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Summary: The interleukin-1 (IL-1), IL-18, and IL-33 families of cytokines are related by mechanism of origin, receptor structure, and signal transduction pathways utilized. All three cytokines are synthesized as precursor molecules and cleaved by the enzyme caspase-1 before or during release from the cell. The NALP-3 inflammasome is of crucial importance in generating active caspase-1. The IL-1 family contains two agonists, IL-1α and IL-1β, a specific inhibitor, IL-1 receptor antagonist (IL-1Ra), and two receptors, the biologically active type IL-1R and inactive type II IL-1R. Both IL-1RI and IL-33R utilize the same interacting accessory protein (IL-1RAcP). The balance between IL-1 and IL-1Ra is important in preventing disease in various organs, and excess production of IL-1 has been implicated in many human diseases. The IL-18 family also contains a specific inhibitor, the IL-18-binding protein (IL-18BP), which binds IL-18 in the fluid phase. The IL-18 receptor is similar to the IL-1 receptor complex, including a single ligand-binding chain and a different interacting accessory protein. IL-18 provides an important link between the innate and adaptive immune responses. Newly described IL-33 binds to the orphan IL-1 family receptor T1/ST2 and stimulates T-helper 2 responses as well as mast cells.

Keywords: *interleukin-1, interleukin-18, interleukin-33, cytokines, inflammatory diseases*

Introduction

The interleukin-1 (IL-1), IL-18, and IL-33 families of cytokines are related by mechanism of origin, receptor structure, and signal transduction pathways utilized. The term IL-1 family is alternatively used to generically refer to the larger group encompassing all three cytokines. The ligands for the restricted IL-1 family include IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), and some newer related molecules. The IL-18 family includes IL-18 and IL-18-binding protein (IL-18BP), and the IL-33 family to date contains only IL-33. The receptors for these families include the following: for IL-1, types I and II IL-1 receptors (IL-1RI and II) and the IL-1R accessory protein (IL-1RAcP); for IL-18, the IL-18 receptor and the IL-18R accessory protein (IL-18RAcP); and for IL-33, the IL-1R-related protein T1/ST2 and IL-1RAcP. The major extracellular forms of these cytokines, IL-1β, IL-18, and IL-33, are all synthesized as biologically inactive precursor molecules inside

cells and are cleaved by the enzyme caspase-1 to the biologically active mature forms that are released from cells.

This review will discuss IL-1, IL-18, and IL-33, emphasizing both newer aspects of these families of cytokines and contributions by the authors. Under the section on IL-1, will be discussed the inflammasome, a molecular scaffold in the cytoplasm of cells that contains caspase-1 and controls its activity.

The IL-1 family

IL-1 ligands and receptors

Three ligands compose the IL-1 family: IL-1α, IL-1β, and IL-1Ra (1, 2). IL-1α and IL-1β are synthesized by multiple cells including monocytes, macrophages, neutrophils, hepatocytes, and tissue macrophages throughout the body. In the human, pro-IL-1α is synthesized in the cytoplasm as a 31 kDa precursor that is biologically active, i.e. is capable of binding to type IL-1R and activating cells. Both IL-1α and IL-1β lack signal peptides, or leader sequences, and are not released from cells by the usual mechanism of vesicular transport form the Golgi apparatus. Pro-IL-1α may be cleaved by calpain, a membrane-bound cysteine protease that requires calcium, leading to release of mature 17 kDa IL-1α from the cell. However, the majority of IL-1α remains either bound to the plasma membrane or inside the cell with some localization in the nucleus. Pro-IL-1α may travel to the nucleus and serve as an autocrine growth factor. IL-1β is also synthesized in the cytoplasm as a 31-kDa molecule and is processed and released from cells by a mechanism involving an enzyme called IL-1β-converting enzyme (ICE), now known as caspase-1 (see below for description). Pro-IL-1β is biologically inactive and must be converted to the mature 17 kDa IL-1β to acquire the ability to bind to receptors and activate cells.

There are two forms of IL-1R. IL-1RI possesses a long cytoplasmic domain and is capable of activating cells. IL-1RII has only a short intracellular domain and is biologically inert. However, IL-1RII may negatively regulate cell activation by acting in the membrane to compete for ligand binding with IL-1RI. In addition, IL-1RII is readily released from cells where it may bind IL-1 in the cell microenvironment, preventing interaction with cell surface IL-1RI. After IL-1 binds to IL-1RI, a second chain called the IL-1RAcP joins with IL-1/IL-1RI to form a complex, leading to cell activation mediated by the cytoplasmic domains of both receptor chains. This complex recruits a number of intracellular adapter molecules, including MyD88 (myeloid differentiation factor 88), IRAK (IL-1R-associated kinase), and TRAF6 [tumor necrosis factor (TNF) receptor-associated factor 6], to activate signal transduction pathways such as nuclear factor-κB (NF-κB), AP-1 (activator protein-1), JNK (c-Jun N-terminal kinase), and p38 MAPK (mitogen-associated protein kinase).

The IL-1Ra molecule is closely related structurally to the other IL-1 ligands but has undergone mutations rendering it incapable of interacting with IL-1RAcP (2). Thus, IL-1Ra binds avidly to types I and II IL-1R but fails to activate cells, functioning as a specific inhibitor of IL-1. The major isoform of IL-1Ra, secretory IL-1Ra (sIL-1Ra), is synthesized in the Golgi with a leader sequence and is secreted largely from the same cells that release IL-1β. Three intracellular structural variants of IL-1Ra (icIL-1Ra) have been described. Type 1 icIL-1Ra (icIL-1Ra1) is formed by an alternative transcriptional splice mechanism from a unique upstream exon and lacks a leader sequence. Eighteen kilodalton icIL-1Ra1 is a major protein in keratinocytes and other epithelial cells, endothelial cells, fibroblasts, and macrophages. Type 2 icIL-1Ra (icIL-1Ra2) also contains an additional upstream exon, but the mRNA may not be translated, as the predicted 25-kDa protein has never been identified *in vivo*. Type 3 icIL-1Ra (icIL-1Ra3) is produced by alternative translational initiation, primarily from the sIL-1Ra mRNA, and is a major protein in hepatocytes and neutrophils. icIL-1Ra1 binds avidly to IL-1RI, but icIL-1Ra3 exhibits weak binding. The ligands and receptors of the IL-1 family are depicted in *Fig. 1*.

The inflammasome

Structure and function

The innate immune system possesses two major recognition systems, or pattern-recognition receptors (PRRs), for microbial surface components, nucleic acids, and products of tissue destruction. The Toll-like receptors (TLRs) detect pathogen-associated molecular patterns (PAMPs) from bacterial cell walls and nucleic acids and have been implicated in many human diseases (3). The TLRs are primarily located on cell membranes, but some members of this family are found in the cytosol. The nucleotide binding and oligmerization domain (NOD)-like receptors (NLRs) are present only in the cytosol and include NOD1, NOD2, and IPAF (ICE-protease activating factor), all of which function as intracellular PRRs (4). Binding of microbial molecules or of endogenous factors to NLRs leads to the activation of caspase-1 from a pro-molecule. Tschopp *et al.* (5) described a caspase-activating complex in the cytosol containing caspases-1 and -5, an adapter protein ASC (apoptosis-associated speck-like protein CARD domain), and the sensor protein NALP1; this complex was termed the inflammasome. Since then, multiple inflammasomes have been identified and defined by the NLR protein that they contain (6). The

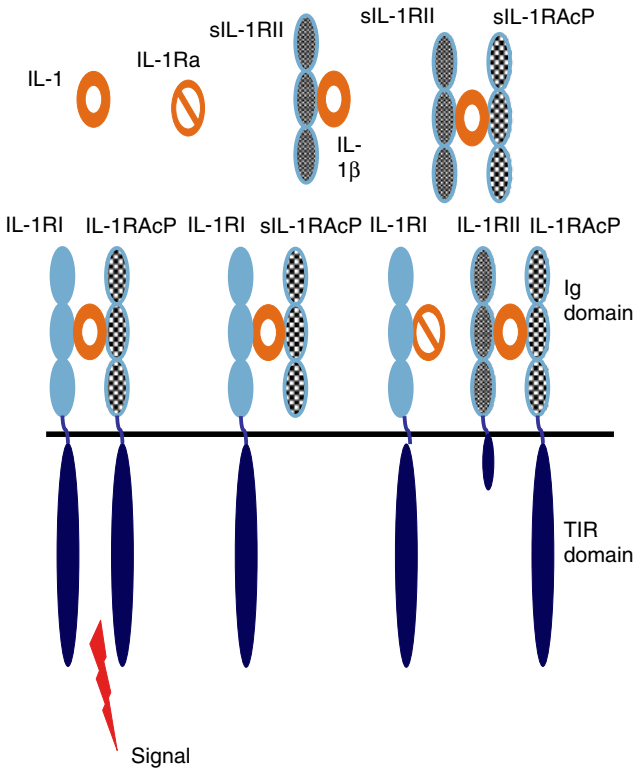

***Fig. 1.* Ligands and receptors of the IL-1 family.** The two agonist ligands, IL-1α and IL-1β, are represented by IL-1 and the antagonist ligand by IL-1Ra. IL-1RI has a long cytoplasmic domain and, along with IL-1RAcP, activates signal transduction pathways. IL-1Ra functions as an IL-1 inhibitor by binding to IL-1R1 but not allowing interaction with IL-1RAcP. IL-1RII does not activate cells but functions as an IL-1 inhibitor both on the plasma membrane and in the cell microenvironment as a soluble receptor. IL-1RAcP can also inhibit IL-1 signals by cooperating with IL-IRII in binding IL-1 either on the plasma membrane or as a soluble molecule.

NALP3 inflammasome (or cryopyrin) has proven particularly important for human disease, as mutations within the nucleotide-binding domain of NALP3 are associated with many diseases characterized by an over-production of IL-1, as discussed below.

The mechanisms and regulation of IL-1β production have great relevance to many acute and chronic inflammatory diseases. It is currently hypothesized that two signals are required for IL-1β release from normal human monocytes. The first signal appears to be TLR induction of transcription of pro-IL-1β with subsequent storage in the cell (6, 7). Lipopolysaccharide (LPS) is a common stimulus for signal 1 through binding to TLR4. The second signal is NLR-induced IL-1β processing and release through a caspase-1-dependent mechanism involving the $P2X_7$ receptor and binding of adenosine triphosphate (ATP). A variety of processes, including cell stress, lead to release of ATP into the cell microenvironment. ATP binding to the cell surface nucleotide receptor $P2X_7$ induces potassium efflux from the cell. The mechanism whereby loss of potassium from the cell leads to activation of caspase-1 is not completely known, but it requires the NALP3 cyropyrin molecule and the adapter protein ASC (8, 9). Studies in cryopyrin-deficient mice indicate a requirement for cryopyrin in TLR- and ATP-induced assembly of the inflammasome (8, 9). Thus, stimulation through both TLRs and NLRs as well as an intact NALP3 inflammasome are all required for processing and release of IL-1β, IL-18, and IL-33 from normal monocytes (10).

Four different mechanisms have been proposed for the release of leaderless IL-1β from cells (discussed in 11). Both pro-IL-1β and caspase-1 are present within lysosomes in monocytes. IL-1β processing may occur in this location by the NALP3 inflammasome during trafficking to the plasma membrane. ATP binding to the $P2X_7$ receptor may then lead to release of mature IL-1β from the cell by fusion of these vesicles with the plasma membrane and exocytosis through a mechanism dependent on calcium and phospholipases (12). A second mechanism of IL-1β release is hypothesized to occur through micro-blebbing of these vesicles from the plasma membrane (13). A third mechanism has been proposed where pro-IL-1β is processed in the cytosol, following activation of the $P2X_7$ receptor, with mature IL-1β passing through the plasma membrane via protein transporters (14). The results of recent studies suggest a fourth mechanism where a $P2X_7$ receptor-induced concentration of caspase-1 inflammasomes and pro-IL-1β occurs in the cytosol within the region of recycling endosomes. This is followed by the formation of multivesicular bodies containing entrapped IL-1β with eventual exocytosis of IL-1β, caspase-1, other inflammasome components, and membrane marker proteins (11). The possibility exists that the mechanisms of IL-1β processing and secretion may vary with the cell examined and its degree of activation or differentiation.

Autoinflammatory diseases

The term autoinflammatory diseases was first proposed in 1999 to encompass a group of inherited disorders characterized by recurrent episodes of fever with inflammatory responses in multiple organs including the joints, skin, eyes, ears, and central nervous system. This group of diseases is characterized by over-production of IL-1β and has been linked to various mutations in the *CIAS1* gene encoding the NALP3 crypyrin molecule, leading to enhanced caspase-1 activity (15, 16). These diseases include neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic, cutaneous, articular syndrome (CINCA),

Muckle–Wells syndrome (MWS), and familial cold urticaria (FCU). The *CIAS1* gene mutations in these diseases all produce changes in the structure of the NALP3 NACHT domain that is responsible for oligomerization within the inflammasome complex. These mutations are hypothesized to lead to spontaneous assembly and activation of the inflammasome with increased caspase-1 activation and spontaneous IL-1β release (17–20). However, the possibility also exists that the mutations may block an inhibitor of inflammasome assembly. Most patients with these diseases exhibit a rapid response to treatment with the IL-1Ra molecule (anakinra) or with other therapeutic agents that block IL-1β effects (21–25). These dramatic responses validate the importance of IL-1β overproduction as the mechanism of autoinflammatory disease.

The molecular mechanisms linking mutations in the *CIAS1* gene with increased IL-1β secretion and the clinical response to anakinra in patients with CINCA and MWS have been elucidated in recent studies (25, 26). The requirement for ATP stimulation in IL-1β release from monocytes in normal individuals was bypassed in patients with *CIAS1* mutations. This observation suggested that mutations in the *CIAS1* gene released the NALP3/cryopyrin protein from the necessity of ATP for activation. In addition, the rapid and dramatic response to treatment with anakinra was accompanied by a large decrease in IL-1β release from the monocytes. It was hypothesized that in addition to blocking the inflammatory effects of IL-1β on target cells, anakinra blocked the endogenous production of IL-1β induced by itself (26). It is well known that IL-1β potently induces its own production. The concept was suggested that IL-1β derived from background inflammation *in vivo* may be the endogenous stimulant of increases in synthesis of both caspase-1 and pro-IL-1β in patients with mutations in the *CIAS1* gene and autoinflammatory diseases.

Uric acid and gout

The proposal that the immune system developed to respond to endogenous and exogenous stress signals rather than to distinguish between self and foreign antigens was termed the 'Danger Model' by Matzinger in 2002 (27). An important role for the NALP3 inflammasome in the innate immune response to stress has been reviewed (28–30). The results of recent studies indicated that the release of uric acid from injured cells served as a principal endogenous danger signal (31). Uric acid stimulates the maturation of dendritic cells and enhances the *in vivo* responses of $CD8^+$ T cells to antigens. Both monosodium urate (MSU) and calcium pyrophosphate (CPPD) crystals, the inciting agents in gout and pseudogout, bound to the NALP3 inflammasome leading to the production of IL-1β and IL-18 (32). Neutrophil influx into the peritoneum of mice was markedly impaired after injection of MSU or CPPD crystals into mice deficient in caspase-1 or ASC, indicating an important role for the NALP3 inflammasome.

Myeloid differentiation primary response protein 88 (MyD88) is an adaptor molecule involved in signal transduction through the IL-1RI, IL-18R, and some TLR. MyD88 was required for acute gouty inflammation in mice and this response also required the IL-1RI, indicating a dependence on IL-1β in MSU-triggered inflammation (33). The bone marrow-derived cells in the peritoneum, such as monocytes and macrophages, produced the IL-1β in this model of crystal-induced inflammation whereas the non-bone marrow cells, such as endothelial cells and fibroblasts, responded to the released IL-1β (33). The hypothesis was proposed that IL-1β induction of adhesion molecules and chemokines was critical for the migration of polymorphonuclear neutrophils into the site of inflammation (34). Blockade of IL-1β by treatment with anakinra led to rapid resolution of episodes of acute gout in 10 patients who had failed standard anti-inflammatory therapies (35). Thus, IL-1β and the inflammasome represent promising therapeutic targets in patients with gout, where the usual treatments are ineffective or contraindicated (34).

Role of IL-1β in human diseases and the effects of treatment with anakinra

The role of IL-1β in human diseases and the benefits of treatment with the IL-1Ra molecule anakinra have been reviewed (1, 2, 36, 37). Considerable evidence supports the hypothesis that maintaining a balance between IL-1Ra and IL-1β is important in the prevention of many human diseases. An allelic polymorphism in the second intron of the IL-1Ra gene may predispose to disease through inadequate production of IL-1Ra in a particular organ (38) (*Table 1*). The results of recent studies on the role of IL-1 in a few diseases and the effects of treatment with anakinra are summarized below.

Arthritis

The importance of IL-1Ra in maintaining homeostasis and avoiding disease is illustrated by the spontaneous development of a T-cell-dependent chronic inflammatory arthropathy resembling rheumatoid arthritis (RA) in BALB/cA mice rendered genetically deficient in production of all isoforms of IL-1Ra (39). These mice also possessed elevated levels of autoantibodies, such as rheumatoid factors, and antibodies to double-stranded DNA and collagen type II. The mRNAs for

Table 1. **Diseases associated with IL-1Ra allele two**

Lichen sclerosis
Alopecia areata
Early-onset psoriasis
Ulcerative colitis in certain population groups
Multiple sclerosis in certain population groups
Severe forms of Sjögren's syndrome
Skin disease in systemic lupus erythematosus
Juvenile rheumatoid arthritis
Henoch–Schönlein purpura
IgA nephropathy
Gastric cancer
Diabetic nephropathy
Severe sepsis
Early-onset periodontitis
Nonatopic asthma
Fibrosing alveolitis
Silicosis in coal minors
Severity of GVHD
Idiopathic recurrent miscarriage
Ankylosing spondylitis
Single vessel coronary artery disease
Increased risk of death from acute stroke

pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα were elevated in the joints of these arthritic mice, indicating an important regulatory role for IL-1Ra in the cytokine network.

The results of subsequent studies indicated that the absence of IL-1Ra led to enhanced T-cell-dependent antibody production through IL-1-induced CD40 ligand and OX40 expression on T cells (40). The arthropathy in *IL-1Ra*$^{-/-}$ mice also required TNFα, IL-23, and IL-17. TNFα induced expression of the costimulatory molecule OX40 on T cells. IL-23 produced by myofibroblasts acted as the link between IL-1 and IL-17, the latter produced by Th17 cells (41–43). Because IL-17 can induce IL-1 production, the absence of IL-1Ra set up an inflammatory loop between IL-1, IL-23, IL-17, and IL-1 again (43). Lastly, spontaneous arthritis did not develop in germ-free *IL-1Ra*$^{-/-}$ mice, indicating a dependence on TLR activation by microbial flora (44). TLR2 downregulated the arthritis through control of regulatory T cells and of interferon γ (IFNγ)-producing T-helper 1 (Th1) cells, whereas TLR4 enhanced the disease by activating Th17 cells and increasing IL-17 production. Thus, in the absence of IL-1Ra, engagement of TLRs by products of microbial flora induced the spontaneous development of arthritis acting through an imbalance in the cytokine network and alterations in T-cell function.

IL-1β has been invoked as an important mediator molecule in the joints of patients with RA, but the efficacy of daily injections of anakinra overall have been modest and not as robust as the effects of TNF-blocking agents. This lack of a potent clinical effect may be due to the weak pharmacokinetics of IL-1Ra with a failure to maintain consistent high blood levels. Alternatively, the possibility exists that an important role for IL-1β in pathophysiology of RA is present only in a minor subset of patients. Clinical trials with other IL-1 blocking agents such as monoclonal antibodies to IL-1 or to the IL-1RI, or the IL-1 trap molecule, are necessary to clarify this question. However, IL-1 blockade with anakinra has been highly beneficial in systemic-onset juvenile idiopathic arthritis and in adult onset Still's disease (45, 46). These observations support a key role for excess IL-1β production, or a lack of endogenous inhibition, in these diseases. Specific gene expression profiles have been identified in children with systemic-onset juvenile idiopathic arthritis, allowing distinction from patients with other febrile disorders and possible value in following the response to therapy (47).

Pulmonary fibrosis

IL-1 has been invoked in the pathophysiology of a variety of inflammatory and immune lung diseases including asthma, pulmonary hypertension, pulmonary fibrosis, and granuloma formation (38). Bleomycin-induced pulmonary inflammation and fibrosis in mice required IL-1RI, signaling through MyD88, and the presence of the inflammasome adapter molecule ASC (48). This experimental model of pulmonary fibrosis in humans was markedly ameliorated by treatment with IL-1Ra, the latter possibly produced in the lung by mesenchymal stem cells (48, 49). Thus, bleomycin-induced pulmonary fibrosis in mice appears to involve excess IL-1β production mediated by the NALP3 inflammasome. A similar mechanism may exist in some forms of pulmonary fibrosis in humans.

Diseases of the central nervous system

An extensive literature exists on the production of IL-1β by microglial and other cells in the brain, primarily in the hypothalamus (50, 51). A role for IL-1β in normal physiology of the central nervous system remains unclear. IL-1Ra is also produced in the brain, primarily by neurons, but only after stimulation and at a later time point than IL-1β. The administration of IL-1Ra to experimental animals suggests an important role for IL-1β in host defense responses to systemic disease including mediation of fever, hypophagia, slow-wave sleep, sickness behavior, and neuroendocrine changes (50). For example, IL-1β is a potent pyrogen and acts on specific sites in the hypothalamus through interaction with IL-6 to increase body temperature. In addition, IL-1β plays a key role in a variety of ischemic, hypoxic, excitotoxic, traumatic, and

degenerative conditions, such as Alzheimer's disease, of the central nervous system.

Based on the beneficial effects of IL-1Ra administration in acute cerebral ischemia in rodents, a randomized, double blind, placebo-controlled trial of recombinant human IL-1Ra was carried out in patients with acute stroke (52). Patients with acute ischemic or hemorrhagic stroke were treated within 6 h of the onset of symptoms with a continuous intravenous infusion of anakinra over 72 h. This treatment was well tolerated and in this preliminary study led to an improvement in clinical outcome at 3 months after the cortical infarct, using multiple scoring systems. Additional larger controlled clinical trials are necessary to establish the optimal dose and to identify which stroke patients may benefit.

Diabetes mellitus

An imbalance between IL-1β and IL-1Ra has been invoked in metabolic diseases including types 1 and 2 diabetes mellitus and obesity (53). The disease mechanism in type 1 diabetes is thought to be a T-cell-mediated autoimmune response against β cells, while insulin resistance appears to be the underlying metabolic abnormality in type 2 diabetes. IL-1β has been shown to decrease insulin secretion by pancreatic β cells *in vitro* and to alter various β-cell functions. Treatment with IL-1Ra may prevent or ameliorate animal models of diabetes. These observations and the finding that IL-1Ra is decreased in β cells obtained from patients with type 2 diabetes led to the hypothesis that targeting IL-1β may preserve β-cell functions in patients with type 2 diabetes. A double-blind clinical trial was carried out in patients with type 2 diabetes by administering anakinra once daily for 13 weeks (54). This treatment improved glycemia and β-cell insulin secretory capacity as well as reduced markers of systemic inflammation. Additional studies are necessary to determine the possible beneficial effects of anti-IL-1 therapies possessing a more prolonged half-life and administered over a longer period of time on restoration of β-cell mass and function in patients with type 2 diabetes.

Cardiovascular disease

In addition to sIL-1Ra, icIL-aRa1 lacks a leader sequence and usually remains inside keratinocytes, macrophages, fibroblasts, and endothelial cells (55). However, like IL-1β, icIL-1Ra1 may be released from macrophages and endothelial cells through ATP stimulation of the $P2X_7$ receptor (56, 57). icIL-1Ra1 may carry out unique functions inside cells including alteration of cytokine mRNA stability in epithelial cells (58), binding to the COP9 signalosome with inhibition of IL-6 and IL-8 production by keratinocytes (59), and decreasing collagenase and matrix metalloproteinase-1 (MMP-1) production by fibroblasts (60).

Many human diseases involving epithelial and endothelial cells are associated with the IL-1Ra allele 2, including single vessel coronary artery disease (61). Human endothelial cells from umbilical veins or coronary arteries from individuals with IL-1Ra allele 2 produce decreased levels of icIL-1Ra1 (62). This imbalance in the IL-1 system may predispose individuals with IL-1Ra allele 2 to inflammatory and atherosclerotic vascular disease. MF1 mice genetically deficient in production of all isoforms of IL-1Ra spontaneously develop an inflammatory arteritis, further suggesting the importance of endothelial cell icIL-1Ra1 in preventing vascular disease (63).

Other IL-1 ligands and receptors

Six additional members of the IL-1 family of ligands have been identified on the basis of sequence homology, three-dimensional structure, gene location, and receptor binding (64, 65). A new system of terminology has been proposed for the IL-1 cytokines where IL-1α, IL-1β, IL-1Ra, and IL-18 become IL-1F1, IL-1F2, IL-1F3, and IL-1F4, respectively. The new IL-1 cytokines are termed IL-1F5–1F11, the latter representing IL-33. IL-1F6, IL-1F8, and IL-1F9 are ligands for the IL-1R-related protein 2 (IL-1Rrp2), requiring the IL-1RAcP for activity, and IL-1F5 may represent a receptor antagonist of IL-1Rrp2. IL-1F7 interacts with the IL-18BP to reduce IL-18 activity, and IL-1F10 binds to soluble IL-1RI with an unknown effect. The functions of IL-1F11, or IL-33, are described below. IL-1Rrp2 is highly expressed on epithelial cells in the skin and gastrointestinal tract as well as on fibroblasts and chondrocytes, suggesting a possible role in host defense in these organs. These IL-1-like ligands and receptor are summarized in *Fig.* 2.

Dysregulated expression of IL-1F6, IL-1F5, and IL-1Rrp2 may play a role in skin inflammation (66). Transgenic mice expressing IL-1F6 in basal keratinocytes developed skin abnormalities characterized by acanthosis, hyperkeratosis, a mixed inflammatory cell infiltrate, and increased cytokine and chemokine production (67). These skin changes were dependent on IL-1Rrp2 and IL-1RAcP and were inhibited by IL-1F5 as deficiency of this IL-1Rrp2 antagonist led to worse disease. Expression of IL-1Rrp2 and IL-1F6 were increased in the dermal plaques of psoriasis patients, and IL-1F5 was present throughout the epidermis including both plaques and non-lesional skin. However, not all of the histological features of psoriasis were reproduced in this animal model. These unique observations suggest a possible role for these new IL-1 family members in inflammatory skin disease.

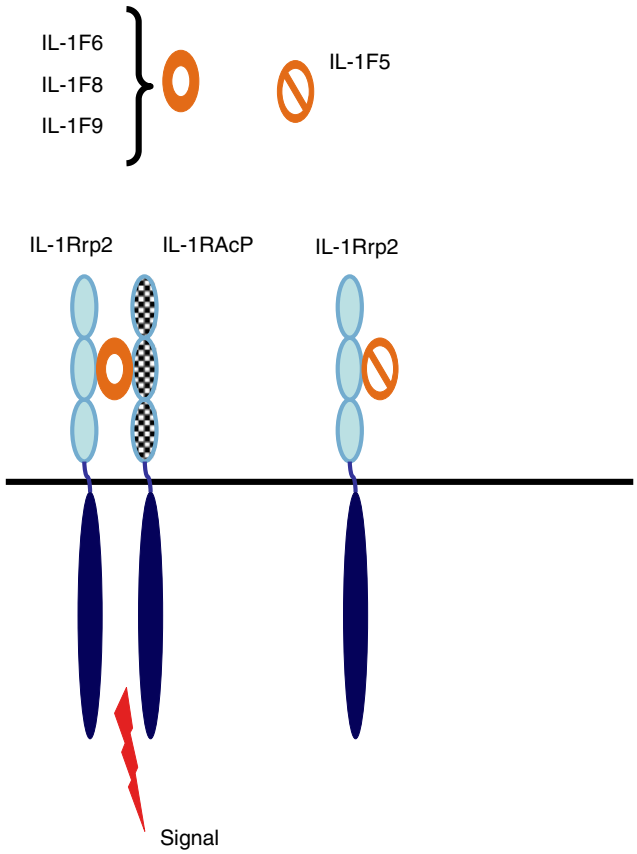

***Fig. 2.* Additional ligands and receptor of the IL-1 family.** Three IL-1 homologues, IL-1F6, IL-1F8, and IL-1F9, bind IL-1Rrp2 and also use IL-1RAcP as a coreceptor. IL-1F5 may function as a specific receptor antagonist of the IL-1Rrp2.

The IL-18 family

IL-18 and the IL-18 receptor

IL-18 was originally identified as an IFN-γ-inducing factor (IGIF), which circulated during endotoxemia in mice primed with *Propionibacterium acnes* (67). IL-18 has structural similarities with the IL-1 family of proteins. Like IL-1β, IL-18 is synthesized as a 23-kDa biologically inactive precursor peptide, which is subsequently cleaved by caspase-1 (68). However, in contrast to IL-1β there is a substantial pool of IL-18 inside cells and inflammatory stimulations have little impact on IL-18 precursor production. Thus, the regulation of IL-18 biological activity is mainly due to caspase-1-mediated pro-IL-18 processing. The gene encoding IL-18 maps to chromosome 11 in the human and to chromosome 9 in the mouse, whereas most genes of the IL-1 family are located on chromosome 2 in both humans and mice. Pro-IL-18 is expressed in macrophages, dendritic cells, Kupffer cells, keratinocytes, chondrocytes, synovial fibroblasts, and osteoblasts (69–72).

The IL-18 receptor is remarkably similar to the IL-1R complex. The binding chain is termed IL-18Rα and its sequence was found to be identical to the previously identified IL-1Rrp1. A signaling peptide, IL-18Rβ also termed accessory protein-like, is related to the IL-1RAcP. IL-18Rβ itself does not bind IL-18 but is recruited to form a high-affinity heterotrimeric complex with IL-18Rα and IL-18. This high-affinity complex recruits the same intracellular adapter molecules (MyD88, IRAK, and TRAF6) as IL-1 and results in similar responses (NF-κB, JNK, p38 MAPK) (73). The ligand-binding chain IL-18Rα is expressed on naive T cells, on mature Th1 lymphocytes and NK cells, as well on macrophages, B cells, neutrophils, basophils, mast cells, endothelial cells, smooth muscle cells, synovial fibroblasts, chondrocytes, and epithelial cells (74–80). Expression of the IL-18R complex, in particular of IL-18Rβ is modulated by various cytokines (74, 81–86), and it appears that the synergism of IL-12, IL-23, IL-21, IL-2, or IL-15 with IL-18 for induction of IFN-γ production can be mainly attributed to upregulation of IL-18Rβ (84, 87–89). The ligands and receptors for the IL-18 family are summarized in *Fig.* 3.

IL-18BP

Methods of purification of cytokine-binding molecules from human urine led to the identification of a 38-kDa IL-18BP (90). IL-18BP is not a soluble form of IL-18Rα, although it possesses many of the characteristics of a decoy receptor similar to type 2 IL-1R in the IL-1 system. No transmembrane or cytoplasmic domains of IL-18BP have been found. Thus, IL-18BP represents a unique soluble protein. Structurally, IL-18BP has one immunoglobulin (Ig) domain, which displays some sequence homology to the third Ig domain of IL-18Rα (91). IL-18BP binds to mature IL-18, but not pro-IL-18, with high affinity and prevents its interaction with cell surface receptors, thus acting as a natural inhibitor (92).

The human IL-18BP gene encodes four different isoforms (IL-18BPa, b, c, d), whereas two isoforms (IL-18BPc and IL-18BPd) have been identified in the mouse. These IL-18BP isoforms are produced by alternative mRNA splicing and differ primarily in their C-terminal region. IL-18BPa exhibits the greatest affinity for IL-18 with a dissociation constant of 399 pM. IL-18BPc shares the Ig domain with IL-18BPa, except for 29 amino acids in the C-terminal region. IL-18BPc has 10 times less binding affinity for IL-18 than IL-18BPa. IL-18BPa and IL-18BPc neutralize $>$ 95% of IL-18 at a molar excess of 2. Human IL-18BPa and IL-18BPc lack a complete Ig domain and do not have the ability to bind or inhibit IL-18. Both mouse IL-18BP isoforms possess an identical Ig domain and are able to neutralize $>$ 95% of murine IL-18 activities.

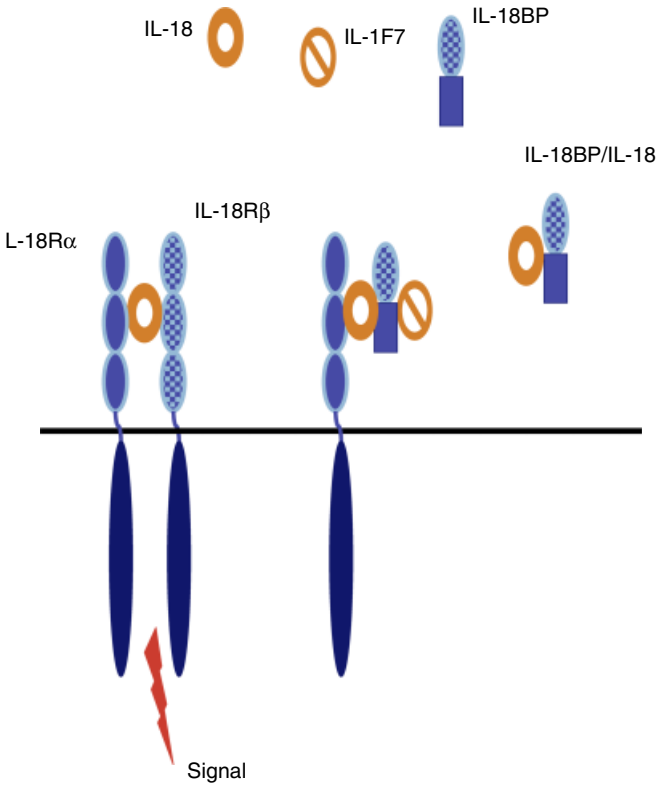

***Fig. 3.* Ligands and receptors for the IL-18 family.** IL-18 binds to the IL-18Rα chain, and this complex then engages the IL-18β chain to initiate intracellular signals. The soluble protein IL-18BP functions as an inhibitor of IL-18 by binding this ligand in the fluid phase, preventing interaction with the IL-18Rα chain. IL-1F7 appears to enhance the inhibitory effect of IL-18BP.

Murine IL-18BPd, which shares a common C-terminal motif with human IL-18BPa, is also able to inhibit human IL-18 (92).

The production of IL-18BP appears to be upregulated by IFN-γ. In human epithelial cell lines, IFN-γ induces the production and release of IL-18BPa. These observations indicate that, like other cytokines, IL-18 indirectly increases the production of its own inhibitor in a feedback loop (93). By Northern blot analysis, IL-18BP appears to be expressed constitutively in the spleen in the human and mouse. In addition, IL-18BP mRNA is detected constitutively in the intestinal tract and in the prostate (90). Endothelial cells and monocyte/macrophages also represent important sources of IL-18BP. The circulating levels of IL-18BP in healthy individuals range from 0.5 to 7 ng/ml, while elevated IL-18BP levels have been described in several autoimmune or inflammatory diseases (77, 94–97). In Crohn's disease, IL-18BPa, IL-18BPc, and IL-18BPd isoforms were elevated in samples from patients with active disease, and intestinal endothelial cells and macrophages were the major source of IL-18BP in the submucosa (98). In general, the molar excess of IL-18BP to IL-18 is in the order of 20–30-fold. In secondary hemophagocytic syndrome, a highly inflammatory condition occurring in systemic-onset juvenile idiopathic arthritis and more rarely in autoimmune diseases, an overproduction of IL-18 due possibly to the activation of casapse-1 may explain the presence of an IL-18/IL-18BP imbalance (99). Given the high binding affinity of IL-18BP for IL-18, IL-18BP represents an important regulator of the immune and inflammatory response in IL-18-associated diseases.

IL-1F7

IL-1F7 has been recently identified by DNA sequence homology as a member of the IL-1 family of cytokines in humans. However, no IL-1F7 ortholog has been found in the mouse. IL-1F7b, a mRNA splice variant of IL-1F7, was shown to bind to IL-18Rα with a weaker affinity than IL-18 (100-fold less), but did not recruit IL-18Rβ, and thus did not exert any agonistic effect. IL-1F7 alone had also no inhibitory activity on the IFN-γ production induced by IL-18. In contrast, IL-1F7 enhanced the inhibitory effect of IL-18BP by binding to IL-18BP. The IL-1F7 then complexed with cell-bound IL-18Rβ, and the resulting ternary complex prevented the β chain from forming a functional complex with IL-18Rα (100).

IL-18-independent functions of IL-18Rα

Two recent studies revealed unexpected discrepancies between IL-18 and IL-18Rα-deficient mice and cells. One study showed that IL-18-deficient mice were susceptible to experimental autoimmune encephalomyelitis (EAE), a Th-17-mediated mouse model of multiple sclerosis, while IL-18Rα-deficient mice were resistant, suggesting involvement of an IL-18Rα ligand other than IL-18 in the pathogenesis of EAE. In fact, engagement of IL-18Rα on antigen-presenting cells was required for the generation of pathogenic IL-17-producing Th cells, while IL-18 was dispensable (101). Similarly, divergent responses of IL-18 or IL-18Rα-deficient pancreatic islets were observed in a mouse model of allograft rejection (102). The results of this second study suggested that IL-18Rα is used to convey an anti-inflammatory signal, which is independent of IL-18, in the context of inflammation-mediated islet injury. It is unresolved whether these observations involve a second ligand for IL-18Rα and/or a novel receptor accessory chain and what the identity of such a second ligand might be. Since both studies were performed in mice, IL-1F7 is not a candidate.

IL-18 as a link between innate and adaptive immune responses

IL-18 is produced by monocytes/macrophages in the presence of different microbial components and plays a major role in the innate immune responses to pathogens. IL-18 is particularly important for the clearance of intracellular pathogens, which requires the induction of IFN-γ, and of viruses, which involves induction of cytotoxic T cells (reviewed in 103). PRRs, such as TLRs and NLRs, play an essential role in the detection of invading pathogens.

Several TLR agonists have been reported to induce IL-18 production. Release of mature IL-18, however, requires concomitant stimulation with an activator of caspase-1. Indeed, in healthy human subjects, LPS at a dose of 1 or 2 ng/kg was not sufficient to induce an increase in circulating levels of IL-18. In contrast, IL-18 levels were markedly elevated in septic patients, suggesting that in addition to LPS, other bacterial components are necessary to activate the release of IL-18 outside the cells (104). Similarly, human dendritic and peripheral blood mononuclear cells released only trace amounts of IL-18 when stimulated with TLR2 and TLR4 agonists. In contrast, when used in combination with aluminum hydroxide, a well-known adjuvant that activates caspase-1, TLR agonists induced the secretion of large amounts of both IL-1β and IL-18. LPS also induced the release of IL-18 in a TLR4- and caspase-1-dependent manner in murine Kupffer cells (105). Finally, the TLR-5 agonist flagellin was also shown to induce release of mature IL-18 by monocytes stimulated with nigericin or ATP to activate caspase-1 (106).

NLRs are intracellular sensors for pathogens, products of damaged cells, or endogenous metabolites, and are potentially involved in the generation and amplification of the immune response. In response to *Anaplasma phagocytophilum*, an obligate intracellular pathogen, the caspase-1-activating recruiting domain (ASC)/PYCARD, a central adapter in the NLR pathway, plays a critical role in the release of IL-18. ASC and caspase-1-deficient mice were more susceptible to infection due to the absence of IL-18 secretion and reduced IFN-γ levels (107).

IL-18 amplifies the innate immune response by inducing the expression of cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, IL-1β and chemokines such as IL-8 by peripheral blood mononuclear cells (108). Human peripheral blood neutrophils also constitutively express IL-18R subunits. IL-18 induced the release of cytokines and chemokines, upregulated CD11b expression, induced granule formation, and enhanced respiratory burst in neutrophils following exposure to fMLP. Injection of IL-18 promoted the recruitment of neutrophils, whereas IL-18 inhibition suppressed the severity of local inflammation following carrageenan injection (109).

IL-18 alone or in combination with IL-15 augmented NK cell activity (110–112). IL-18 enhanced Fas ligand expression on T cells and NK cells and induced apoptosis in Fas-expressing cells (113). In murine-mixed lymphocyte cultures, IL-18 also enhanced the development of $CD8^+$ effector T cells with strong cytolytic activity (114). Finally, IL-18 has T-cell chemoattractant properties *in vitro* and *in vivo* (115).

Early studies on IL-18 stressed its IFN-γ-inducing abilities and promoted its role as an inducer of Th1 responses (67). IL-18 induced IFN-γ production by activated murine and human T cells, in synergy with IL-12 (116). As mentioned earlier, the upregulation of IL-18Rα gene and surface expression by IL-12 contributed to this effect (74). Although IL-18 is a potent inducer of IFN-γ production by Th1 cells, unlike IL-12, IL-18 did not induce Th1 development by itself (116). The importance of the cooperative activity of IL-18 and IL-12 in IFN-γ production and Th1 development was confirmed *in vivo* using mice lacking one or both of these cytokines (111, 117). However, IFN-γ production in response to IL-18 was not restricted to Th1 cells. The combination of IL-18 and IL-12 acting on $CD8^+$ T cells, NK cells, and activated B cells also induced upregulation of the IL-18Rα chain and the production of large amounts of IFN-γ (114, 118, 119).

In addition to its effect on IFN-γ production, IL-18 is also able to stimulate Th2 responses. In combination with IL-2, IL-18 enhanced the production of IL-13 by cultured T lymphocytes and NK cells. IL-18 can potentially induce IgG1, IgE, and Th2 cytokines such as IL-4, IL-5, and IL-10 production in murine experimental models. Transgenic mice overexpressing IL-18 produced high levels of both Th1 and Th2 cytokines and of IgE and IgG1 (120).

More recently, IL-18 was reported to take part in the differentiation of Th17 cells by amplifying the IL-17 production of polarized Th17 cells in synergy with IL-23 (121). However, as mentioned above, Gutcher *et al.* (101) recently reported that in the mouse EAE model IL-18 was dispensable, while engagement of IL-18Rα on antigen-presenting cells was required for the generation of pathogenic Th17 cells. Th17 polarizing effects of IL-18 and IL-18Rα may contribute to their roles in the inflammatory process in several chronic autoimmune diseases. The effects of IL-18 on immune responses are summarized in *Table* 2.

Table 2. **Effects of IL-18 on immune responses**

Stimulates the expression of adhesion molecules
Induces the production of GM-CSF, TNF, IL-6
Induces the production of chemokines (IL-8)
Induces the production of granules in neutrophils
Enhances the respiratory burst of neutrophils
Stimulates the activity of NK cells
Stimulates the expression of FasL on T and NK cells
Stimulates the cytotoxic activity of $CD8^+$ effector T cells
Stimulates Th1 responses in combination with IL-12
Stimulates Th2 responses in combination with IL-2
Stimulates Th17 responses in combination with IL-23

Potential Role of IL-18 in disease

IL-18 expression and effector function have been described in several autoimmune and inflammatory diseases, such as multiple sclerosis, arthritis, inflammatory bowel diseases, and psoriasis. In addition, IL-18 has also been suggested to play a role in the metabolic syndrome, in atherosclerosis, and in cancer.

Multiple sclerosis

The role of IL-18 in the pathogenesis of multiple sclerosis has been suggested by the presence of elevated levels of IL-18 in the circulation and cerebrospinal fluid of patients, which correlated with clinical signs of disease activity (122–124). In mice, antigen-specific T cells treated with IL-18 successfully transferred the disease to normal recipients (125). In addition, the administration of neutralizing anti-IL-18 antibodies in EAE inhibited IFN-γ production by T cells *in vitro* and the development of cerebral lesions *in vivo*. However, by using gene knockout mice, recent results indicated that IL-18Rα signaling in antigen-presenting cells, rather than IL-18, is involved in the development of EAE (101).

RA

IL-18 mRNA and protein were expressed in the rheumatoid synovium with significantly higher levels than in osteoarthritis tissues. IL-18 receptor expression was detected on synovial lymphocytes and macrophages. Together with IL-12 or IL-15, IL-18 induced IFN-γ production by synovial tissues *in vitro*. IL-18 independently promoted GM-CSF and nitric oxide (NO) production, and it induced significant TNF-α synthesis by macrophages. IL-18 production in synovial cultures and purified synovial fibroblasts was upregulated by TNF-α and IL-1β (71).

Articular chondrocytes produced pro-IL-18 and, in response to IL-1 stimulation, secreted the mature form of IL-18. Studies regarding IL-18 effects on chondrocytes showed that it inhibited cell proliferation, enhanced NO production, and stimulated the production of stromelysin, IL-6, and COX2. Treatment of normal human articular cartilage with IL-18 increased the release of glycosaminoglycans. IL-18 is thus a cytokine that exerts a catabolic effect on cartilage (70). In contrast, IL-18 may have a protective effect on bone erosions. Osteoblastic stromal cells produced IL-18, which inhibited osteoclast formation, apparently through the release of GM-CSF by T cells (72).

In vivo studies have confirmed the role of IL-18 in the pathogenesis of arthritis. IL-18 administration to mice with collagen-induced arthritis (CIA) facilitated the development of an erosive, inflammatory arthritis, suggesting that IL-18 can be pro-inflammatory *in vivo* (71). In contrast, knockout mice lacking IL-18 have a reduced frequency and severity of CIA (126). The administration of neutralizing anti-IL-18 antibodies or IL-18BP significantly reduced the clinical severity of CIA (127, 128). Attenuation of disease severity was associated with reduced cartilage destruction on histology (127). Consistent with these results, administration of an adenoviral vector containing the coding sequence of mouse IL-18BP significantly attenuated the disease severity in the treated knee joints (129).

Anti-IL-18 antibodies significantly suppressed joint inflammation and cartilage damage in streptococcal cell wall-induced arthritis. In contrast, the administration of recombinant IL-18 exacerbated the severity of arthritis. This inhibitory effect of anti-IL-18 antibodies was independent of IFN-γ, as similar results could be observed in mice deficient in IFN-γ (130). Interestingly, IL-18-deficient mice develop antigen-induced arthritis similarly to wildtype mice, indicating that the involvement of IL-18 in the pathogenesis of arthritis may also be dependent on the model examined (131).

Inflammatory bowel diseases

Circulating levels of IL-18 are elevated in patients with inflammatory and autoimmune bowel diseases, including Crohn's disease, ulcerative colitis, and celiac disease (132–134). In addition, IL-18, IL-18R, and caspase-1 levels are increased in chronically inflamed mucosa as compared with early lesions or normal tissue. In the inflamed lesions, both epithelial and dendritic cells account for the increased production of IL-18 (135, 136). Levels of IL-18BP are elevated in the plasma of patients with inflammatory bowel diseases; however, the increased concentrations are not sufficient to bind all of the excess IL-18 (132).

The role of IL-18 has been investigated in animal models of inflammatory bowel disease. IL-18-deficient mice are resistant to the induction of experimental colitis, whereas transgenic mice overexpressing IL-18 exhibit a higher susceptibility to the

induction of intestinal inflammation (137). Treatment with IL-18BP or antibodies against IL-18 decreased the severity of colitis (138). Interestingly, mice deficient in IFN regulatory factor-1 exhibited a more severe form of experimental colitis, which was associated with decreased levels of colon IL-18BP, suggesting that the balance between IL-18 and its natural inhibitor plays a major role in the control of experimental colitis (139).

Psoriasis

Increased levels of IL-18 are present in the plaques and in the serum of patients with psoriasis, and the latter correlates with the extension of skin lesions (140–142). Keratinocytes are able to produce IL-18, which can be processed and released under certain circumstances (143). In addition, Langerhans and dendritic cells in the skin are able to produce mature IL-18 in response to inflammatory stimulation (144, 145). The role of IL-18 has not been examined in models of psoriasis. However, it has been shown that transgenic mice overexpressing IL-18 develop a severe and persisting skin reaction in response to topical irritants (146).

IL-18 and the metabolic syndrome/atherosclerosis

IL-18-deficient mice develop a marked increase in body weight and several manifestations of metabolic syndrome including insulin resistance and hyperglycemia, altered lipid metabolism, and atherosclerosis. Similar observations were also present in IL-18Rα-deficient mice as well as in transgenic mice overexpressing IL-18BP. Obesity is the result of a loss of circadian regulation of food intake and appetite. Analysis of the glucose metabolism in IL-18-deficient mice revealed the presence of hyperinsulinemia with insulin resistance and enhanced expression of gluconeogenesis genes in the liver. The regulatory mechanisms of IL-18 on insulin resistance were mediated through the activation of STAT3 but not the MyD88 pathway (147).

A study on human carotid artery and aorta specimens showed that atheroma *in situ* expressed IL-18 and that elevated levels of its IL-18R subunits were present in atherosclerotic as compared with non-diseased tissue. Western blot analysis confirmed that IL-18 was present in atherosclerotic lesions, not in non-atherosclerotic arteries, and that mature 18 kDa IL-18 is the predominant form. Consistent with this finding, active caspase-1 was also detected in the same tissue samples. IL-18 staining colocalized with macrophages, whereas IL-18R subunits were detected in smooth muscle cells, endothelial cells, and macrophages. The presence of IL-18 *in situ* correlated with signs of atherosclerotic plaque destabilization (148). In culture, IL-18 stimulated the production of IL-6 by endothelial cells and smooth muscle cells, as well as IL-8, MMPs, and IFN-γ by smooth muscle cells (76). In apolipoprotein E-deficient mice, an experimental model of atherosclerosis, the electroporation of an expression plasmid encoding IL-18BP attenuated the development of atherosclerotic plaques (149). Thus, IL-18 appears to have opposing effects on atherosclerosis, depending on the model examined. Chronic IL-18 inhibition may favor the development of a metabolic syndrome and atherosclerosis, but it appears that IL-18 inhibition can also prevent the development of vascular inflammatory lesions leading to the development of instable atherosclerotic plaques with a clinical impact on cardiovascular events.

IL-18 and cancer

Several experimental results suggest that IL-18 plays a dual role in tumor progression on the one hand by inducing an immune response to cancer cells and, on the other hand, by favoring the development of tumors and the progression of metastasis. IL-18 induces Th1 responses and production of IFN-γ, which play an important role in host defense. Intra-tumoral injection of IL-18 DNA enhanced IFN-γ production and caused liver tumor regression (150). In addition, gene therapy with IL-18 can also serve as a powerful adjuvant when used in combination with a tumor antigen (151). IL-18-stimulated NK cell activation and proliferation and upregulated perforin-mediated cytotoxicity (110, 152). The administration of IL-18 in combination with the B7-1 costimulatory molecule resulted in melanoma regression with increased NK cell infiltration at the site of tumor tissue. The persistence of the anti-tumor effect after T-cell depletion suggested that the cytotoxicity was mainly related to NK cells (153).

Elevated levels of IL-18 are present in cancer patients and several tumor cells are able to secrete IL-18 both *in vitro* (154) and *in vivo* (155). IL-18 may favor the progression of cancer by its pro-angiogenic effects (156). The vascular endothelial growth factor (VEGF) produced in response to IL-18 can in turn induce the production of IL-18, thus leading to a positive feedback mechanism in cancer cells (157). IL-18 also induced the production of MMP-9 in the human myeloid leukemia cell line HL-60, thus favoring the degradation of the extracellular matrix and the migration and invasiveness of cancer cells (158). In addition, IL-18 can also support the development of tumor metastasis in the liver by inducing the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) on hepatic sinusoidal endothelium (159). Interestingly, as opposed to its positive effects on

T lymphocytes and NK cells, IL-18 can also reduce the immune surveillance against cancer by inducing the expression of Fas ligand on tumor cells. The expression of Fas ligand will lead to the apoptosis of immune cells bearing Fas on their surface (160). Taken together, due to the complex role of IL-18 in the relation between host defense and tumor cells, therapeutic strategies aimed to manipulate IL-18 in the management of patients with cancer should be examined very carefully.

IL-18 as a therapeutic target

Different strategies have been developed to inhibit the biological effects of cytokines in immune-mediated inflammatory diseases, including monoclonal antibodies against cytokines or their receptors, soluble receptors, receptor antagonists, inhibitors of cytokines processing, and cytokine-induced intracellular signals. Some of these therapeutic approaches are currently in clinical practice, for example TNF and IL-1 antagonists, while others are still being tested in clinical trials or in preclinical development.

The two major strategies of blocking the effects of IL-18 include either the use of inhibitors neutralizing the effects of IL-18 by antibodies or soluble receptors, or treatments blocking the processing and release of IL-18. In experimental models, the administration of monoclonal anti-IL-18 antibodies or IL-18BP was effective in attenuating the inflammatory process, although antibodies were more efficacious than IL-18BP in collagen-induced arthritis (127). A fusion protein of IL-18BP coupled to the Fc fragment of human IgG1 binds to IL-18 and neutralizes its effect in several models of inflammatory diseases. This molecule is in clinical trial in RA and other inflammatory diseases.

Vaccination against cytokines has been contemplated as a possible strategy to generate autologous neutralizing antibodies against pro-inflammatory cytokines. Experiments in murine models provided interesting results in the blockade of TNF in arthritis (161). However, safety issues need to be solved before the application of this approach in patients with autoimmune diseases.

Caspase-1 processes precursor forms of IL-1β, IL-18, and IL-33 to generate mature and biologically active cytokines. The administration of caspase-1 inhibitors attenuated the course of collagen-induced arthritis (162) and inhibited the pro-inflammatory responses of monocytes isolated from patients with familial cold autoinflammatory syndrome (163). Pralnacasan, a caspase-1 inhibitor was tested in a randomized, placebo-controlled clinical trial in patients with RA, but the results were disappointing (164). In addition, clinical trials with pralnacasan were stopped due to long-term liver toxicity observed in treated animals. Other caspase-1 inhibitors are currently in clinical trial for the treatment of psoriasis.

Safety issues can be a concern in strategies aimed to inhibit IL-18, as this cytokine plays an important role in both innate and adaptive immune responses against pathogens. An increased rate of infections has been reported with the use of TNF antagonists, a cytokine also involved in host responses to microorganisms (165). Similar observations were also reported for therapies blocking TNF and IL-1 (166) or IL-6 (167). However, despite these potential problems, the risk benefit ratio is still considered as positive for the use of biologic treatments in patients with inflammatory diseases.

The IL-33 family

IL-33 and the T1/ST2 receptor

IL-33 (or IL-1F11) was recently identified as a ligand for the orphan IL-1 family receptor T1/ST2. IL-33 is produced as a 30-kDa propeptide and, like IL-1β and IL-18, is cleaved by caspase-1 to generate mature 18 kDa IL-33, at least *in vitro* (168). Interestingly, pro-IL-33 had been previously described as a nuclear protein, nuclear factor-high endothelial venules (NF-HEV), and thus exhibited a subcellular localization similar to that of the IL-1α precursor (169). The IL-33 propeptide contains a nuclear localization sequence (NLS) and a homeodomain-like helix-turn-helix DNA-binding domain. Like pro-IL-1α, nuclear pro-IL-33 appeared to exert unique biologic activities independent of caspase-1 cleavage and cell surface receptor binding (169–171).

Over the last 10 years, a number of studies established the T1/ST2 receptor (also referred to as ST2L) as a selective marker of both murine and human Th2 lymphocytes (reviewed in 172). In addition to Th2 lymphocytes, T1/ST2 is also highly expressed on mast cells throughout differentiation, starting from the earliest detectable committed mast cell progenitor (173). Finally, T1/ST2 expression was also described on some mesenchymal and epithelial cell types (174, 175). In a recent study, IL-33 and T1/ST2 were shown to participate in a paracrine signaling system between cardiac fibroblasts and cardiomyocytes to modulate cardiac hypertrophy and fibrosis (175).

T1/ST2 exists also as a soluble isoform (sST2), obtained by differential mRNA processing. sST2 is identical with the extracellular region of the long T1/ST2 isoform, except for nine additional amino acids which are present at the C-terminus of the molecule. The sST2 isoform was recently formally demonstrated to act as an antagonistic decoy receptor for IL-33 (176). The expression of sST2 was induced in

fibroblasts, macrophages, and monocytes stimulated with LPS, TNF-α or IL-1, as well as in activated Th2 clones (172). Serum concentrations of sST2 are elevated in patients suffering from various disorders associated with an abnormal Th2 response, including systemic lupus erythematosus and asthma, as well as in inflammatory conditions that are mainly independent of a Th2 response, such as septic shock or trauma (172, 177).

In humans, a third splice variant of ST2 has been described, ST2V, where alternative splicing leads to a change in the C-terminal portion of sST2, causing it to gain a hydrophobic tail instead of the third Ig-like domain (178, 179). The function of ST2V remains completely unknown. The ligands and receptors for the IL-33 family are summarized in *Fig.* 4.

IL-33 signaling

The biological effects of the IL-1 family of cytokines are typically mediated by their binding to a specific receptor followed by the recruitment of a coreceptor, required for elicitation of signaling. Studies conducted before the identification of IL-33 suggested the possibility of active T1/ST2 homodimers, based on the observation of signaling induced by antibody-mediated cross-linking of T1/ST2 (180, 181). However, the signals induced were different from a classical IL-1 type response, since extracellular signal-regulated kinase (ERK), p38, and JNK, but not NF-κB were activated (181). In contrast, activation of T1/ST2 by IL-33 induced signaling through the NF-κB pathway as well as through MAPKs (168, 182, 183). T1/ST2-dependent IL-33 responses thus resemble classical IL-1-like signaling, consistent with IL-33 receptor signaling via the recruitment of a coreceptor rather than by T1/ST2 homodimerization. In fact, several recent studies identified the IL-1RAcP as the coreceptor involved in IL-33 signaling (182, 184, GP, CG manuscript submitted). IL-1RAcP associated with T1/ST2 in a ligand-dependent manner and was required for the effects of IL-33 *in vitro* and *in vivo*. IL-1RAcP thus represents a shared coreceptor within the IL-1 family that is essential for IL-33 signaling via T1/ST2 in addition to IL-1 and IL-1F6, IL-1F8, and IL-1F9 signaling.

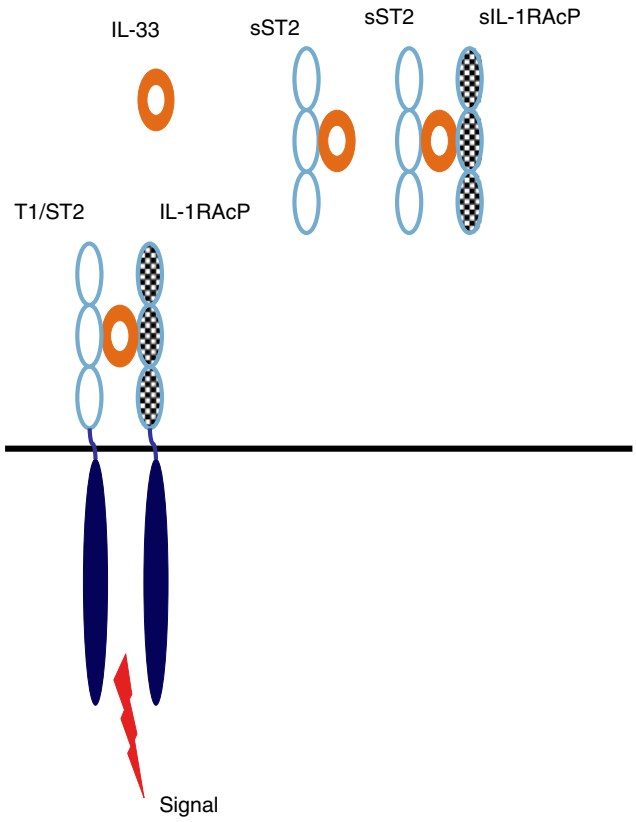

***Fig.* 4. Ligands and receptors of the IL-33 family.** IL-33 binds to the T1/ST2 receptor and this complex engages the IL-1RAcP as a co-receptor. A soluble form of ST2 (sST2) may function as an inhibitor of IL-33 by binding IL-33 in the cell microenvironment and soluble IL-1RAcP may enhance the inhibitory effects of sST2.

Effects of IL-33 on Th2 responses

IL-33 drives production of Th2-associated cytokines from *in vitro* polarized Th2 cells (168, 182). In mice, IL-33 injection induced the expression of IL-4, IL-5, and IL-13 and led to severe pathological changes in the lung and the digestive tract (168). Very recently, IL-33 was also shown to act as a chemoattractant for Th2 cells, both *in vitro* and *in vivo* (185). Before the identification of IL-33, numerous studies addressed the role of T1/ST2 and sST2 in Th2-mediated disease models, yielding sometimes contradictory results (186, 187). While studies using anti-T1/ST2 antibodies or ST2-Fc fusion proteins demonstrated an important role for T1/ST2 as an effector molecule in Th2 responses (188, 189), experiments on ST2 knockout mice provided conflicting evidence concerning the role of this receptor in Th2-cell-mediated immunity (190–192). With the description of IL-33 as the T1/ST2 ligand, future studies will certainly provide additional information concerning the role of the IL-33-ST2 system in adaptive immunity and clarify as yet controversial issues. The effects of IL-13 on immune responses are summarized in *Table* 3.

Effects of IL-33 on mast cells

It was recently reported that IL-33 acts both alone and in concert with thymic stromal lymphopoietin to accelerate the *in vitro* maturation of human $CD34^+$ mast cell precursors and to induce the secretion of several cytokines and chemokines in human mast cells (193). IL-33 was also described to promote survival and adhesion as well as IL-8 and IL-13 production in human umbilical cord blood-derived mast cells (183).

***Table* 3. Effects of IL-33 on immune responses**

Increases production of IL-4, IL-5, and IL-13 by polarized Th2 cells
Increases production of IL-4, IL-5, and IL-13 by antigen-stimulated splenocytes
Chemoattraction of polarized Th2 cells
Increases production of IL-6, IL-1β, TNF-α, and PGD2 by bone-derived mast cells
Synergic effect with IgE cross-linking on production of IL-6 and IL-13 by bone-derived mast cells
Increases production of Th2 cytokines and chemokines by human peripheral blood and cord blood-derived mast cells
Increases survival and adhesion of human cord blood derived mast cells
Systemic repeated injections of IL-33 results in splenomegaly, eosinophilia, lung, and digestive tract pathology

In primary mouse bone marrow-derived mast cells (BMMCs), IL-33 stimulated secretion of IL-6, IL-1β, TNF-α, monocyte chemoattractant protein-1 (MCP-1), and prostaglandin D2 (184, 194, 195). In addition, induction of IL-13 secretion by IL-33 in BMMCs was reported in one study (194) but not confirmed in another (184). Finally, IL-33 also enhanced IgE cross-linking-induced IL-8 and IL-13 production in human mast cells and IL-6 and IL-13 production in mouse BMMCs (183, 194). The effects of IL-33 on human and mouse mast cells occurred independently of degranulation (183, 194, 195). Collectively, these data suggest that in addition to promoting Th2 responses, IL-33 exhibits pro-inflammatory potential by inducing the production of a number of inflammatory mediators in mast cells.

T1/ST2 and sST2 in inflammation and arthritis

Several reports described a role of T1/ST2 and sST2 in regulating inflammatory responses which are not Th2 mediated. Both the long T1/ST2 and the sST2 isoforms have been described to exert anti-inflammatory effects in a mouse model of septic shock. Indeed, the presence of the long T1/ST2 isoform was required for endotoxin tolerance in mice and, in this context, T1/ST2 was shown to negatively regulate TLR4 and IL-1RI signaling by sequestrating the adapter molecules MyD88 and Mal (196). Administration of sST2 also reduced LPS-induced inflammatory response and mortality (197). The mechanism proposed to explain this effect was the direct inhibition of macrophage activation by sST2 via a putative sST2 receptor expressed on the macrophage surface. More recently, sST2 has been described to exert anti-inflammatory effects in two different models of ischemia-reperfusion injury (198, 199).

Increased levels of sST2 have been observed in the synovial fluid of patients with RA, when compared to osteoarthritis patients (200). Interestingly, mast cells have been recognized as important mediators of the pathogenesis of arthritis (201, 202), suggesting a role for IL-33-mediated mast cell activation in joint inflammation. Injection of an anti-T1/ST2 antibody had been reported to exacerbate CIA, but it has been suggested that this effect might be due to complement dependent Th2 clone lysis rather than an effect of the antibody on T1/ST2 signaling (203). Indeed, another study indicated that administration of sST2 decreased CIA (204). At the time, the mechanism proposed to explain this effect was again direct inhibition of macrophage activation by sST2. However, the recent identification of IL-33 as the *bona fide* ligand for T1/ST2 suggests neutralization of IL-33 by sST2 (176) as an alternative explanation.

IL-33, the most recently described member of the IL-1 family of cytokines, stimulates the production of pro-inflammatory mediators by mast cells in addition to its effects on Th2 responses, opening new perspectives for the treatment of inflammatory diseases by targeting IL-33.

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