1)
   B. IL-2
   C. IL-4
   D. IL-17

3. Which of the following cytokines is essential for mucocutaneous immunity against *Candida albicans*?
   A. Transforming growth factor-β (TGFβ)
   B. IL-3
   C. IL-6
   D. IL-17

4. Blockade of which of the following cytokines ameliorates rheumatoid arthritis (RA) and endotoxic shock?
   A. IL-7
   B. IL-12
   C. IL-21
   D. Tumor necrosis factor (TNF)