IL-18 in autoimmunity: review

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ABSTRACT. IL-18 is among the cytokines responsible for immune-mediated pathologies and is probably one of the factors that contribute to the pathogenesis of autoimmune diseases. Identification of the causes of uncontrolled IL-18 production and activity in autoimmunity would allow for novel therapeutic targets to effectively block autoimmune activation and inhibit concomitant tissue damage. IL-18 is produced mainly by monocytes/macrophages in response to stimuli of viral/bacterial origin, its production being therefore one of the effects of innate immunity initiated by host-pathogen interaction. In this review, we summarise the evidence supporting both the effector and the pathogenic role of IL-18 in autoimmunity, and propose that the disturbed mechanism of innate immunity, resulting from macrophage activation through innate immunity receptors (TLR/IL-1R family), may be the basis of pathologically high levels of IL-18 production and activation. Unravelling the mechanisms of IL-18 production and activity in autoimmune diseases will allow the identification of targets for more effective therapeutic intervention.

Keywords: IL-18, autoimmunity, inflammation, macrophage, Toll-like receptor, IL-18BP

MECHANISMS OF INNATE IMMUNITY IN THE INITIATION OF AUTOIMMUNITY

In autoimmune diseases, immune activation is inappropriately directed against self antigens. It is widely recognised that the autoimmune process is triggered by unknown events, possibly in combination with predisposing genetic tracts. It has also been hypothesized that traumatic, stressful and infectious events may take part in the initiation of autoimmune reactions in susceptible hosts, and that molecular similarity between viral/bacterial molecules and self antigens may be at the root of autoimmune recognition.

Immune activation is initiated in response to invading/stressful events of different origin (both exogenous and endogenous). The innate immune system discriminates between self and alien/abnormal molecular patterns and mounts the first set of inflammatory and defence responses to eliminate the unrecognised element(s), and to initiate the slower and more specific adaptive response. The first interaction between the host and the stress elements (viruses, bacteria, foreign particles, trauma) occurs through the interaction with host cellular sensing structures, in the first place the receptors of the TLR/IL-1R family. This is an important class of receptors involved in the initiation of the inflammatory response and of the innate immune reactions. These receptors share a common signalling pathway and include the TLR receptor family (Toll-like receptors; at least ten different chains in humans), and the IL-1R/IL-18R superfamily. TLR are germline, encoded receptors that recognise different microbial structures of bacterial, viral, fungal, and protozoal origin (LPS, lipopeptide, dsRNA, flagellin, CpG, etc.) as well as endogenous, stress-related proteins (heat shock proteins 60 and 70, fibrinogen), thereby triggering responses and activating inflammatory reactions. TLR are mainly expressed by myeloid cells (macrophages), although their presence has been described in T lymphocytes and in several other cells and organs [1]. The IL-1R/IL-18R superfamily includes the receptors for the inflammatory/immunoenhancing cytokines IL-1 and IL-18 [2-4], for the regulatory cytokine IL-33 [5-7], and for a series of orphan receptors, including the putatively inhibitory receptors TIR8/SIGIRR [8-10], and RP105 [11, 12].

Macrophages are among the first cells which are recruited to the site of inflammation and come in contact with invading micro-organisms or foreign agents. Macrophages are versatile, plastic cells, which respond to environmental signals with diverse functions. Classical macrophage activation in response to microbial products (e.g., LPS) and interferon-γ (IFN-γ) has long been recognised and gives rise to potent effector macrophages (M1), which kill microorganisms and tumour cells and produce proinflammatory cytokines and chemokines (including IL-12, TNF-α, IL-1, IL-6, IL-8, MIP-1α). More recently, it has been shown that anti-inflammatory molecules, such as glucocorticoid hormones, IL-4, IL-13 and IL-10, are more than simple inhibitors of macrophage activation, in that they induce a distinct activation pathway (alternatively activated macrophages) [13, 14]. Alternative macrophage activation with IL-4 and IL-13 induces M2 macrophages, which can regulate inflammatory responses and adaptive

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Th1 immunity, scavenge debris, and promote angiogenesis, tissue remodelling and repair [15, 16]. Classically and alternatively activated (polarised) macrophages have been referred to as M1 and M2, in analogy with the Th1/Th2 dichotomy in T cell responses.
M1 or M2 polarised macrophages differ in terms of receptor expression, cytokine and chemokine production, and effector function. Differential cytokine production characterises polarised macrophages. The M1 phenotype includes IL-12 and TNF-α, while M2 macrophages typically produce IL-10, the IL-1 receptor antagonist (IL-1Ra) and the type II IL-1 receptor (IL-1RII). Differential production of chemokines, which attract Th1 *versus* Th2 or T regulatory cells, integrates M1 and M2 macrophages in circuits of amplification and regulation of polarised T cell responses. The microenvironment thus influences macrophage activation and their subsequent functions.
In this light, genetic and environmental conditions that promote M1/Th1 polarisation and inhibit M2/Th2 regulatory activity may contribute to the establishment of a chronic inflammatory condition. This may develop into autoimmunity following triggering events (e.g., an infection or trauma) that would induce an autoimmune adaptive response, through mechanisms of molecular mimicry.

M1/Th1–M2/Th2–M17/Th17 NETWORK AND IL-18

Based on the above considerations, it would be important to analyse the regulatory circuits determining the activation of innate immunity cells for the production of IL-18, in particular the development of M1 *versus* M2 macrophages in autoimmune diseases, and their mutual role in initiating and maintaining the autoimmune reaction. In addition, recent data suggest the pivotal role of IL-17-producing T helper cells (Th17) in chronic inflammatory-autoimmune diseases [17, 18]. The production of the Th17-polarising cytokines, in particular TGF-β and IL-6, depends on macrophages/dendritic cells, in response to certain pathogenic stimuli. Indeed, "type 17" pathogens are represented by extracellular pathogenic bacteria, against which Th17 cells appear to have a key protective role [17], as opposed to the protective role of Th1 for intracellular pathogens, and of Th2 for multicellular parasites. Thus, it may be proposed that macrophages producing Th17-polarising cytokines in response to these pathogens be called M17 macrophages. The role of IL-18 in Th17 responses appears to be that of activating/amplifying IL-17 production in already polarised Th17 cells, in a TCR-independent manner in synergy with IL-23, similar to its role in TCR-independent activation of Th1 cells together with IL-12 [17, 18]. The expression pattern of different receptors of the TLR/IL-1R family, and their capacity to react to infectious/stress-related stimuli by producing IL-18 may allow identification of the possible role of triggering events such as infections or traumas in the initiation of the autoimmune dysegulation. Not to be forgotten is the analysis of polymorphisms in the genes coding for the relevant TLR/IL-1R and those coding for the IL-18 ligands, receptors, IL-18BP. This analysis may show whether there is a genetic basis for the development of IL-18-associated autoimmunity. Indeed, enhanced production and activity of IL-18 appears to be at a fundamental level in autoimmune pathologies. The production of bioactive IL-18 is a multistep process involving synthesis of the precursor, synthesis and activation of the cleaving enzyme caspase-1, maturation and extracellular transport [3, 4]. IL-18 effects are further dependent on the expression of the two receptor chains IL-18Rα, the ligand binding chain, and IL-18Rβ, the accessory chain [3, 4], on regulation of the expression of the four IL-18BP isoforms (two able to bind and inhibit IL-18, two unable to bind and possibly inhibiting the activity of the binding isoforms) [19], on the presence of IL-1F7, a ligand of IL-18Rα which enhances the IL-18-inhibiting activity of IL-18BP [20], on the presence of active caspase-3, which cleaves and inactivates the IL-18 protein [21], and on the expression of TIR8/SIGIRR, which could act as downstream inhibitors of TLR/IL-1R signal transduction [8-10].
The unravelling of the molecular basis of dysregulated IL-18 overproduction and activity in autoimmune diseases will help to define novel therapeutic targets to limit pathological IL-18 excess. In particular, the correlation of the TLR/IL-1R expression pattern in macrophages with their activation state and IL-18 production capacity, and analysis of macrophage polarisation and IL-18 production and activity in autoimmune states would allow:
– definition of the role of innate immunity receptors in the regulation of IL-18 production and activity in autoimmune diseases;
– identification of novel targets to re-program macrophage polarisation/activity towards anti-inflammatory regulatory balancing.
Identification of the anomalies leading to excessive IL-18 production by polarised macrophages in autoimmune patients, and the relevance of TLR triggering in this excessive activation would allow us to devise ways to bias macrophage polarisation or to re-direct the activity of already polarised macrophages toward homeostatic control of IL-18 activation. Also, members of the TLR/IL-1R family may be identified as possible targets for novel therapeutic treatments aimed at inhibiting the excessive IL-18 production at the basis of autoimmune stimulation.

CYTOKINES IN AUTOIMMUNE DISEASES: PATHOLOGICAL *VERSUS* PATHOGENIC ROLE

Increasing evidence indicates that dysregulation of effector cytokines in the maintenance of immune and inflammatory activation is the basis of autoimmune reactions. The host response to infection initiates a brisk cytokine response, which facilitates mechanisms for eliminating the invading organism. Once danger is eliminated, cytokine production is turned-off and tissue damage resolves. In contrast, persistent, dysregulated cytokine production results in progressive tissue damage. Since the autoimmune pathologies are based on the hyperactivation of the immune response, it is not surprising that immune-related factors are produced in excessive amounts as a consequence of dysregulated immune activation, and that they contribute to the effector phases of the disease, mediating tissue and organ damage. Thus, therapeutic approaches based on cytokine inhibition may have a beneficial effect in limiting the activity of the damage-inducing effector molecules. An example is the use of TNF-blocking therapies (with soluble receptors or with monoclonal antibodies) for rheumatoid arthritis and chronic inflammatory bowel disease (including Crohn's disease). In addition,

blocking IL-1 activity with the IL-1 receptor antagonist (IL-1Ra) is entering clinical use for the same diseases with encouraging results [22]. However, of major importance for the efficacy of anti-cytokine therapies would be to identify the pathogenic role of these factors, *i.e.* their involvement in the first steps of dysregulated immunological triggering that initiates the disease.

In experimental animal models and in human disease, $CD4^+$ T cells play a central role, and both Th1 and Th2-related cytokines are apparently involved in maintaining autoimmune disturbances [23]. More recent findings also indicate a major role in chronic and destructive inflammatory/autoimmune pathologies for Th17 cells [17, 18]. A major pathogenic role is attributed to Th1- and Th17-related cytokines in many autoimmune conditions, particularly those involving chronic inflammation. In addition, Th1 cytokines also sustain autoimmune activation by expanding the pathological T cell clones.

By examining the autoimmune role of Th1-related cytokines, a central pathological effect has been described for the inflammatory Th1-dependent cytokine IFN-γ. For instance, in murine lupus, the ratio of IFN-γ- to IL-4-secreting cells (*i.e.* the Th1/Th2 ratio) increases with disease progression [24]. Administration of IFN-γ exacerbates the disease in humans and mice [25-28], whereas mice deficient in IFN-γ or IFN-γR develop a less acute disease and have slower disease progression [29-31]. The characteristic pathology-associated double negative ($CD4^-$ $CD8^-$) T cells and autoantibodies are absent in IFN-γ-deficient mice [32]. In IFN-γR-deficient mice, the renal damage is dramatically reduced [29, 31]. Other studies indicate that IFN-γ accounts for the fatal kidney disease in *lpr* mice [33, 34]. In EAE, a severe experimental demyelinating disease in rats and mice resembling human multiple sclerosis, IFN-γ and Th1 activation apparently play a major role in the pathological progression [32, 35].

IFN-γ-INDUCING CYTOKINE IL-18

IFN-γ production is amplified by the cytokine IL-18, in true synergy with other Th1-related cytokines, IL-2, IL-15, IL-12 and IL-23 [36-39]. IL-18, the cytokine previously known as IFN-γ-inducing factor (IGIF), is a potent activator of polarised Th1 cells and induces IFN-γ production and lymphocyte proliferation [36, 40]. Similar to the closely related inflammatory cytokine IL-1, IL-18 is synthesized as an inactive precursor molecule, which is cleaved by the IL-1β converting enzyme ICE (caspase-1) resulting in active (mature) IL-18 [41, 42]. *figure 1* summarises the features of IL-18 production, processing and release.

IL-18 RECEPTORS

As shown in *figure 2*, two chains of the IL-18 receptor are required for initiation of signal transduction. The α chain

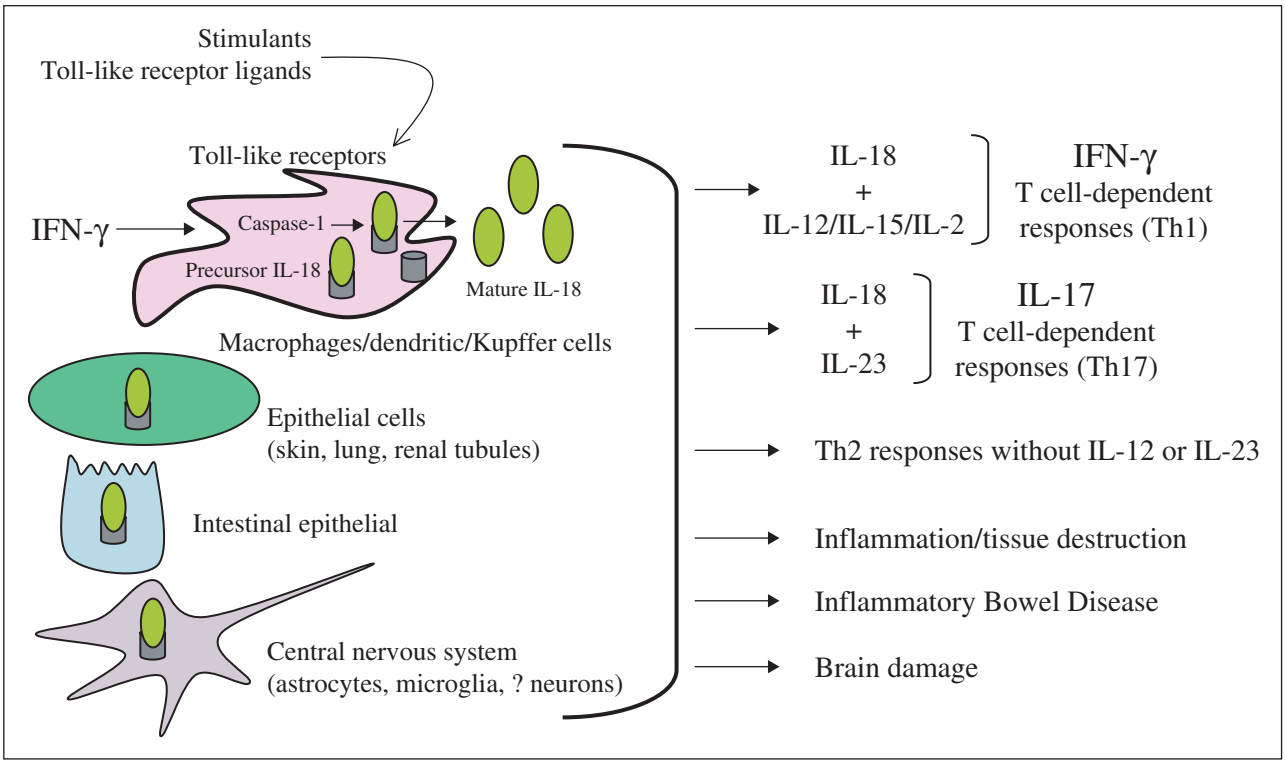

Figure 1

Cell sources of the IL-18 precursor. As shown, the IL-18 precursor is found constitutively expressed in many cells [419]. Upon activation of caspase-1 by TLR triggering, macrophagic cells, dendritic cells, or Kupffer cells process the inactive IL-18 precursor into an active, mature form, which is released from the cell [41, 42]. The precursor piece remains inside the cells and undergoes ubiquitination. IL-18 alone does not induce IFN-γ but rather requires co-stimulation with IL-12, IL-15 or IL-2 [36-39]. As a result of true synergism, IFN-γ is produced by $CD4^+$ T cells, $CD8^+$ T cells, NK and NK T lymphocytes. The role of these co-stimulators for the production of IL-18-dependent IFN-γ is thought to be the upregulation of the IL-18 receptors, particularly the β chain [43, 50]. In turn, IFN-γ promotes expression of the caspase-1 gene and activation of caspase-1 from inactive precursor [377, 467]. Alternatively, in synergy with IL-23, IL-18 activates Th17 cells to produce IL-17 [18]. In the absence of known synergies, IL-18 can activate Th2 responses [397].

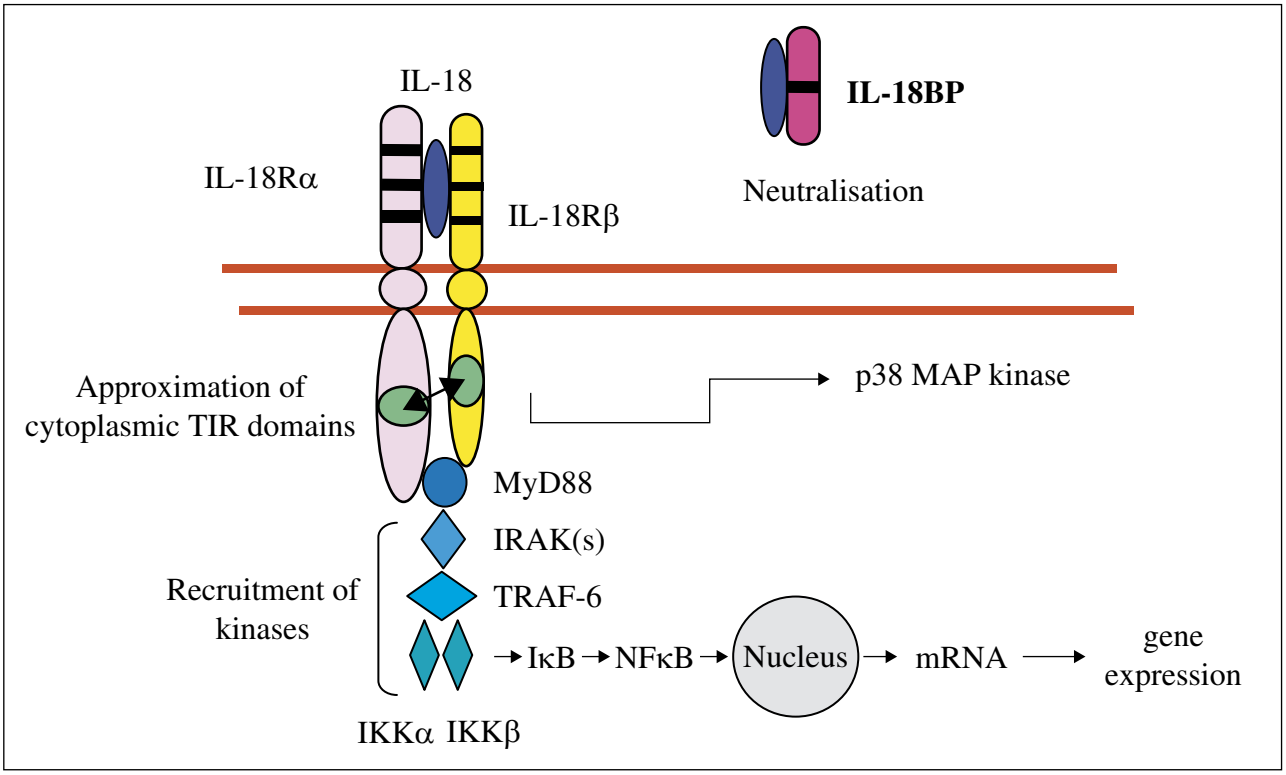

Figure 2

IL-18 receptors. The two chains of the IL-18 receptors get close to each other, and trigger the TIR domains (shaded area). This approximation results in the cascade of kinases activating the degradation of IκB. An alternative activation pathway has been described which involves phosphorylation of MAPK p38 [55-58].

of IL-18R is required for ligand binding, whereas the β chain does not bind IL-18 but is required for signalling. IL-18Rα and IL-18Rβ are members of the IL-1R superfamily, with an extracellular domain comprising three Ig-like domains and with an intracellular segment responsible for signal transduction. The ligand-binding chain IL-18Rα is expressed on the surface of Th1 lymphocytes and NK cells, and on a variety of other cells including macrophages and B cells, neutrophils and basophils, endothelial cells, smooth muscle cells, synovial fibroblasts, chondrocytes, and epithelial cells [43-49]. After binding of IL-18 to the IL-18Rα, the accessory chain, IL-18Rβ, is recruited into a signalling complex [50, 51]. Signal transduction is initiated by the approximation of the Toll-IL-1 receptor (TIR) domains present in the intracellular segment of the receptor chains [52]. The signalling pathway, shared with other receptors of the TLR/IL-1R family, involves recruitment of the adapted molecule MyD88 and of the kinase IRAK, followed by interaction with TRAF6. Activation of IKK causes degradation of IκB and subsequent activation of NFκB [53, 54]. An additional signalling pathway has been described in IL-18-stimulated cells, which involves activation of MAPK p38 [55-59]. Expression of chains of the IL-18R complex is upregulated by cytokines such as IL-12 and IL-2, and inhibited by IL-4 [43, 60-65]. In particular, it has been shown that IL-12 can modulate the cell response to IL-18 by upregulating expression of the accessory chain IL-18Rβ. Indeed, true synergism of IL-12, IL-23, IL-21, IL-2, and IL-15 with IL-18 for IFN-γ production can be mainly attributed to upregulation of IL-18Rβ [63, 66-68]. The IL-18Rα chain can bind with low affinity another molecule of the IL-1 cytokine family, *i.e.* IL-1F7 [20], a binding that however does not recruit the accessory chain IL-18Rβ, and therefore which does not initiate IL-18Rβ-dependent signalling. That IL-18Rα could be activated by ligands other than IL-18, possibly using a different co-receptor, is suggested by recent data in an experimental model of autoimmune encephalitis, in which deletion of the IL-18 gene did not change susceptibility to disease induction, whereas deletion of the IL-18Rα gene made mice resistant [69]. Since mice do not express IL-1F7, another IL-18-like ligand able to activate IL-18Rα for initiation of autoimmune-related inflammation is currently being sought.

IL-18 BINDING PROTEIN

IL-18BP is a naturally occurring, secreted protein, which possesses high affinity binding to IL-18 (dissociation constant of 400 pM), and therefore neutralises the biological activity of IL-18 [19, 70]. IL-18BP is specific for mature IL-18 and does not bind the IL-18 precursor when assessed by ELISA [71] or BIAcore binding [19]. With the exception of IL-1F7 [20], IL-18BP does not bind to other members of the IL-1 family or several cytokines tested.

IL-18BP is not a soluble form of the membrane-bound IL-18Rα, although it has many characteristics of a soluble receptor similar to the IL-1 type II decoy receptor [72]. Unlike all members of the IL-1 receptor family, which have three Ig-like domains in the extracellular receptor segment, IL-18BP has only one Ig-like domain. It seems that the transmembrane and the first two extracellular domains of the ancestral IL-18 receptor were deleted during evolution. The only amino acid identity with the IL-18Rα chain and IL-18BP is found in the third Ig domain of

the α chain [73]. There is limited amino acid homology between IL-18BP and the IL-1 type II decoy receptor. In fact, IL-18BP is similar biologically to the IL-1 decoy receptor in that its function is primarily to bind and neutralise the ligand rather than act as a ligand passer.

The human IL-18BP gene is located on chromosome 11q13. Using Northern blot analysis, IL-18BP is highly expressed in spleen and the intestinal tract, both immunologically active tissues. There are four isotypes of human IL-18BP and two isotypes of murine IL-18BP [19]. These isotypes are formed by alternate mRNA splicing of the respective genes. A single copy of the IL-18BP gene exists for humans, mice and rats [74]. Only those isoforms that retain the intact Ig domain are biologically functional, by neutralising IL-18 [19]. For example, human IL-18BP has four isotypes termed IL-18BPa, b, c and d. Only IL-18BPa and IL-18BPc have the intact Ig domain and neutralise IL-18 [19]. The other two isoforms, although they are produced in humans, do not bind and do not neutralise IL-18. However, the mRNA splicing that creates these isoforms is not a haphazard event in that the spliced mRNA has an open reading frame, which results in the same carboxyl terminal for all isoforms. It is possible that IL-18BP isoform b and d bind another member of the IL-1 family. The mouse has two isoforms, IL-18BPc and IL-18BPd. Murine IL-18BPc and IL-18BPd isoforms, possessing the identical Ig domain, also neutralise > 95% murine IL-18. However, murine IL-18BPd, which shares a common C-terminal motif with human IL-18BPa, also neutralises human IL-18 [19].

The sites for binding of IL-1 to the IL-1 receptor type I were used to model the binding of IL-18 to IL-18BP [19]. Modelling predicted a large mixed electrostatic and hydrophobic binding site in the Ig domain of IL-18BP, which could account for its high affinity binding to the ligand. By mutational analysis, two residues in IL-18, glutamic acid at position 35 and lysine at position 89, were found to be important both for binding to IL-18Rα and subsequent biological activity [73, 75], and for binding to IL-18BP and subsequent neutralisation [73].

The regulation of IL-18BP gene expression appears to be *via* IFN-γ [76]. In a human colon carcinoma epithelial cell line, IFN-γ induced gene expression and release of IL-18BPa. The increase in IL-18BP was also observed in a variety of intestinal cell lines and in a human keratinocyte cell line. The histone deacetylase inhibitor sodium butyrate suppressed IFN-γ-induced IL-18BP gene and protein expression [76]. The promoter for IL-18BP has been described as including two IFN-γ responsive elements [77]. Thus, like other genes encoding cytokine inhibitors (soluble receptors, receptors antagonists and binding proteins), the cytokine itself or a related cytokine induces its own negative regulator in a feed-back loop. Therefore, in a Th1 response, the production of IL-18-dependent IFN-γ contributes to the suppression of IFN-γ by increasing the production of IL-18BP.

The serum levels of IL-18BPa in a cohort of healthy subjects as determined by a specific ELISA were 2.15 ± 0.15 ng/mL (range 0.5-7 ng/mL) [70]. In patients with sepsis and acute renal failure, the levels rose to 21.9 ± 1.44 ng/mL (range 4-132 ng/mL), due to increased production and not to renal retention. Using the law of mass action and knowing the dissociation constant of IL-18BP to IL-18, total IL-18 and free IL-18 were calculated. Total IL-18 in healthy individuals was 64 ± 17 pg/mL and approximately 85% was in the free form [70]. Total IL-18 and IL-18BPa were both elevated in sepsis patients upon admission (1.5 ± 0.4 ng/mL and 28.6 ± 4.5 ng/mL, respectively). At these levels, most of the IL-18 is bound to IL-18BPa, however the remaining free IL-18 in sepsis patients is still higher than in healthy individuals. One can conclude from these studies that IL-18BPa considerably inhibits circulating IL-18 in sepsis. Nevertheless, exogenous administration of IL-18BP may further reduce circulating IL-18 activity.

The relative gene expression of the IL-18-neutralising (a and c) and non-neutralising (b and d) isoforms of IL-18BP was studied in Crohn's disease during active phases of the disease [78]. Intestinal endothelial cells and macrophages were the major source of IL-18BP within the submucosa, similar to what was observed in cultured human endothelial cells and peripheral blood monocytes. Gene expression, as measured by steady state mRNA levels for IL-18BP as well as the IL-18BP protein, were elevated in intestinal biopsies from patients with active disease [78]. Unbound IL-18BP isoforms a and c and inactive isoform d were present in specimens from patients with active disease as well as in tissues from control patients. The IL-18BP isoform b was not detected. Elevated IL-18BP has been described in several autoimmune diseases including rheumatoid arthritis [46, 79-81], in hepatitis C treated with IFN-α [82] and in patients with chronic liver diseases [83].

IL-18Rα- AND IL-18BP-BINDING CYTOKINE IL-1F7

The IL-1 homologue IL-1F7 has been discovered from expressed sequence tag database searches [84-87]. Among the several isoforms of IL-1F7, present exclusively in the human genome [88], the splice variant IL-1F7b can be matured by caspase-1 to give rise to a mature protein able to bind to IL-18Rα, although with low affinity (about 100-fold lower than that of IL-18) [89]. Possibly due to such low affinity, binding of IL-1F7b to IL-18Rα does not induce recruitment of the accessory chain IL-18Rβ, nor cell activation in terms of IFN-γ production [89]. Likewise, IL-1F7b does not antagonise the IFN-γ-inducing capacity of IL-18 [89]. A possible down-regulatory role in IL-18-induced activation has been suggested for IL-1F7 by the observation that IL-1F7 can bind to IL-18BP [20]. Indeed, binding of IL-1F7 to IL-18BP amplifies IL-18 inibition by IL-18BP. This can be explained by the fact that, similarly to what occurs with IL-1 bound to soluble IL-1RII [90], the IL-1F7 bound to IL-18BP can form a complex with the accessory chain IL-18Rβ and prevent it from forming a functional receptor complex [20]. A possible agonist activity (IL-12- and IFN-γ-dependent antitumour activity) has been also proposed for IL-1F7, based on results of *in vivo* gene transfer in the mouse [91]. Overall, the role of IL-1F7 in health and disease still needs to be fully explored. IL-1F7 transcripts have been detected in several normal tissues and in carcinoma cells [86, 89]. Of particular relevance however, is the fact that IL-1F7 is significantly expressed in monocytes [20], suggesting a role for IL-1F7 as natural modulator of IL-18 in the initiation of innate defence responses.

INHIBITORY RECEPTORS TIR8/SIGIRR AND RP105

Recent evidence attributes a regulatory role to at least two receptors of the TLR/IL-1R family, namely TIR8/SIGIRR [8-10], and RP105 [11, 12].

TIR8/SIGIRR is a unique receptor of the IL-1R/IL-18R superfamily which, at variance with other members of the family, encompasses a single Ig-like domain in its extracellular portion [92]. The intracellular domain of TIR8/SIGIRR has the highest similarity to the intracellular adapter MyD88 among members of the TLR/IL-1R family [93]. TIR8/SIGIRR does not interact with IL-1α, IL-1β or IL-1Ra, and its intracellular domain is unable to transduce signals [92]. On the other hand, TIR8/SIGIRR apparently plays a central role in the down-regulation of inflammation mediated by TLR/IL-1R. Indeed, TIR8/SIGIRR-deficient mice and cells are more susceptible to stimulation with IL-1, IL-18 and TLR agonists (LPS, CpG oligonucleotides), whereas TIR8/SIGIRR-overexpressing cells were less susceptible to IL-1 and IL-18 stimulation [9, 10]. TIR8/SIGIRR expression is ubiquitous; however, it is preferentially expressed by epithelial cells (kidney, gut, liver) and is possibly involved in the control of intestinal inflammation [8, 10]. On the other hand, TIR8/SIGIRR is poorly expressed in leukocytes and cannot be induced by a series of inflammatory/anti-inflammatory stimuli [8]. Notably, expression of TIR8/SIGIRR in the mouse was significantly decreased in every organ/cell following *in vivo* administration of LPS [8]. The mechanism by which TIR8/SIGIRR down-regulates TLR/IL-1R-mediated activation is possibly based on the ability of the TIR-containing intracellular domain of TIR8/SIGIRR to compete for the adapter MyD88 and the signalling intermediate TRAF6, thus removing them from the signal transduction pathway of TLR/IL-1R [9]. More recently, with the use of different deletion mutants of TIR8/SIGIRR it has been shown that while for inhibition of TLR4 signalling only the intracellular TIR-containing domain of TIR8/SIGIRR was necessary, the presence of the extracellular Ig-like domain was also required for inhibiting IL-1R signalling, possibly through interference with the interaction between IL-1R and IL-1RAcP [94].

RP105 (CD180) is a transmembrane receptor protein first identified in murine B cells and involved in B cell proliferation and protection from apoptosis [95]. The extracellular portion of RP105 is a leucine-rich repeat domain structurally similar to that of TLR, implying a role in pathogen sensing, in particular in mediating LPS effects on B cells [96, 97] in concert with the accessory molecule MD-1 [98, 99]. A possible down-regulatory role of RP105 can be hypothesized on the basis of a series of experimental evidence. In humans, anti-inflammatory M2-biased macrophages (tumour-associated macrophages generated *in vitro*) showed up-regulation of mRNA and protein expression for both RP105 and MD-1 [100]. In autoimmune patients with lupus, Sjögren's syndrome, and dermatomyositis, there is a significant increase in the population of RP105-negative B cells, which are responsible of autoantibody production [101-104]. Finally, recent data indicate that RP105, in concert with MD-1, can down-modulate TLR4/MD-2- and IL-1R-mediated activation by a still undefined mechanism [11, 12].

RECEPTOR T1/ST2 AND ITS LIGAND IL-33

T1/ST2 is a receptor of the IL-1R/IL-18R superfamily which, at variance with other receptors but similarly to TIR8/SIGIRR, does not induce an inflammatory response [105-108]. Initially, T1/ST2 was found to be unable to bind known members of the IL-1 family [109-111]. Two putative ligands of T1/ST2 have been identified; membrane and secreted protein which bound T1/ST2 with low affinity but which could not trigger TIR-dependent NFκB activation upon binding [109, 110]. Besides the membrane form of the receptor (ST2L), two alternatively spliced forms have been identified, the soluble ST2, corresponding to the extracellular domain of the membrane receptor [112], and the membrane-anchored ST2V protein [113]. T1/ST2 is preferentially expressed by fibroblasts, mast cells, and Th2 cells (as opposed to Th1 cells which selectively express the IL-18R) [114-116], and appeared to be involved in Th2 anti-inflammatory/allergic effector function [116-120]. It has been shown that T1/ST2 can down-regulate TLR2, TLR4, TLR9, and IL-1RI signalling, but not the MyD88-independent TLR3 signal transduction, based on the capacity of sequestering the adapters MyD88 and Mal through the intracellular TIR domain [7]. It was therefore hypothesized that all signalling pathways involving MyD88 and/or Mal may be regulated by T1/ST2. Recent data indicate that soluble ST2 could inhibit LPS-induced IL-6 production in THP-1 cells by inhibiting IκB degradation and the consequent binding of NFκB to the IL-6 promoter [121]. Recently, a novel member of the IL-1 family, IL-33, has been reported to be the specific ligand for T1/ST2 [5]. IL-33 is the eleventh identified member of the IL-1 family (IL-1F11), is synthesized as a pro-cytokine which should be cleaved by caspase-1 to generate the mature active form, and, within the IL-1 family, is most closely related to IL-18 [5]. Upon binding to T1/ST2, IL-33 recruits the IL-1RAcP as co-receptor (Michael U. Martin, personal communication), activates NFκB and MAP kinases, and induces IL-4, IL-5, and IL-13, but not IFN-γ, as expected for a Th2-type cytokine [5, 122]. *In vivo* administration of IL-33 in mice induces pathological changes such as eosinophilic infiltration and mucus secretion in airways and intestine, and increase in IgA and IgE, all effects consistent with classical Th2 diseases, such as asthma [5]. Mice deficient in T1/ST2 do not develop a Th2 response to Schistosoma egg antigen [118]. Thus, many of the inflammation-inhibitory effects of T1/ST2 activation may be due to activation of Th2 regulatory responses. Physiologically, T1/ST2 is induced by inflammatory stimuli, and appears to be involved in the late control of the inflammatory response (presumably by activating anti-inflammatory Th2 cells), including endotoxin tolerance [7, 107, 123]. In clinical situations, expression of T1/ST2 in human breast tumours is predictive of relapse-free survival [124]. Soluble T1/ST2 was found at increased levels in serum of patients with pulmonary inflammation [125], heart failure [126], and autoimmune lupus [127], and in the CSF of patients with subaracnoid hemorrhage [128]. The role of T1/ST2 in chronic inflammatory pathologies and autoimmune diseases still needs to be fully explored. In a first study in an experimental model of arthritis (collagen-induced arthritis in the mouse), the use of a fusion protein composed of soluble T1/ST2 coupled to the Fc immunoglubulin portion could achieve a significant decrease in the circulating levels of inflammatory cytokines and a pro-

found reduction in the pathology (joint infiltration and erosion, synovial hyperplasia) [129].

INTRACELLULAR NOD-LIKE RECEPTORS

NOD-like receptors (NLR) are a family of intracellular proteins that share some structural features with TLR/IL-1R and are involved in the regulation of apoptosis, inflammation, and host defence [130-133]. Structurally, NLR proteins usually include three distinct domains: the N-terminal effector-binding domain (*e.g.*, CARD, caspase-recruitment domain), the nucleotide-binding oligomerisation domain (NOD), the C-terminal ligand-recognition domain. The latter is mostly a leucine-rich repeat similar to the binding domain of TLR receptors and of RP105. The increasingly growing family of NLR encompasses members of animal, plant, fungal and bacterial origin, including over 20 human proteins. The ability of NLR to activate or inhibit caspases (either directly or through adapter proteins, by homotypic CARD-CARD interaction, in a intracellular complex called inflammosome) is at the basis of their involvement in regulation of apoptosis (activation of apoptotic caspases) and inflammation (activation of caspase-1 and subsequent maturation of IL-1 and IL-18, activation of caspase-3 and subsequent degradation of IL-18) [134-139]. It has been suggested that NLR, in particular NOD1 (CARD4; ubiquitously expressed) and NOD2 (CARD15; expressed mainly by monocytes and antigen-presenting cells), are involved in intracellular pathogen sensing, as they can recognise different moieties of Gram-negative peptidoglycans and initiate the inflammatory defence response [140-147]. Of particular interest is the recent notion that different mutations in the gene coding for NOD2/CARD15 underlie the intestinal inflammatory disease of a significant proportion of Crohn's disease patients [144, 145, 148-155], and is at the basis of the auto-inflammatory disease Blau syndrome (or familial juvenile systemic granulomatosis, a rare form of uveitis, arthritis, and dermatitis) [151, 156-158]. Based on these observations, it was proposed that NOD2 acts physiologically as an activator of the TLR2-dependent anti-inflammatory response and IL-10 production, thus its loss-of-function mutations result in excessive TLR2-dependent activation of Th1 responses and persistent inflammation [159, 160].

Mutations in another protein of the NLR family, NALP3, are apparently involved in systemic inflammatory diseases, a series of autosomal dominant, severe pathologies characterised by persistent and generalised inflammation. These diseases include the Muckle-Wells syndrome (characterised by recurrent fevers, leukocytosis, cold-urticaria, painful arthropathies, serum amyloid A and CRP elevations, chronic conjuctivitis, uveitis, rashes, death due to renal amyloidosis), the chronic infantile neurological cutaneous and articular (CINCA) syndrome and the neonatal onset multisystem inflammatory disease (NOMID) (both characterised by intermittent fevers, chronic sterile meningitis, uveitis, sensorineural hearing loss, urticarial skin rash, deforming arthritis), and the familial cold autoinflammatory syndrome (FCAS) (urticarial skin rash, arthropathies, fever, leukocytosis, serositis). These diseases are all due to gain-of-function/loss-of-inhibition mutations in the NACHT nucleotide-binding site domain of NALP3 [136, 161-163]. NALP3 (cryopyrin) displays an N-terminal PYR effector binding domain, which interacts with the PYR domain of the adapter protein ASC, which in turn activates caspase-1 maturation after homotypic CARD-CARD interaction. Disease-related mutations in NALP3 cause de-regulation of NALP3 signalling which induces persistent activation of caspase-1, with subsequent increase in the production of caspase-1-dependent inflammatory cytokines (IL-1, and possibly IL-18) and establishment of the chronic inflammatory disease [130, 131, 136, 162, 164]. Very interestingly, the clinical symptoms of diseases due to increased or poor control of caspase-1 activity (CIAS, Muckle-Wells syndrome, adult onset Still's disease, systemic onset juvenile idiopathic arthritis) often include skin rashes and/or pruritic urticaria. This is likely due to the fact that caspase-1 is also responsible for the maturation of IL-33, which through T1/ST2, activates Th2 responses, IgE production, and mast cell degranulation. A schematic representation of the NALP3 inflammosome is shown in *figure 3*.

IL-18 IN AUTOIMMUNITY

Increased levels of IL-18 often correlate with the severity of autoimmune pathologies in experimental models of autoimmunity and also in clinical situations. That IL-18 may have a pathologic/pathogenic role is been suggested by the fact that blocking IL-18 has a beneficial effect in several models of autoimmune/inflammatory diseases (*table 1*).

Multiple sclerosis

The possible pathological role of IL-18 in EAE (experimental autoimmune encephalitis, the experimental model of multiple sclerosis) has been suggested by the correlation of the level of steady state mRNA for IL-18 and caspase-1 with the severity of the disease stage [165, 166]. Moreover, IL-18-treated antigen-specific T cells successfully transferred the disease to normal recipients [167]. On the other hand, IL-18-deficient mice were reportedly resistant to disease induction [168], whereas caspase-1 deficient mice exhibit decreased disease severity [169]. Recent data however claim that deletion of the IL-18 gene does not affect susceptibility to disease induction, whereas deletion of the IL-18Rα gene does [69]. The evidence is that accessory cells of IL-18Rα-deficient mice do not support the development of IL-17-producing T helper cells (Th17), responsible for the pathology [69]. That IL-18 is anyway involved in EAE (either by Th1 activation or possibly by amplifying the Th17 response) is suggested by the use of neutralising anti-IL-18 antibodies, which inhibited autoantigen-induced IFN-γ production by T cells *in vitro* and cerebral lesions *in vivo* [166], and by the targeted overexpression of IL-18BP in the CSN that increases Th2 polarisation and suppresses ongoing EAE [170].

In human multiple sclerosis, there are reports that disease activity correlates with elevated circulating and CSF levels of IL-18 and caspase-1. In addition, IL-18 positive cells have been observed in demyelinating lesions [171-181].

Myasthenia gravis

In experimental myasthenia gravis in the rat, blockade of IL-18 with specific antibodies suppresses disease develop-

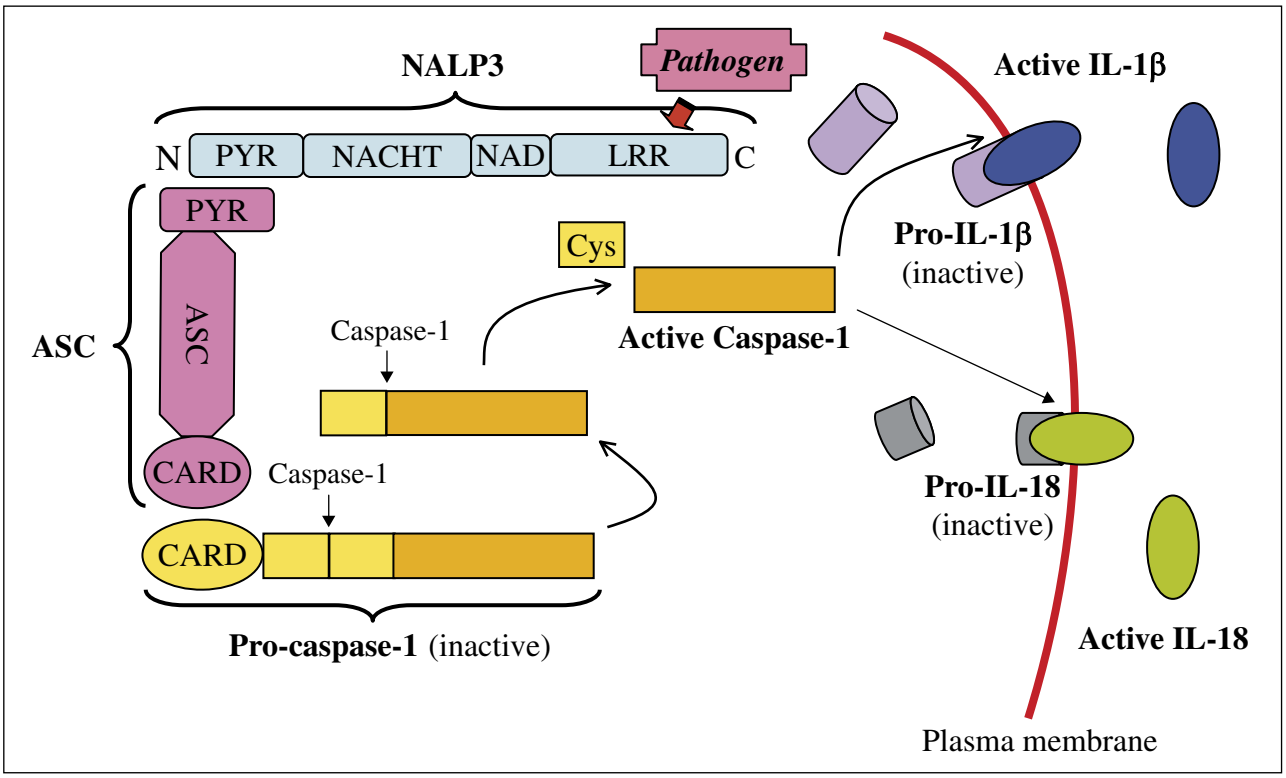

Figure 3

The IL-1β/IL-18 inflammosome.
Schematic representation of the IL-1β/IL-18 inflammosome. Activation of an intracellular NOD-like receptor (here NALP3, as an example), through interaction of its LRR domain with a pathogen structure, induces formation of the inflammosome complex, where the PYR domain of NALP3 interacts with the homologous domain of the adapter protein ASC, which in turn binds to inactive pro-caspase-1 through homotypic interaction of their CARD domains. Pro-caspase-1 is then matured into active caspase-1 by sequential cleavages by active enzyme molecules. Active caspase-1 is responsible for cleavage of inactive intracellular precursor forms of IL-1β, IL-18, and possibly IL-33, and of their extracellular export (see *figure 1*).

ment [182, 183]. In a murine model of myasthenia gravis, IL-18 deficiency (IL-18-/- mice) suppressed the generation of anti-acetylcholine receptor autoantibodies [184]. Elevated circulating IL-18 occurs in humans with myasthenia gravis [185, 186].

Rheumatoid arthritis

In experimental models of arthritis, administration of IL-18 exacerbated the disease. Initial studies were carried out using streptococcal cell wall (SCW)-induced arthritis [187]. A neutralising rabbit anti-murine IL-18 antibody was injected shortly before induction of arthritis by intra-articular injection of SCW fragments. Significant suppression of joint swelling (> 60%) was noted on days 1 and 2 of SCW arthritis after blockade of endogenous IL-18, and joint TNF-α and IL-1 levels were also decreased. Severe reduction of chondrocyte proteoglycan synthesis is a prominent component of SCW-induced arthritis but a near

Table 1
Reduction in autoimmune and/or inflammatory disease severity upon neutralisation of endogenous IL-18

(DSS) dextran sodium sulfate-induced colitis	[331, 333, 334]
(TNBS) trinitrobenzene sulfonic acid-induced colitis	[330, 334]
CD62L transfer-induced colitis	[337]
(SCW) Streptococcal Cell Wall-induced arthritis	[187]
Collagen-induced arthritis	[193-195]
Steptozotocin-induced diabetes	[395]
EAE in rats	[166]
Experimental myasthenia gravis in rats	[182, 183]
Diabetes in NOD mice	[396]
ConA-induced hepatitis	[427, 461]
Endotoxin-induced pulmonary neutrophils	[462]
Ischemia-induced acute renal failure	[463]
Ischemia-induced myocardial dysfunction	[464, 465]
Endotoxin-induced myocardial dysfunction	[466]
Nephritis and lymphadenopathy in murine lupus	[294, 295]

complete reversal of the depressed chondrocyte proteoglycan synthesis was observed in the anti-IL-18-treated animals. These studies clearly established the pathological role for endogenous IL-18 in this model. The effect of IL-18 is apparently independent of IFN-γ since anti-IL-18 antibodies could equally inhibit SCW arthritis in mice deficient in IFN-γ [184]. That IL-18 is pathogenic in experimental group B strepococcal arthritis was confirmed by amelioration of the disease upon administration of anti-IL-18 antibodies and exacerbation following administration of exogenous IL-18 in mice [188].

IL-18 also plays a role in collagen-induced arthritis (CIA) [189-191]. IL-18 was injected into DBA-1 mice immunised with collagen in incomplete Freund's adjuvant. There was an increase in the erosive and inflammatory component of the condition [192]. Using mice deficient in IL-18, CIA was less severe compared to wild-type controls [190]. Histological evidence of decreased joint inflammation and destruction was observed. Levels of bovine collagen-induced IFN-γ, TNF-α, IL-6 and IL-12 from spleen cell cultures were decreased in IL-18-deficient mice. Thus, there is likely a pathological role for IL-18 in CIA. However, it should be noted that IL-18 can also have a beneficial effect, as serum anti-collagen antibody levels are significantly reduced in the IL-18-deficient mice.

Blocking of IL-18 was used in CIA models [193-195]. Wild-type DBA-1 mice were treated with either neutralising antibodies to IL-18 or the IL-18BP after clinical onset of disease. The therapeutic efficacy of neutralising endogenous IL-18 was assessed using different pathological parameters of disease progression. The clinical severity in mice undergoing CIA was significantly reduced after treatment with either IL-18 inhibitor [195]. Attenuation of the disease was associated with histological evidence of reduced cartilage erosion. The decreased cartilage degradation was further documented by a significant reduction in the levels of circulating cartilage oligomeric matrix protein (an indicator of cartilage turnover). Both IL-18 inhibitory strategies efficiently slowed disease progression, but only anti-IL-18 antibody treatment significantly decreased an established synovitis. Serum levels of IL-6 were significantly reduced with both neutralising strategies. *In vitro*, neutralising IL-18 resulted in a significant inhibition of TNF-α, IL-6, and IFN-γ secretion by macrophages [195]. Mice with established CIA (21 days after the primary immunisation with collagen) were treated for 3 weeks with murine IL-18BP as a fusion protein with the Fc portion of murine IgG1 [194]. Both the clinical disease activity scores and the histological scores of joint damage were reduced by 50%. Proliferation of collagen-stimulated spleen and lymph node cells, as well as the change in serum levels of IgG1 and IgG2a antibodies to collagen, were also decreased. Cell sorting analysis showed a decrease in spleen NK cells and an increase in $CD4^+$ T cells. The production of IFN-γ, TNF-α, and IL-1β in cultured spleen cells was reduced. The steady state mRNA levels of IFN-γ, TNF-α, and IL-1β in isolated joints were likewise decreased. Thus, the mechanisms of IL-18BP inhibition of CIA include reduction in cell-mediated and humoral immunity to collagen as well as a decrease in production of proinflammatory cytokines in the spleen and joints. In CIA of BB rats, administration of IL-18 exacerbated arthritic symptoms, whereas anti-IL-18 neutralising antibodies attenuated CIA [196].

Employing an adenoviral vector containing the murine IL-18BP, intra-articular over-expression of IL-18BP significantly reduced the incidence of CIA in treated knee joints [193]. Affected knee joints of IL-18BP-treated mice showed less severe arthritis, with reduced cellular infiltration and less bone erosion. Reduction in cartilage loss was also observed in treated mice. IgG1 anti-collagen type II antibodies were similar to those in the control vector group.

In experiments with mice deficient in IL-18 or in IL-12p40 (lacking both IL-12 and IL-23), antigen-induced arthritis could develop in IL-18-deficient mice as well as in wild type animals, whereas no disease symptoms or antibodies to methylated BSA were evident in mice lacking IL-12p40 [197]. Additional studies with IL-12p35-deficient mice (lacking IL-12 only) and with IL-23p19–deficient animals (lacking IL-23 only) showed that only IL-23-deficient mice were resistant to disease induction [198]. Thus, the role of IL-18 (as well as IL-12) in experimental arthritis appears to be redundant, as compared to the key role for the IL-12p40 cytokine IL-23.

In human rheumatoid arthritis (including juvenile RA, adult-onset Still's disease, and psoriatic arthritis), IL-18 is present at increased levels in serum and in the rheumatoid synovium, as well as in the bone marrow [79-81, 192, 199-220]. Rheumatoid subcutaneous nodules have the features of Th1 granulomas, with abundant expression of inflammatory cytokines including IFN-γ and IL-18 [221]. Polymorphisms in the promoter region of the IL-18 gene have been found associated with adult onset Still's disease, RA, and juvenile arthritis [219-226]. IL-18 bioactivity in affected joints of patients with rheumatoid arthritis has been reported to correlate with disease activity [202, 227, 228]. IL-18 is mainly present as precursor protein, but the mature active form is also abundantly detected in macrophages and synovial fibroblasts. IL-18Rα and β receptor chains are found expressed on patients' T lymphocytes, macrophages, and synoviocytes [79, 192, 202, 229, 230]. Elevated levels of IL-18BP are also present [46, 79, 80]. Synovial tissue from 29 patients with rheumatoid arthritis has been studied using specific staining for IL-18. IL-18 was detectable in 80% of the patients, in both the lining and sublining of synovial tissues from knees. There was a strong correlation between IL-18 and IL-1β expression but less with TNF-α staining [210]. Moreover, IL-18 expression correlated with macrophage infiltration and local inflammation scores. IL-18 staining also correlated with the erythrocyte sedimentation rate, a biomarker of systemic inflammation. Of considerable interest was the observation that in patients with co-expression of IL-18 and IL-12, there were also greater levels of IL-17 [231]. Blocking of endogenous IL-17 with specific inhibitors resulted in a protective inhibition of bone destruction [231-233]. Furthermore, IL-18 can inhibit chondrocyte proliferation and induce production of stromelysin and the inflammatory enzymes iNOS and COX-2, and promote cartilage degradation and glycosaminoglycan release [234]. IL-18 was also found to be able to induce production of serum amyloid A in RA synoviocytes, and to be responsible for acute liver failure in adult onset Still's disease [235, 236]. More-

over, IL-18 participates in anomalous macrophage activation in hemophagocytic syndrome, a clinicopathological entity associated with adult onset Still's disease, juvenile chronic arthritis, and possibly lupus erythematosus [237]. It is therefore conceivable to hypothesize a role for IL-18 in the maintenance of the destructive autoimmune and inflammatory processes of rheumatoid diseases, perhaps also by regulating the activities of IL-1β, TNF-α, IFN-γ, and IL-17. Indeed, treatments that ameliorate rheumatoid pathology concomitantly decrease IL-18 production [238]. The possibility of targeting IL-18 in the treatment of arthritis and more generally of chronic inflammatory diseases, is therefore receiving increasing attention [192, 239-249].

Autoimmune uveitis and Behcet's disease

IL-18 is constitutively expressed in the epithelial cells of iris, ciliary body, and retina of normal mice, and is found at elevated levels after induction of experimental uveoretinitis (EAU) in susceptible rats and mice [250-252]. However, IL-18-deficient DBA1 mice were fully susceptible to induction of EAU, suggesting that the role of IL-18 is not essential to disease development [251]. Indeed, the non-essential, redundant role of IL-18 in the pathogenesis of EAU was confirmed in mice deficient in MyD88 or IL-1R, which were resistant to CFA-induced disease, whereas mice deficient in IL-18, TLR9, TLR4, or TLR2 were fully susceptible [252].

In human Behcet's disease, a strong Th1-skewed response is apparently associated with disease severity. Elevated expression of IL-18 is found in serum, skin lesions, and pulmonary lavage fluid, and increased IL-18 production was observed in bronchoalveolar cells *upon in vitro* stimulation [210, 253-256]. Although no particular polymorphism in the IL-18 promoter gene could be associated with disease sucsptibility, a clear correlation was found between a particular genotype and the risk of developing ocular lesions [257].

Psoriasis

In psoriasis, serum IL-18 levels correlate with disease severity and skin lesions, and increased IL-18 expression can be found in psoriatic keratinocytes [258-262]. Normal keratinocytes produce IL-18 but do not process it, conceivably because of the lack of the cleaving enzyme caspase-1 [262]. However, inflammatory and toxic agents (LPS, dinitrochlorobenzene, UVB) can induce production of biologically active IL-18 in keratinocytes, while immunosuppressive agents such as 1,25-dihydroxyvitamin D3 decrease it [263-267]. While caspase-1 induction and activation can be hypothesized in inflamed keratinocytes, potent caspase-1 activity and IL-18 production is present in activated Langerhans and dendritic cells in the skin [268-270]. In psoriasis and atopic dermatitis, the IL-18Rα is upregulated in keratinocytes with consequent inflammatory activation in response to IL-18 [271]. High levels of IL-18 have been detected in serum and scales of psoriatic patients [272-275], which correlate with disease severity, and are possibly relevant to the pathogenesis of skin lesions [276]. In mice overexpressing mature IL-18 in the skin, a stronger and persistent inflammatory skin reaction could be achieved in response to topical irritants as compared to controls [277]. Approaches to inhibit IL-18 in autoimmune skin diseases are underway [272, 278, 279].

Autoimmune thyroiditis

Analysis of inflammatory cytokine expression in the obese strain of chickens (a model of spontaneous autoimmune thyroiditis) showed upregulation of IL-18 expression, along with other cytokines, in the thyroid of autoimmune chicken as compared to normal birds [280]. In experimental autoimmune thyroiditis, IL-18 showed the same capacity as LPS in inducing TNF-α and autoreactivity in IL-12 p40-deficient mice [281]. Increased IL-18 can be found in serum and thyrocytes of patients with autoimmune Hashimoto's thyroiditis and Graves' ophthalmology [282-285]. In corticosteroid-responding patients, treatment with methylprednisolone could induce a significant decrease in the circulating IL-18 levels paralleling an amelioration of disease symptoms [284]. However, in another study, no increase in IL-18 levels in serum or orbital tissue of Graves' ophthalmology patients could be found when compared to normal individuals [286, 287]. A closer analysis of the serum of patients as compared to healthy controls apparently showed that an IL-18 increase is evident in Hashimoto's thyroiditis, which is mainly a Th1 disease, whereas Grave's ophthalmology is mostly characterized by an increase in Th2 cytokines (IL-4, IL-5) with no clear-cut enhancement of IL-18 levels [288]. No association between autoimmune thyroid disease with or without diabetes and a particular polymorphism of the IL-18 gene could be found [289].

Systemic lupus erythematosus, Sjögren syndrome, and autoimmune myopathies

In different models of murine lupus, including the MRL/MP *lpr/lpr* mouse (a model of the lupus autoimmune lymphoproliferative syndrome ALPS, and of Sjögren syndrome), elevated IL-18 levels were found in serum and organs, including kidney [290-294]. Inhibition of IL-18 effects in *lpr/lpr* mice resulted in a delay in disease development and a decrease in its severity [293-296]. Elevated plasma levels of IL-18 can be detected and correlate with disease activity and renal damage in human SLE [291, 297-314], so that therapeutic strategies targeting IL-18 are envisaged [315-319]. Increased expression of the IL-18 protein can be detected in serum, salivary gland and lacrimal duct tissues of Sjögren's syndrome patients and of affected mice [212, 320-322]. IL-18 has been found to cause atrophy of the lacrimal and salivary glands through elevation of NO production [322]. In autoimmune inflammatory myopathies (dermatomyositis and polymyositis), high levels of IL-18 could be found both in serum and in muscle biopsies of patients [323]. IL-18 was produced by macrophages and dendritic cells in the affected tissue, while the IL-18 receptor was upregulated in $CD8^+$ T cells and endothelial cells.

Inflammatory bowel disease (IBD) and Crohn's disease

Several reports support the possible involvement of IL-18 in the pathogenesis of Crohn's disease, an autoimmune

inflammatory bowel disease characterised by a pathogenic role of Th1 cells. The role of IL-18 in inducing/perpetuating intestinal inflammation is also evident in non-autoimmune conditions, e.g. in shigellosis or by direct administration [324-327], with a strict correlation between the presence of IL-18 and the severity of inflammation. In experimental models of colitis in the mouse and rat, the inflammatory pathology correlates with increased levels of tissue and serum IL-18, whereas anti-IL-18 antibodies, IL-18 antisense mRNA, and the inhibitory IL-18BP can decrease the pathological signs [328-342]. In addition, induction of experimental colitis could not be achieved in IL-18-deficient mice [332], whereas mice overexpressing IL-18 are significantly more susceptible to induction of experimental colitis [343]. Drugs that inhibit development of experimental colitis inhibit, in parallel, IL-18 expression [344, 345]. Mice deficient in caspase-1, the enzyme that matures both IL-1 and IL-18, were also resistant to induction of experimental colitis, which was paralleled by a significant decrease in the spontaneous production of IL-1, IL-18 and IFN-γ [336, 346]. Similar inhibition of colitis was obtained by treatment with inhibitors of caspase-1 [336, 347]. Mice deficient in the interferon regulatory factor-1 develop a significantly more severe experimental colitis. The increased severity does not correlate with changes in the expression of tissue IL-18, but levels of colonic IL-18BP were drastically reduced. Administration of exogenous IL-18BP could reverse the severity of the disease [348]. The ability of IL-18 to prevent immunological tolerance to orally administered antigens may contribute to the establishment of autoimmune gut disease [349]. In human Crohn's disease, ulcerative colitis, and coeliac disease, increased levels of IL-18 are found in serum, and IL-18, IL-18R chains, and active caspase-1 are increased in chronically inflamed mucosa as compared to early lesions or to normal colonic mucosa [350-362]. Increased IL-18 is evident in mucosal epithelial cells, but is also due to the increase in IL-18-producing DC-SIGN$^+$ mucosal DC in Crohn's patients [363]. Moreover, IL-18 is a potent proliferative stimulus for intestinal mucosal lymphocytes of Crohn's patients, which, at variance with normal mucosal lymphocytes, show upregulation of the IL-18R chains and are therefore constitutively susceptible to IL-18 activation [339, 364, 365]. Polymorphisms in the promoter and/or coding region of the IL-18 gene have been found to be associated with either increased susceptibility to Crohn's disease and ulcerative colitis, or to disease severity to varying degrees depending on the population cohort [366-370].

Levels of the IL-18 natural inhibitor IL-18BP are also increased in the plasma of patients with Crohn's disease and ulcerative colitis [78, 360]. This mechanism of control of IL-18 activity however, does not appear to be effective, as the overall levels of free active IL-18 (*i.e.* not bound and inhibited by IL-18BP) are still signficantly higher in Crohn's patients [360]. That IL-18BP is an important player in controlling intestinal damage is suggested by data from experimental models. The increased severity of experimental colitis in IRF-1-deficient mice is associated with decreased levels of colon IL-18BP [348], while the gut lesions in experimental colitis are decreased by administration of IL-18BP [333].

Intestinal inflammation and damage in experimental colitis is associated with an increase in active caspase-1 in the tissue [340, 371, 372]. It is interesting to note that intestinal parasites such as *Entamoeba histolitica* cause intestinal damage through proteases with caspase-1 activity [373]. Agents that induce apoptosis of colonic epithelial cells concomitantly increase active caspase-1, and inhibition of caspase-1 activity concomitantly inhibits mucosal cell death [374, 375]. Association of Crohn's disease with loss-of-function mutantions in the gene of NOD2/CARD15, an intracellular protein involved in the caspase-1-activating inflammasome in macrophages, further underlines the importance of caspase-1 products such as IL-18 in the pathogenesis of the disease [143, 144, 148-155, 376, 377]. Treatments that provide therapeutic benefits in Crohn's patients (e.g. anti-TNF-α antibodies) re-establish appropriate apoptosis of mucosal lymphocytes by increasing the pro-apoptotic caspase pathway [378]. It is notable that therapy-induced increase of caspase-3, which has a major role in lymphocyte apoptosis, is concomitantly expected to decrease the levels of active IL-18, as casapse-3 is the main IL-18 degrading enzyme [379]. Biological therapies targeting IL-18 and other inflammatory cytokines mainly produced by macrophages, are being developed for more effective treatment of IBD [380-383].

Autoimmune type I diabetes (IDDM)

In murine models of insulin-dependent diabetes (IDDM) (NOD mice, streptozotocin, reovirus type 2), IL-18 correlated with disease progression and severity [384-392]. Islets from a non-obese, diabetic mouse strain exhibited IL-18 expression prior to T cell invasion [393], and IL-18 administration promoted disease development [394]. In the genetically diabetic NOD mouse, the IL-18 gene colocalizes to the same region of chromosome 9 as the diabetes susceptibility gene *idd2* [385]. NOD mice overexpressing a diabetogenic TcR have increased production of IL-18, IL-12 and TNF-α [388]. On the other hand, experimental IDDM induction could be prevented in IL-18-deficient mice or with administration of IL-18BP [394-396]. However, there is evidence that IL-18, when administered exogenously to adult NOD mice, can delay the disease onset [387]. On the other hand, in a different study, systemic administration of IL-18 by means of IL-18-expressing plasmid delivery did promote diabetes development in young NOD mice [393]. This discrepancy may be explained in light of the dual role of IL-18 as modulator of either Th1 or Th2 responses depending on the cytokine micro-environment [397]. In addition, in response to inflammatory stimuli, islet β cells can produce IL-18 but do not express the IL-18R chains, suggesting that IL-18 does not have a direct effect on them [398]. In fact, *in vitro* treatment of pancreatic islets with IL-18 does not have a significant effect on insulin accumulation, or on glucose-stimulated insulin release [399]. Activation of the IL-1- and IL-18-converting enzyme caspase-1, increases in pancreatic and retinal tissues during diabetes development in mice and correlates with increased apoptosis [400-402]. Inflammatory stimuli such as IFN-γ and TNF-α increase both caspase-1 expression and activation, and apoptosis in

pancreatic β cells [403], while inhibitors of caspase-1 could block β cell apoptosis [404]. However, caspase-1 processing of IL-18 or IL-1β does not appear to be an absolute requirement in the pathogenesis of autoimmune diabetes, since NOD mice deficient for expression of caspase-1 fully develop both the spontaneous and the chemically-induced (streptozotocin) disease [405].

In human IDDM, elevated IL-18 levels can be detected in high-risk individuals, before the development of the disease [406], whereas in patients there is a correlation between IL-18 levels and autoantibody status [407]. As in mice, the human gene for IL-18 maps to an interval, on chromosome 9, where the diabetes susceptibility locus *Idd2* resides [408].

Although many of the autoimmune effects of IL-18 in different models and clinical situations are mediated through IFN-γ, and are amplified by IL-12, in some experimental models a direct pathological role for IL-18 has been described. However, IL-18 cannot be considered as an exclusively Th1 cytokine, as its presence may be unrelated to that of IFN-γ. Indeed, IL-18 takes part in the Th17 responses by amplifying the IL-17 production of polarised Th17 cells in synergy with IL-23, thus contributing to the destructive inflammation in several chronic inflammatory, autoimmune diseases [18]. On the other hand, IL-18 can act as a Th2 cytokine in some circumstances [397]. Indeed, in the presence of IL-4 and IL-2, IL-18 can induce significant production of the Th2 cytokines IL-4 and IL-13 by Ag-stimulated T cells, whereas IFN-γ is produced in the absence of IL-4 [409, 410]. Moreover, IL-18R is present on mast cells and basophils, which produce large amounts of IL-4 and IL-13 in response to IL-18 and IL-3 [411]. Thus, IL-18 has been found to play a dual role in Th2-dependent responses such as in helminthic infections and allergic asthma in the mouse. Together with IL-12, IL-18 can suppress IgE production, Th2 cell development, lung hyper-reactivity and eosinophil infiltration, by biasing the immune response to allergen towards Th1 [397, 412, 413]. Moreover, IL-18 deletion could enhance pulmonary eosinophil infiltration [414, 415]. On the other hand, administration of IL-18 induced eotaxin production and subsequently provoked enhanced eosinophil accumulation in pulmonary lesions, and also induced increased synthesis of Th2 cytokines and IgE [410, 415-418]. Thus, although IL-18 has a major role in inflammatory responses, it can become an anti-inflammatory, Th2-biasing factor depending on the cytokine micro-environment (e.g., presence or absence of IL-12).

IL-18 IN METABOLIC SYNDROME

As mentioned above, several properties of IL-18 are independent of IFN-γ, e.g., induction of joint inflammation and induction of septic shock. In contrast to other proinflammatory cytokines such as IL-1β, TNF-α or IL-12, there is a constitutive intracellular pool of the IL-18 precusor [419], and exposure to inflammatory stimuli has little effect on IL-18 gene transcription. The increase in mature IL-18 observed under these circumstances is largely due to caspase-1-mediated cleavage of pro-IL-18. In addition, it is thought that the bioactivity of IL-18 is kept in balance by high concentrations of IL-18BP in blood and tissues [71].

In humans, IL-18 concentrations are reported to be increased in patients with type 2 diabetes mellitus, in obese individuals with the metabolic syndrome [71]. Infusion of glucose into normal volunteers and patients with impaired glucose tolerance induces an acute increase in serum IL-18 concentrations. It has been therefore hypothesized that the increased IL-18 concentrations have a pathophysiological role in insulin resistance and lipid deposition.

Unexpectedly, we observed that IL-18-deficient mice have a markedly increased body weight compared to the wild-type littermates of the same age, and have found that in the absence of IL-18, mice develop several features characteristic of the metabolic syndrome: obesity, insulin resistance and hyperglycemia, lipid abnormalities, atherosclerosis [420]. We reported these pathological conditions associated with the metabolic syndrome in mice deficient in IL-18 or the IL-18Rα chain, as well as in mice transgenic for expression of IL-18BP [420]. These mice, in contrast to wild-type mice, eat several times a day and the increased food intake accounts for the obesity. IL-18 deficiency results in a loss of the circadian regulation of food intake and appetite suppression [420]. Because of the large, constitutively-expressed intracellular pool of the IL-18 precursor, especially in liver cells, additional roles for the cytokine other than those played in innate immunity are suspected, and the loss of appetite control appears to a manifestation of the non-immune mechanisms of IL-18.

Obesity in IL-18-deficient mice was due to accumulation of fat tissue based on increased food intake. IL-18-deficient mice also displayed hyperinsulinemia, consistent with insulin-resistance and hyperglycemia. Further analysis of the glucose metabolism in IL-18-deficient mice showed insulin resistance at the hepatic level causing hyperglycemia in these mice, with enhanced expression of gluconeogenesis genes in the liver. In addition, the molecular mechanisms responsible for the hepatic insulin resistance in the IL-18-deficient mice likely involved defective phosphorylation of STAT3, one of the intracellular pathways activated by IL-18. In contrast, MyD88, which mediates a second pathway of activation by IL-18 receptor, was not involved in this process. Recombinant IL-18 reversed hyperglycemia in IL-18-deficient mice through activation of STAT3 phosphorylation. These findings demonstrate a new role of the cytokine IL-18 in the homeostasis of energy intake and insulin sensitivity.

Role of IL-18 in the loss of insulin-producing β-cells

Several studies report that the levels of IL-18 in various transplant models, as well as in kidney transplant patients, correlate with graft failure. Using mice that overproduce IL-18BP as diabetic islet graft recipients, it was reported that IL-18 indeed plays a role in the damage inflicted upon transplanted islets. In view of the wide distribution of IL-18-producing cells, it was essential to identify the cellular sources of the damaging IL-18. To address this issue directly, islets from IL-18-deficient mice were transplanted into wild type mice recipients resulting in a greater survival compared to wild-type islets transplanted into wild-type mice [421]. This finding supports the concept of local endogenous islet IL-18 being sufficient to promote β-cell injury during islet transplantation. In fact, lack of islet-derived IL-18 from grafted islets resulted in a similar outcome to that obtained by reduced activity of IL-18 in

mice transgenic for IL-18BP, suggesting that host-derived IL-18 plays a negligible role in islet graft failure [421].

Deficiency in IL-18 and IL-18Rα reveal distinctly opposing phenotypes

An unexpected finding emerged upon transplantation of islets from IL-18Rα-deficient mice into wild-type recipient mice. It was anticipated that implantation of islets that lack IL-18Rα would result in a similar protected phenotype as that of IL-18-deficient islets. However, graft failure in IL-18Rα-deficient islets was accelerated compared to islets from wild-type donors [421]. Remarkably, the median survival time of IL-18Rα-deficient islets grafted into a wild-type diabetic host was 9 days whereas the median survival time of IL-18-deficient islets in a wild-type host was 14.5 days [421]. One explanation is that excess IL-18 from IL-18Rα-deficient islets exits into the surrounding host tissue where it triggers the production of IL-18-induced injurious mediators. In fact, IL-18Rα-deficient islets spontaneously produce 2-fold greater IL-18 levels. IL-18Rα deficient splenocytes also produced more IL-18 than wild-type cells. However, isolated IL-18Rα-deficient macrophages, although unresponsive to IL-18, produced more TNF-α than wild-type macrophages *in vitro*. This finding challenged the underlying assumption that the IL-18Rα is specific to the IL-18 pathway, and prompted further examination of the differences between IL-18 and IL-18Rα-deficient cells.

Alternate signaling of IL-18Rα

The unexpected increase in islet failure, observed in wild-type mice transplanted with islets from IL-18Rα-deficient mice, was associated with increased spontaneous production of IL-18 from IL-18Rα-deficient islets and splenocytes, and of TNF-α from macrophages. Splenocytes from IL-18Rα-deficient mice stimulated *in vitro* by ConA, TLR2 engagement or by anti-CD3 antibodies consistently produced more proinflammatory cytokines compared to wild-type cells, whereas IL-18-deficient cells produced less than wild-type [421]. For example, IL-18Rα-deficient splenocytes released nearly three-fold greater TNF-α and MIP-1α than IL-18-deficient cells upon stimulation by *Staphylococcus epidermidis*.

The divergence of responses between IL-18Rα- and IL-18-deficient cells is unexplained. More likely, the data suggest the existence of an IL-18-independent inhibitory pathway that converges with the IL-18 pathway at the IL-18Rα. Accordingly, in cells deficient in the receptor, a putative inhibitory signal, along with the pro-inflammatory IL-18 signal pathway, is absent. Gutcher *et al*. also provided clear evidence that an IL-18-independent engagement of IL-18Rα exists [69]. In murine experimental autoimmune encephalomyelitis (EAE), IL-18-deficient mice are susceptible to disease progression whereas IL-18Rα-deficient mice are protected. As such, these investigators concluded that there are two distinct pathways converging on the IL-18R: one signal requires IL-18 and the other involves an unknown ligand.

The study comparing islet survival in IL-18- and 18Rα-deficient mice differs from the EAE model in several aspects. Islets from mice deficient in IL-18 or IL-18Rα implanted into a wild-type animal allow for responses of an intact immune system to the genetically altered cells. In the EAE, altered immune system responses are inherent to

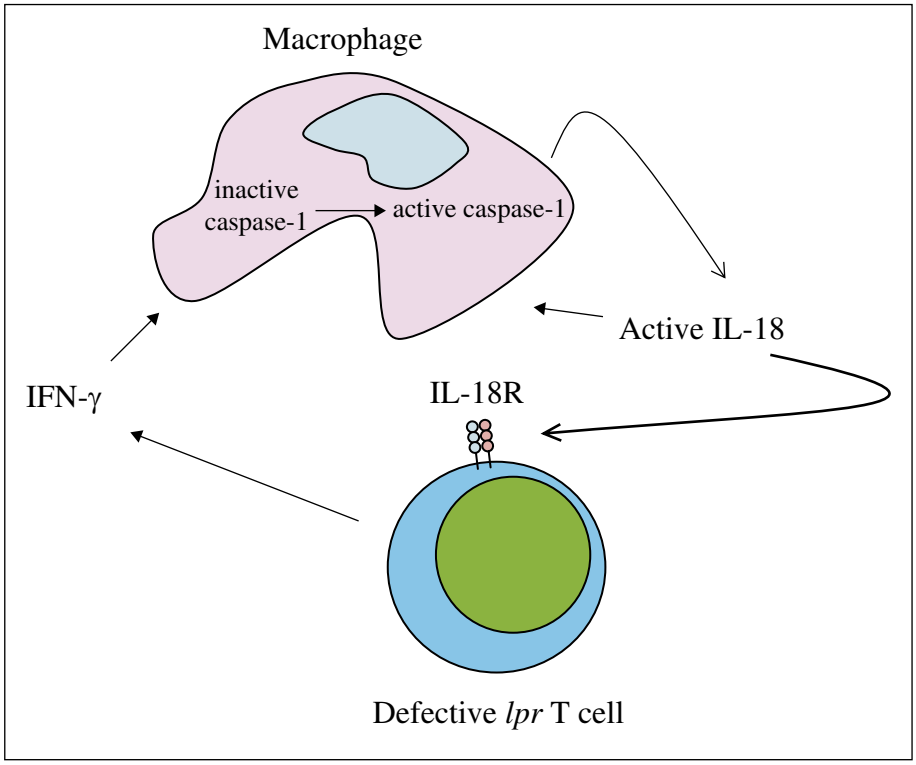

Figure 4

IL-18 in autoimmune activation of *lpr* mice. IFN-γ-stimulated macrophages process inactive caspase-1 into the active enzyme. This, in turn, cleaves and activates precursor IL-18 and allows its release. Defective *lpr* T cells constitutively express the IL-18 receptor complex (IL-18Rα and IL-18Rβ) necessary for IL-18-dependent cell activation. Active IL-18 binds to the IL-18 receptor complex and induces IFN-γ production.

the knock-out gene. Additionally, in the transplanted islet, early responding cells, such as macrophages, most probably mediate damage; the EAE model provides insights into mechanisms of cell-mediated, autoimmune-processes. Nevertheless, with striking similarity to the islet transplantation data, deficiency in IL-18Rα chain confers an opposite phenotype to that observed in IL-18 deficiency.

Whether the convergence upon the IL-18Rα chain involves a second ligand or a novel receptor accessory chain is presently unknown. IL-1F7, a member of IL-1 family with significant sequence homology with IL-18, binds to IL-18BP and IL-18Rα chain [20, 86]. Upon binding to IL-18Rα, IL-1F7 does not induce IFN-γ production and exhibits no apparent competition with IL-18 [20]. The combination of IL-18BP and IL-1F7 results in greater inhibition of IL-18 activity compared to IL-18BP alone, conferring on IL-1F7 the property of a naturally occurring modulator of IL-18 activity [20]. For any signal in the IL-1 family of receptors to occur, an accessory chain is recruited, the binding of which in this case would result in inhibition of IL-18 activity. Whether the accessory chain is the established IL-18Rβ chain or a novel receptor chain is yet undetermined. However, it was reported that mixing IL-1F7 with soluble IL-18Rα and IL-18Rβ chains did not result in a ternary complex, as formed in the presence of IL-18 and the same receptor subunits. Therefore, we speculate that the accessory receptor chain recruited for IL-1F7 is novel. This model provides a mechanism by which lack of the IL-18Rα chain results in the loss of a negative signal, accompanied by the appearance of a heightened inflammatory response.

PATHOGENIC ROLE OF IL-18 IN AUTOIMMUNITY

There is evidence that IL-18 is involved in autoimmune pathogenesis, and is essential for the first steps of autoimmune hyperactivation. Moreover, it appears that IL-18 also contributes to down-stream autoimmune amplification and detrimental effects. The pathogenic role of IL-18 was demonstrated during an experimental study in one murine model of lupus, the lymphoproliferative syndrome caused by the *lpr* gene [290, 293, 294]. The *lpr/lpr* homozygous mice exhibit each of the signs of the lymphoproliferative syndrome by 10 weeks of age, and develop progressive multiorgan damage culminating in early death from renal failure. In these mice, well before the first pathological signs are apparent, the elevated level of IL-18 (both as steady state mRNA and as protein) was consistently observed in all organs. Likewise, the expression of both IL-18 receptor chains was observed, a situation that sensitises cells to activation by IL-18. In healthy mice, the IL-18Rβ chain is usually not expressed unless in a "danger" situation, when both chains of the IL-18 receptor are transiently upregulated. Thus, in *lpr/lpr* mice the IL-18 activity is abnormally regulated at two levels, hyperproduction of IL-18 and hyperexpression of IL-18 receptors. This latter event is possibly due to up-regulation by IL-12, which is also produced at excessive levels in models of autoimmune disease, including *lpr/lpr* mice. In a preliminary study in lymph nodes of young *lpr/lpr* mice (*i.e.* before appearance of the lupus-like disease symptoms), mRNA expression of IL-18 was examined and compared to that of the IL-18 inhibitor IL-18BP and of the IL-18 cleaving enzyme caspase-1 (Martinelli, Neumann, Quattroni and Boraschi, in preparation). As compared to healthy controls, *lpr* lymph nodes express higher levels of IL-18 and of caspase-1, and lower levels of IL-18BP, suggesting that increased production of free active IL-18 precedes disease development. The putative pathway of IL-18-dependent cell activation in the *lpr* mouse is summarised in *figure 4*. Defective *lpr* T lymphocytes spontaneously produce high levels of IFN-γ, which induces expression and activation of caspase-1 in macrophages and other cells [50, 422]. Active caspase-1 cleaves and activates precursor IL-18 and promotes its release. Soluble, mature IL-18, in the absence of high levels of IL-18BP, binds to the IL-18 receptor complex (upregulated in defective *lpr* T cells) and induces abundant production of IFN-γ in a self-sustaining amplification loop.

The confirmation of the pathogenic role of IL-18 in the development of the autoimmune syndrome was obtained using a vaccination approach to inhibit the excess production of endogenous IL-18. A cDNA vaccination strategy was designed, with an expression plasmid carrying the gene for the IL-18 precursor. Vaccination was performed in young *lpr/lpr* mice, which at the time had no signs of the disease, but which already showed increased IL-18 levels in various organs. After vaccination in the muscle tissue, the IL-18 plasmid synthesized the IL-18 protein, and consequently an anti-IL-18 response was generated. Why an antibody response against an autologous protein occurs after cDNA vaccination is not completely clear. One cannot rule out that the autoimmune-prone background of the recipient plays a role. The anti-IL-18 response triggered by vaccination significantly reduced the activity of IL-18 in the organs of *lpr/lpr* mice, and thus disease development was significantly delayed and was less severe, as judged by the pathological parameters of lymphadenopathy, renal damage, proteinuria, and early death [293]. Decrease in disease progression can also be detected when vaccination is performed in older mice with overt disease (P Bossù and D Neumann, unpublished observations). On the basis of the results obtained with anti-IL-18 vaccination, and following the notion that IL-18 acts in synergy with IL-12 in inducing Th1 inflammatory responses having a central role in several autoimmune syndromes, another study was carried out in *lpr/lpr* mice, by vaccinating animals with cDNA for both IL-12 and IL-18 [423]. Concomitant administration of cDNA coding for the two cytokines induced a potent inhibition of lymphadenopathy and splenomegaly (the most striking characteristics of the disease), and practically abolished the kidney damage and proteinuria. In addition, the strong inflammatory infiltrate evident in lungs of *lpr/lpr* mice was absent in IL-18/IL-12-vaccinated animals.

To confirm the pivotal role of IL-18 in the autoimmune pathogenesis, IL-18Rα-deficient *lpr/lpr* mice were shown to survive longer and have significant reduction in renal pathology. Skin lesions, lymphadenopathy, and lung pathology were also diminished in IL-18Rα-deficient *lpr/lpr* mice [424]. In agreement with results obtained with cDNA vaccination and with analysis of gene expression in kidney (Martinelli *et al*., in preparation), IL-18Rα-deficient *lpr/lpr* mice did not show a decrease in autoantibody production or in end-organ disease, stressing the hypoth-

esis that IL-18 is mainly involved in the initiation of the autoimmune syndrome rather than in mediating its destructive, downstream effects [425].
Thus, taking the above data together, IL-18 plays an essential role in the pathogenic process in murine lupus. Further evidence for a pathogenic role of IL-18 in autoimmunity comes from IL-18-deficient mice (e.g., diabetes following induction with streptozotocin, collagen-induced arthritis) [190, 394]. In addition, IL-18BP inhibits the hyperglycemia and insulitis that precedes streptozotocin-induced diabetes [395]. IL-18 is upregulated during progression from insulitis to diabetes in TcR transgenic mice treated with cyclophosphamide [388]. In human situations, there are increased levels of IL-18 in individuals at high risk of developing IDDM [406].

THERAPEUTIC APPROACHES TO INHIBIT IL-18 IN AUTOIMMUNITY

Besides vaccination against IL-18, other therapeutic approaches under investigation to inhibit IL-18 in experimental models and in clinical trials for autoimmune diseases include the use of neutralising antibodies to IL-18, IL-18 receptor blocking antibodies, the IL-18 binding protein IL-18BP, and caspase-1 inhibitors.
IL-18BP is in clinical trials for a variety of autoimmune diseases including rheumatoid arthritis. A divalent fusion protein of human IL-18BP linked human IgG1 Fc (IL-18BP:Fc) binds and neutralises human, mouse, and rat IL-18 with a dissociation constant of 0.3-5 nM. Using *E. coli*-derived endotoxin, with a lethal dose of 90%, IL-18BP:Fc administered 10 minutes prior to the endotoxin, significantly reduced mortality [426]. IFN-γ levels were also reduced in these mice. Because of the long plasma half-life of Fc fusion protein, IL-18BP:Fc reduced endotoxin-induced IFN-γ when administered 6 days before the endotoxin challenge. IL-18BP:Fc reduced hepatic injury as well as expression of Fas [426]. IL-18BP:Fc also decreased granuloma formation and production of the chemokines MIP-1α and MIP-2. As shown previously using anti-mouse IL-18 [427], IL-18 mediates the hepatic damage caused by intravenously injected Concanavalin A [426]. Fas ligand expression as well as liver damage induced by *Pseudomonas aeruginosa* exotoxin A or by anti-Fas agonistic antibody were also reduced by IL-18BP [426]. IL-18BP:Fc reduces the severity of CIA [194]. In other experimental models of chronic inflammatory autoimmune pathologies, the IL-18BP:Fc construct was found to ameliorate disease onset and progression, through inhibition of IL-18 [333, 396].
Inhibition of caspase-1 or of caspase-1-activating inflammosomes is a therapeutic option that is being actively pursued [428-431]. Orally active caspase-1 inhibitors went into clinical trials for their efficacy as anti-inflammatory drugs (such as VX-740, pralnacasan, and VX-765). While a rheumatoid arthritis trial with pralnacasan was suspended after detection of long-term liver abnormalities in treated animals, VX-765 is in trials for the treatment of psoriasis and is reported to be effective in blocking the hyperreactivity to inflammatory stimulation of monocytes from FCAS patients, who have excessive caspase-1 activation due to a mutation in the criopyrin gene [432].
Although very promising, each of these approaches have their drawbacks. Repeated administration of recombinant antibodies or proteins (also when fully human) may elicit an immune response that would reduce their therapeutic efficacy. This is a circumstance that occurs with most therapeutic proteins, even of autologous origin, in particular in autoimmune patients. On the other hand, each IL-18 blocking strategy, including vaccination, must be carefully optimised in order to obtain an effective immune response against excess endogenous IL-18, which should be reduced without being abolished. In fact, since IL-18 is important for the adequate Th1-dependent reactions and for the balance with Th2 responses, its complete down-regulation could lead to immunosuppression with severe consequences. Indeed, increased susceptibility to certain infections has been reported in patients undergoing anti-cytokine therapies (reviewed in [433]). As an example, anti-TNF-α therapies in patients with rheumatoid arthritis, although not inducing an obvious immunosuppressed phenotype, increase the incidence or induced re-activation of tuberculosis [433-444]. Studies on the role of cytokines in mycobacterial infections underline the central role of TNF-α and IFN-γ in host reaction to mycobacterial infection [445, 446]. Since IL-18 is the major inducer of IFN-γ, its role in the anti-mycobacterial response likely depends on IFN-γ induction [447, 448]. In patients with active tuberculosis infections, the levels of IL-18 and IFN-γ in serum, pleural effusions and alveolar macophages are significantly increased [445, 449-453]. Administration of IL-18 DNA or transfected cells in mice caused enhanced IFN-γ production and a potent anti-mycobacterial response [454-456]. Likewise, IL-18 transgenic mice show increased resistance to mycobacterial infection [457]. Conversely, mice susceptible to mycobacterial infection produced significantly less IL-18 as compared to genetically resistant mice [458]; IL-18 knock-out mice were defective in IFN-γ production in response to mycobacterial infection and developed non-necrotic granulomas [459, 460].

CONCLUSIONS AND FUTURE PERSPECTIVES

Current information suggests that IL-18 may have a pathogenic role in autoimmunity. Based of this information, future studies should aim firstly, at verifying this hypothesis, and secondly at investigating the possibility that the pathogenic excess of IL-18 in autoimmunity could be due to dysregulated TLR/IL-1R-mediated activation of M1 macrophages and imbalance with M2 macrophages. In fact, macrophages are the major producers of IL-18 in the body, and its production is stimulated by agents of infectious origin. IL-18 production is one of the first events of the defensive innate immune reaction, and is very important in initiating both the Th1- and the Th17-dependent, inflammatory type immune response necessary to resolve the infectious/stressful event and to re-establish homeostasis. The role of innate immune cells (e.g. M1 or "M17" inflammatory effector macrophages) and receptors (e.g. TLR/IL-1R receptors) in the initiating events of autoimmunity thus needs to be investigated. The initiating causes of autoimmune pathologies are elusive, although they are clearly multiple and can include both a genetic predisposition and one or more triggering events. TLR/IL-1R activation in M1 and M17 macrophages can be one of these events and the cause of excessive IL-18 production/activity, in association with defective down-regulation of

this activation (e.g. at the level of equilibrium with M2 macrophages). Analysis of genetic polymorphisms in the TLR/IL-1R genes and of the genes coding for IL-18, its receptors and inhibitors, may shed some light on the reasons for this defective down-regulation. Understanding the role of innate immune mechanisms in the initial events of autoimmunity will allow the design of better targeted therapeutic strategies, aimed at blocking the initial stages of autoimmune pathogenesis, and consequently its chronicisation. A therapeutic approach based on the re-balancing of the dysregulated reaction is bound to be more effective and prone to fewer side-effects than any therapy based on inhibition of a single downstream effector molecule (particularly because these have a vital defence role and cannot be eliminated without consequence). For the future, if indeed TLR/IL-1R were to be identified as the molecules responsible for autoimmune pathogenesis, the study of their regulation by environmental, toxic, and infectious agents may allow us to identify possible pathogenic co-causes and to design preventive strategies.

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REFERENCES

1. Takeda K, Kaisho T, Akira S. Toll-like receptors. *Annu Rev Immunol* 2003; 21: 335.
2. Dinarello CA. Interleukin-1, interleukin-1 receptors and interleukin-1 receptor antagonist. *Int Rev Immunol* 1998; 16: 457.
3. Dinarello CA. Interleukin-18. *Methods* 1999; 19: 121.
4. Gracie JA, Robertson SE, McInnes IB. Interleukin-18. *J Leukoc Biol* 2003; 73: 213.
5. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanaham TK, Zurawski G, Moshrefi M, Qin J, Li X, Gorman DM, Bazan JF, Kastelein RA. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* 2005; 23: 479.
6. Dinarello CA. An IL-1 family member requires caspase-1 processing and signals through the ST2 receptor. *Immunity* 2005; 23: 461.
7. Brint EK, Xu D, Liu H, Dunne A, McKenzie AN, O'Neill LA, Liew FY. ST2 is an inhibitor of interleukin 1 receptor and Toll-like receptor 4 signaling and maintains endotoxin tolerance. *Nat Immunol* 2004; 5: 373.
8. Polentarutti N, Rol GP, Muzio M, Bosisio D, Camnasio M, Riva F, Zoja C, Benigni A, Tomasoni S, Vecchi A, *et al.* Unique pattern of expression and inhibition of IL-1 signaling by the IL-1 receptor family member TIR8/SIGIRR. *Eur Cytokine Netw* 2003; 14: 211.
9. Wald D, Qin J, Zhao Z, Qian Y, Naramura M, Tian L, Towne J, Sims JE, Stark GR, Li X. SIGIRR, a negative regulator of Toll-like receptor-interleukin 1 receptor signaling. *Nat Immunol* 2003; 4: 920.
10. Garlanda C, Riva F, Polentarutti N, Buracchi C, Sironi M, De Bortoli M, Muzio M, Bergottini R, Scanziani E, Vecchi A, *et al.* Intestinal inflammation in mice deficient in Tir8, an inhibitory member of the IL-1 receptor family. *Proc Natl Acad Sci USA* 2004; 101: 3522.
11. Divanovic S, Trompette A, Atabani SF, Madan R, Golenbock DT, Visintin A, Finberg RW, Tarakhovsky A, Vogel SN, Belkaid Y, *et al.* Negative regulation of Toll-like receptor 4 signaling by the Toll-like receptor homolog RP105. *Nat Immunol* 2005; 6: 571.
12. Divanovic S, Trompette A, Atabani SF, Madan R, Golenbock DT, Visintin A, Finberg RW, Tarakhovsky A, Vogel SN, Belkaid Y, *et al.* Inhibition of TLR4/MD-2 signaling by RP105/MD-1. *J Endotoxin Res* 2005; 11: 363.
13. Gordon S. Alternative activation of macrophages. *Nat Rev Immunol* 2003; 3: 23.
14. Mosser DM. The many faces of macrophage activation. *J Leukoc Biol* 2003; 73: 209.
15. Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol* 2002; 23: 549.
16. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 2004; 25: 677.
17. Harrington LE, Mangan PR, Weaver CT. Expanding the effector CD4 T-cell repertoire: the Th17 lineage. *Curr Opin Immunol* 2006; 18: 349.
18. Weaver CT, Harrington LE, Mangan PR, Gavrieli M, Murphy KM. Th17: an effector CD4 T cell lineage with regulatory T cell ties. *Immunity* 2006; 24: 677.
19. Kim SH, Eisenstein M, Reznikov L, Fantuzzi G, Novick D, Rubinstein M, Dinarello CA. Structural requirements of six naturally occurring isoforms of the IL-18 binding protein to inhibit IL-18. *Proc Natl Acad Sci USA* 2000; 97: 1190.
20. Bufler P, Azam T, Gamboni-Robertson F, Reznikov LL, Kumar S, Dinarello CA, Kim SH. A complex of the IL-1 homologue IL-1F7b and IL-18-binding protein reduces IL-18 activity. *Proc Natl Acad Sci USA* 2002; 99: 13723.
21. Akita K, Ohtsuki T, Nukada Y, Tanimoto T, Namba M, Okura T, Takakura-Yamamoto R, Torigoe K, Gu Y, Su MS, *et al.* Involvement of caspase-1 and caspase-3 in the production and processing of mature human interleukin 18 in monocytic THP. 1 cells. *J Biol Chem* 1997; 272: 26595.
22. Dinarello CA. Therapeutic strategies to reduce IL-1 activity in treating local and systemic inflammation. *Curr Opin Pharmacol* 2004; 4: 378.
23. Bar-Or RL, Segal LA. On the role of a possible dialogue between cytokine and TCR-presentation mechanisms in the regulation of autoimmune disease. *J Theor Biol* 1998; 190: 161.
24. Shirai A, Conover J, Klinman DM. Increased activation and altered ratio of interferon-γ: interleukin-4 secreting cells in MRL-lpr/lpr mice. *Autoimmunity* 1995; 21: 107.
25. Machold KP, Smolen JS. Interferon-γ induced exacerbation of systemic lupus erythematosus. *J Rheumatol* 1990; 17: 831.
26. Graninger WB, Hassfeld W, Pesau BB, Machold KP, Zielinski CC, Smolen JS. Induction of systemic lupus erythematosus by interferon-γ in a patient with rheumatoid arthritis. *J Rheumatol* 1991; 18: 1621.
27. Jacob CO, van der Meide PH, McDevitt HO. In vivo treatment of (NZB X NZW)F1 lupus-like nephritis with monoclonal antibody to γ interferon. *J Exp Med* 1987; 166: 798.
28. Nicoletti F, Di Marco R, Zaccone P, Xiang M, Magro G, Grasso S, Morrone S, Santoni A, Shoenfeld Y, Garotta G, *et al.* Dichotomic effects of IFN-γ on the development of systemic lupus erythematosus-like syndrome in MRL-lpr/lpr mice. *Eur J Immunol* 2000; 30: 438.
29. Haas C, Ryffel B, Le Hir M. IFN-γ is essential for the development of autoimmune glomerulonephritis in MRL/lpr mice. *J Immunol* 1997; 158: 5484.
30. Balomenos D, Rumold R, Theofilopoulos AN. Interferon-γ is required for lupus-like disease and lymphoaccumulation in MRL-lpr mice. *J Clin Invest* 1998; 101: 364.
31. Haas C, Ryffel B, Le Hir M. IFN-γ receptor deletion prevents autoantibody production and glomerulonephritis in lupus-prone (NZB x NZW)F1 mice. *J Immunol* 1998; 160: 3713.

32. Peng SL, Moslehi J, Craft J. Roles of interferon-γ and interleukin-4 in murine lupus. *J Clin Invest* 1997; 99: 1936.

33. Schwarting A, Wada T, Kinoshita K, Tesch G, Kelley VR. IFN-γ receptor signaling is essential for the initiation, acceleration, and destruction of autoimmune kidney disease in MRL-Fas(lpr) mice. *J Immunol* 1998; 161: 494.

34. Schwarting A, Tesch G, Kinoshita K, Maron R, Weiner HL, Kelley VR. IL-12 drives IFN-γ-dependent autoimmune kidney disease in MRL-Fas(lpr) mice. *J Immunol* 1999; 163: 6884.

35. Tuohy VK, Yu M, Yin L, Kawczak JA, Johnson JM, Mathisen PM, Weinstock-Guttman B, Kinkel RP. The epitope spreading cascade during progression of experimental autoimmune encephalomyelitis and multiple sclerosis. *Immunol Rev* 1998; 164: 93.

36. Robinson D, Shibuya K, Mui A, Zonin F, Murphy E, Sana T, Hartley SB, Menon S, Kastelein R, Bazan F, *et al.* IGIF does not drive Th1 development but synergizes with IL-12 for interferon-γ production and activates IRAK and NFκB. *Immunity* 1997; 7: 571.

37. Okamoto M, Kato S, Oizumi K, Kinoshita M, Inoue Y, Hoshino K, Akira S, McKenzie AN, Young HA, Hoshino T. Interleukin 18 (IL-18) in synergy with IL-2 induces lethal lung injury in mice: a potential role for cytokines, chemokines, and natural killer cells in the pathogenesis of interstitial pneumonia. *Blood* 2002; 99: 1289.

38. Nakahira M, Ahn HJ, Park WR, Gao P, Tomura M, Park CS, Hamaoka T, Ohta T, Kurimoto M, Fujiwara H. Synergy of IL-12 and IL-18 for IFN-γ gene expression: IL-18-induced STAT4 contributes to IFN-γ promoter activation by up-regulating the binding activity of IL-18-induced activator protein 1. *J Immunol* 2002; 168: 1146.

39. Okazawa A, Kanai T, Nakamaru K, Sato T, Inoue N, Ogata H, Iwao Y, Ikeda M, Kawamura T, Makita S, *et al.* Human intestinal epithelial cell-derived interleukin (IL-18), along with IL-2, IL-7 and IL-15, is a potent synergistic factor for the proliferation of intraepithelial lymphocytes. *Clin Exp Immunol* 2004; 136: 269.

40. Lebel-Binay S, Berger A, Zinzindohoue F, Cugnenc P, Thiounn N, Fridman WH, Pages F. Interleukin-18: biological properties and clinical implications. *Eur Cytokine Netw* 2000; 11: 15.

41. Gu Y, Kuida K, Tsutsui H, Ku G, Hsiao K, Fleming MA, Hayashi N, Higashino K, Okamura H, Nakanishi K, *et al.* Activation of interferon-γ inducing factor mediated by interleukin-1β converting enzyme. *Science* 1997; 275: 206.

42. Ghayur T, Banerjee S, Hugunin M, Butler D, Herzog L, Carter A, Quintal L, Sekut L, Talanian R, Paskind M, *et al.* Caspase-1 processes IFN-γ-inducing factor and regulates LPS-induced IFN-γ production. *Nature* 1997; 386: 619.

43. Yoshimoto T, Takeda K, Tanaka T, Ohkusu K, Kashiwamura S, Okamura H, Akira S, Nakanishi K. IL-12 up-regulates IL-18 receptor expression on T cells, Th1 cells, and B cells: synergism with IL-18 for IFN-γ production. *J Immunol* 1998; 161: 34007.

44. Nakamura S, Otani T, Okura R, Ijiri Y, Motoda R, Kurimoto M, Orita K. Expression and responsiveness of human interleukin-18 receptor (IL-18R) on hematopoietic cell lines. *Leukemia* 2000; 14: 1052.

45. Gerdes N, Sukhova GK, Libby P, Reynolds RS, Young JL, Schonbeck U. Expression of interleukin (IL-18) and functional IL-18 receptor on human vascular endothelial cells, smooth muscle cells, and macrophages: implications for atherogenesis. *J Exp Med* 2002; 195: 245.

46. Moller B, Kessler U, Rehart S, Kalina U, Ottmann OG, Kaltwasser JP, Hoelzer D, Kukoc-Zivojnov N. Expression of interleukin-18 receptor in fibroblast-like synoviocytes. *Arthritis Res* 2002; 4: 139.

47. Sims JE. IL-1 and IL-18 receptors, and their extended family. *Curr Opin Immunol* 2002; 14: 117.

48. Gutzmer R, Langer K, Mommert S, Wittmann M, Kapp A, Werfel T. Human dendritic cells express the IL-18R and are chemoattracted to IL-18. *J Immunol* 2003; 171: 6363.

49. Airoldi I, Raffaghello L, Cocco C, Guglielmino R, Roncella S, Fedeli F, Gambini C, Pistoia V. Heterogeneous expression of interleukin-18 and its receptor in B-cell lymphoproliferative disorders deriving from naive, germinal center, and memory B lymphocytes. *Clin Cancer Res* 2004; 10: 144.

50. Kim SH, Reznikov LL, Stuyt RJ, Selzman CH, Fantuzzi G, Hoshino T, Young HA, Dinarello CA. Functional reconstitution and regulation of IL-18 activity by the IL-18R β chain. *J Immunol* 2001; 166: 148.

51. Debets R, Timans JC, Churakowa T, Zurawski S, de Waal MR, Moore KW, Abrams JS, O'Garra A, Bazan JF, Kastelein RA. IL-18 receptors, their role in ligand binding and function: anti-IL-1RAcPL antibody, a potent antagonist of IL-18. *J Immunol* 2000; 165: 4950.

52. O'Neill L. The Toll/interleukin-1 receptor domain: a molecular switch for inflammation and host defence. *Biochem Soc Trans* 2000; 28: 557.

53. Dunne A, O'Neill LA. The interleukin-1 receptor/Toll-like receptor superfamily: signal transduction during inflammation and host defense. *Sci STKE* 2003; (2003: re3).

54. Bowie A, O'Neill LA. The interleukin-1 receptor/Toll-like receptor superfamily: signal generators for pro-inflammatory interleukins and microbial products. *J Leukoc Biol* 2000; 67: 508.

55. Kalina U, Kauschat D, Koyama N, Nuernberger H, Ballas K, Koschmieder S, Bug G, Hofmann WK, Hoelzer D, Ottmann OG. IL-18 activates STAT3 in the natural killer cell line 92, augments cytotoxic activity, and mediates IFN-γ production by the stress kinase p38 and by the extracellular regulated kinases p44erk-1 and p42erk-21. *J Immunol* 2000; 165: 1307.

56. Yang J, Zhu H, Murphy TL, Ouyang W, Murphy KM. IL-18 stimulated GADD45 β required in cytokine-induced, but not TCR-induced, IFN-γ production. *Nat Immunol* 2001; 2: 157.

57. Wyman TH, Dinarello CA, Banerjee A, Gamboni-Robertson F, Hiester AA, England KM, Kelher M, Silliman CC. Physiological levels of interleukin-18 stimulate multiple neutrophil functions through p38 MAP kinase activation. *J Leukoc Biol* 2002; 72: 401.

58. Lee JK, Kim SH, Lewis EC, Azam T, Reznikov LL, Dinarello CA. Differences in signaling pathways by IL-1β and IL-18. *Proc Natl Acad Sci USA* 2004; 101: 88150.

59. Shapiro L, Puren AJ, Barton HA, Novick D, Peskind RL, Shenkar R, Gu Y, Su MS, Dinarello CA. Interleukin 18 stimulates HIV type 1 in monocytic cells. *Proc Natl Acad Sci USA* 1998; 95: 12550.

60. Hoshino K, Tsutsui H, Kawai T, Takeda K, Nakanishi K, Takeda Y, Akira S. Generation of IL-18 receptor-deficient mice: evidence for IL-1 receptor-related protein as an essential IL-18 binding receptor. *J Immunol* 1999; 162: 5041.

61. Sareneva T, Julkunen I, Matikainen S. IFN-α and IL-12 induce IL-18 receptor gene expression in human NK and T cells. *J Immunol* 2000; 165: 19338.

62. Smeltz RB, Chen J, Hu-Li J, Shevach EM. Regulation of interleukin (IL-18) receptor α chain expression on CD4(+) T cells during T helper (Th)1/Th2 differentiation. Critical downregulatory role of IL-4. *J Exp Med* 2001; 194: 143.

63. Neumann D, Martin MU. Interleukin-12 upregulates the IL-18Rβ chain in BALB/c thymocytes. *J Interferon Cytokine Res* 2001; 21: 635.

64. Nakahira M, Tomura M, Iwasaki M, Ahn HJ, Bian Y, Hamaoka T, Ohta T, Kurimoto M, Fujiwara H. An absolute requirement for STAT4 and a role for IFN-γ as an amplifying factor in IL-12 induction of the functional IL-18 receptor complex. *J Immunol* 2001; 167: 1306.

65. Smeltz RB, Chen J, Ehrhardt R, Shevach EM. Role of IFN-γ in Th1 differentiation: IFN-γ regulates IL-18Rα expression by preventing the negative effects of IL-4 and by inducing/maintaining IL-12 receptor β2 expression. *J Immunol* 2002; 168: 6165.

66. Strengell M, Sareneva T, Foster D, Julkunen I, Matikainen S. IL-21 up-regulates the expression of genes associated with innate immunity and Th1 response. *J Immunol* 2002; 169: 3600.

67. Strengell M, Matikainen S, Siren J, Lehtonen A, Foster D, Julkunen I, Sareneva T. IL-21 in synergy with IL-15 or IL-18 enhances IFN-γ production in human NK and T cells. *J Immunol* 2003; 170: 5464.

68. Hoeve MA, de Boer T, Langenberg DM, Sanal O, Verreck FA, Ottenhoff TH. IL-12 receptor deficiency revisited: IL-23-mediated signaling is also impaired in human genetic IL-12 receptor β1 deficiency. *Eur J Immunol* 2003; 33: 3393.

69. Gutcher I, Urich E, Wolter K, Pronz M, Becher B. Interleukin 18-independent engagement of interleukin 18 receptor-α is required for autoimmune inflammation. *Nat Immunol* 2006; 7: 946.

70. Novick D, Kim SH, Fantuzzi G, Reznikov LL, Dinarello CA, Rubinstein M. Interleukin-18 binding protein: a novel modulator of the Th1 cytokine response. *Immunity* 1999; 10: 127.

71. Novick D, Schwartsburd B, Pinkus R, Suissa D, Belzer I, Sthoeger Z, Keane WF, Chvatchko Y, Kim SH, Fantuzzi G, *et al.* A novel IL-18BP ELISA shows elevated serum IL-18BP in sepsis and extensive decrease of free IL-18. *Cytokine* 2001; 14: 334.

72. Colotta F, Dower SK, Sims JE, Mantovani A. The type II 'decoy' receptor: a novel regulatory pathway for interleukin 1. *Immunol Today* 1994; 15: 562.

73. Kim SH, Azam T, Novick D, Yoon DY, Reznikov LL, Bufler P, Rubinstein M, Dinarello CA. Identification of amino acid residues critical for biological activity in human interleukin-18. *J Biol Chem* 2002; 277: 10998.

74. Im SH, Kim SH, Azam T, Venkatesh N, Dinarello CA, Fuchs S, Souroujon MC. Rat interleukin-18 binding protein: cloning, expression, and characterization. *J Interferon Cytokine Res* 2002; 22: 321.

75. Kim SH, Azam T, Yoon DY, Reznikov LL, Novick D, Rubinstein M, Dinarello CA. Site-specific mutations in the mature form of human IL-18 with enhanced biological activity and decreased neutralization by IL-18 binding protein. *Proc Natl Acad Sci USA* 2001; 98: 3304.

76. Paulukat J, Bosmann M, Nold M, Garkisch S, Kampfer H, Frank S, Raedle J, Zeuzem S, Pfeilschifter J, Muhl H. Expression and release of IL-18 binding protein in response to IFN-γ. *J Immunol* 2001; 167: 7038.

77. Hurgin V, Novick D, Rubinstein M. The promoter of IL-18 binding protein: activation by an IFN-γ-induced complex of IFN regulatory factor 1 and CCAAT/enhancer binding protein beta. *Proc Natl Acad Sci USA* 2002; 99: 16957.

78. Corbaz A, ten Hove T, Herren S, Graber P, Schwartsburd B, Belzer I, Harrison J, Plitz T, Kosco-Vilbois MH, Kim SH, *et al.* IL-18-binding protein expression by endothelial cells and macrophages is up-regulated during active Crohn's disease. *J Immunol* 2002; 168: 3608.

79. Kawashima M, Yamamura M, Taniai M, Yamauchi H, Tanimoto T, Kurimoto M, Miyawaki S, Amano T, Takeuchi T, Makino H. Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease. *Arthritis Rheum* 2001; 44: 550.

80. Moller B, Kukoc-Zivojnov N, Kessler U, Rehart S, Kaltwasser JP, Hoelzer D, Kalina U, Ottmann OG. Expression of interleukin-18 and its monokine-directed function in rheumatoid arthritis. *Rheumatology (Oxford)* 2001; 40: 302.

81. Bresnihan B, Roux-Lombard P, Murphy E, Kane D, FitzGerald O, Dayer JM. Serum interleukin 18 and interleukin 18 binding protein in rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 726.

82. Kaser A, Novick D, Rubinstein M, Siegmund B, Enrich B, Koch RO, Vogel W, Kim SH, Dinarello CA, Tilg H. Interferon-α induces interleukin-18 binding protein in chronic hepatitis C patients. *Clin Exp Immunol* 2002; 129: 332.

83. Ludwiczek O, Kaser A, Novick D, Dinarello CA, Rubinstein M, Vogel W, Tilg H. Plasma levels of interleukin-18 and interleukin-18 binding protein are elevated in patients with chronic liver disease. *J Clin Immunol* 2002; 22: 331.

84. Busfield SJ, Comrack CA, Yu G, Chickering TW, Smutko JS, Zhou H, Leiby KR, Holmgren LM, Gearing DP, Pan Y. Identification and gene organization of three novel members of the IL-1 family on human chromosome 2. *Genomics* 2000; 66: 213.

85. Kumar S, McDonnell PC, Lehr R, Tierney L, Tzimas MN, Griswold DE, Capper EA, Tal-Singer R, Wells GI, Doyle ML, *et al.* Identification and initial characterization of four novel members of the interleukin-1 family. *J Biol Chem* 2000; 275: 10308.

86. Pan G, Risser P, Mao W, Baldwin DT, Zhong AW, Filvaroff E, Yansura D, Lewis L, Eigenbrot C, Henzel WJ, *et al.* IL-1H, an interleukin 1-related protein that binds IL-18 receptor/IL-1Rrp. *Cytokine* 2001; 13: 1.

87. Smith DE, Renshaw BR, Ketchem RR, Kubin M, Garka KE, Sims JE. Four new members expand the interleukin-1 superfamily. *J Biol Chem* 2000; 275: 1169.

88. Taylor SL, Renshaw BR, Garka KE, Smith DE, Sims JE. Genomic organization of the interleukin-1 locus. *Genomics* 2002; 79: 726.

89. Kumar S, Hanning CR, Brigham-Burke MR, Rieman DJ, Lehr R, Khandekar S, Kirkpatrick RB, Scott GF, Lee JC, Lynch FJ, *et al.* Interleukin-1F7B (IL-1H4/IL-1F7) is processed by caspase-1 and mature IL-1F7B binds to the IL-18 receptor but does not induce IFN-γ production. *Cytokine* 2002; 18: 61.

90. Lang D, Knop J, Wesche H, Raffetseder U, Kurrle R, Boraschi D, Martin MU. The type II IL-1 receptor interacts with the IL-1 receptor accessory protein: a novel mechanism of regulation of IL-1 responsiveness. *J Immunol* 1998; 161: 6871.

91. Gao W, Kumar S, Lotze MT, Hanning C, Robbins PD, Gambotto A. Innate immunity mediated by the cytokine IL-1 homologue 4 (IL-1H4/IL-1F7) induces IL-12-dependent adaptive and profound antitumor immunity. *J Immunol* 2003; 170: 107.

92. Thomassen E, Renshaw BR, Sims JE. Identification and characterization of SIGIRR, a molecule representing a novel subtype of the IL-1R superfamily. *Cytokine* 1999; 11: 389.

93. Du X, Poltorak A, Wei Y, Beutler B. Three novel mammalian toll-like receptors: gene structure, expression, and evolution. *Eur Cytokine Netw* 2000; 11: 362.

94. Qin J, Qian Y, Yao J, Cui G, Li X. SIGIRR inhibits interleukin-1 receptor- and Toll-like receptor 4-mediated signaling through different mechanisms. *J Biol Chem* 2005; 280: 25233.

95. Miyake K, Yamashita Y, Hitoshi Y, Takatsu K, Kimoto M. Murine B cell proliferation and protection from apoptosis with an antibody against a 105-kD molecule: unresponsiveness of X-linked immunodeficient B cells. *J Exp Med* 1994; 180: 1217.

96. Miyake K, Yamashita Y, Ogata M, Sudo T, Kimoto M. RP105, a novel B cell surface molecule implicated in B cell activation, is a member of the leucine-rich repeat protein family. *J Immunol* 1995; 154: 3333.

97. Ogata H, Su I, Miyake K, Nagai Y, Akashi S, Mecklenbrauker I, Rajewsky K, Kimoto M, Tarakhovsky A. The toll-like receptor protein RP105 regulates lipopolysaccharide signaling in B cells. *J Exp Med* 2000; 192: 23.

98. Miyake K, Shimazu R, Kondo J, Niki T, Akashi S, Ogata H, Yamashita Y, Miura Y, Kimoto M. Mouse MD-1, a molecule that is physically associated with RP105 and positively regulates its expression. *J Immunol* 1998; 161: 1348.

99. Miura Y, Shimazu R, Miyake K, Akashi S, Ogata H, Yamashita Y, Narisawa Y, Kimoto M. RP105 is associated with MD-1 and transmits an activation signal in human B cells. *Blood* 1998; 92: 2815.

100. Gottfried E, Faust S, Fritsche J, Kunz-Schughart LA, Andreesen R, Miyake K, Kreutz M. Identification of genes expressed in tumor-associated macrophages. *Immunobiology* 2003; 207: 351.

101. Koarada S, Tada Y, Ushiyama O, Morito F, Suzuki N, Ohta A, Miyake K, Kimoto M, Nagasawa K. B cells lacking RP105, a novel B cell antigen, in systemic lupus erythematosus. *Arthritis Rheum* 1999; 42: 2593.

102. Kikuchi Y, Koarada S, Tada Y, Ushiyama O, Morito F, Suzuki N, Ohta A, Horiuchi T, Miyake K, Nagasawa K. Difference in B cell activation between dermatomyositis and polymyositis: analysis of the expression of RP105 on peripheral blood B cells. *Ann Rheum Dis* 2001; 60: 1137.

103. Koarada S, Tada Y, Kikuchi Y, Ushiyama O, Suzuki N, Ohta A, Nagasawa K. CD180 (RP105) in rheumatic diseases. *Rheumatology (Oxford)* 2001; 40: 1315.

104. Kikuchi Y, Koarada S, Tada Y, Ushiyama O, Morito F, Suzuki N, Ohta A, Miyake K, Kimoto M, Horiuchi T, *et al.* RP105-lacking B cells from lupus patients are responsible for the production of immunoglobulins and autoantibodies. *Arthritis Rheum* 2002; 46: 3259.

105. Yanagisawa K, Takagi T, Tsukamoto T, Tetsuka T, Tominaga S. Presence of a novel primary response gene ST2L, encoding a product highly similar to the interleukin 1 receptor type 1. *FEBS Lett* 1993; 318: 83.

106. Tominaga S, Kuroiwa K, Tago K, Iwahana H, Yanagisawa K, Komatsu N. Presence and expression of a novel variant form of ST2 gene product in human leukemic cell line UT-7/GM. *Biochem Biophys Res Commun* 1999; 264: 14.

107. Sweet MJ, Leung BP, Kang D, Sogaard M, Schulz K, Trajkovic V, Campbell CC, Xu D, Liew FY. A novel pathway regulating lipopolysaccharide-induced shock by ST2/T1 via inhibition of Toll-like receptor 4 expression. *J Immunol* 2001; 166: 6633.

108. Trajkovic V, Sweet MJ, Xu D. T1/ST2 - an IL-1 receptor-like modulator of immune responses. *Cytokine Growth Factor Rev* 2004; 15: 87.

109. Kumar S, Minnich MD, Young PR. ST2/T1 protein functionally binds to two secreted proteins from Balb/c 3T3 and human umbilical vein endothelial cells but does not bind interleukin-1. *J Biol Chem* 1995; 270: 27905.

110. Gayle MA, Slack JL, Bonnert TP, Renshaw BR, Sonoda G, Taguchi T, Testa JR, Dower SK, Sims JE. Cloning of a putative ligand for the T1/ST2 receptor. *J Biol Chem* 1996; 271: 5784.

111. Dunn E, Sims JE, Nicklin MJ, O'Neill LA. Annotating genes with potential roles in the immune system: six new members of the IL-1 family. *Trends Immunol* 2001; 22: 533.

112. Li H, Tago K, Io K, Kuroiwa K, Arai T, Iwahana H, Tominaga S, Yanagisawa K. The cloning and nucleotide sequence of human ST2L cDNA. *Genomics* 2000; 67: 284.

113. Tago K, Noda T, Hayakawa M, Iwahana H, Yanagisawa K, Yashiro T, Tominaga S. Tissue distribution and subcellular localization of a variant form of the human ST2 gene product, ST2V. *Biochem Biophys Res Commun* 2001; 285: 1377.

114. Xu D, Chan WL, Leung BP, Huang F, Wheeler R, Piedrafita D, Robinson JH, Liew FY. Selective expression of a stable cell surface molecule on type 2 but not type 1 helper T cells. *J Exp Med* 1998; 187: 787.

115. Xu D, Chan WL, Leung BP, Hunter D, Schulz K, Carter RW, McInnes IB, Robinson JH, Liew FY. Selective expression and functions of interleukin 18 receptor on T helper (Th) type 1 but not Th2 cells. *J Exp Med* 1998; 188: 1485.

116. Lohning M, Stroehmann A, Coyle AJ, Grogan JL, Lin S, Gutierrez-Ramos JC, Levinson D, Radbruch A, Kamradt T. T1/ST2 is preferentially expressed on murine Th2 cells, independent of interleukin 4, interleukin 5, and interleukin 10, and important for Th2 effector function. *Proc Natl Acad Sci USA* 1998; 95: 6930.

117. Coyle AJ, Lloyd C, Tian J, Nguyen T, Erikkson C, Wang L, Ottoson P, Persson P, Delaney T, Lehar S, *et al.* Crucial role of the interleukin 1 receptor family member T1/ST2 in T helper cell type 2-mediated lung mucosal immune responses. *J Exp Med* 1999; 190: 895.

118. Townsend MJ, Fallon PG, Matthews DJ, Jolin HE, McKenzie AN. T1/ST2-deficient mice demonstrate the importance of T1/ST2 in developing primary T helper cell type 2 responses. *J Exp Med* 2000; 191: 1069.

119. Walzl G, Matthews S, Kendall S, Gutierrez-Ramos JC, Coyle AJ, Openshaw PJ, Hussell T. Inhibition of T1/ST2 during respiratory syncytial virus infection prevents T helper cell type 2 (Th2)- but not Th1-driven immunopathology. *J Exp Med* 2001; 193: 785.

120. Oshikawa K, Kuroiwa K, Tago K, Iwahana H, Yanagisawa K, Ohno S, Tominaga SI, Sugiyama Y. Elevated soluble ST2 protein levels in sera of patients with asthma with an acute exacerbation. *Am J Respir Crit Care Med* 2001; 164: 277.

121. Takezako N, Hayakawa M, Hayakawa H, Aoki S, Yanagisawa K, Endo H, Tominaga S. ST2 suppresses IL-6 production via the inhibition of IκB degradation induced by the LPS signal in THP-1 cells. *Biochem Biophys Res Commun* 2006; 341: 425.

122. Brint EK, Fitzgerald KA, Smith P, Coyle AJ, Gutierrez-Ramos JC, Fallon PG, O'Neill LA. Characterization of signaling pathways activated by the interleukin 1 (IL-1) receptor homologue T1/ST2: a role for Jun N-terminal kinase in IL-4 induction. *J Biol Chem* 2002; 277: 49205.

123. Oshikawa K, Yanagisawa K, Tominaga S, Sugiyama Y. ST2 protein induced by inflammatory stimuli can modulate acute lung inflammation. *Biochem Biophys Res Commun* 2002; 299: 18.

124. Prechtel D, Harbeck N, Berger U, Hofler H, Werenskiold AK. Clinical relevance of T1-S, an oncogene-inducible, secreted glycoprotein of the immunoglobulin superfamily, in node-negative breast cancer. *Lab Invest* 2001; 81: 159.

125. Tajima S, Oshikawa K, Tominaga S, Sugiyama Y. The increase in serum soluble ST2 protein upon acute exacerbation of idiopathic pulmonary fibrosis. *Chest* 2003; 124: 1206.

126. Weinberg EO, Shimpo M, Hurwitz S, Tominaga S, Rouleau JL, Lee RT. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. *Circulation* 2003; 107: 721.

127. Kuroiwa K, Arai T, Okazaki H, Minota S, Tominaga S. Identification of human ST2 protein in the sera of patients with autoimmune diseases. *Biochem Biophys Res Commun* 2001; 284: 1104.

128. Kanda M, Ohto-Ozaki H, Kuroiwa K, Tominaga S, Watanabe E, Iwahana H. Elevation of ST2 protein levels in cerebrospinal fluid following subaracnoid hemorrhage. *Acta Neurol Scand* 2006; 113: 327.

129. Leung BP, Xu D, Culshaw S, McInnes IB, Liew FY. A novel therapy of murine collagen-induced arthritis with soluble T1/ST2. *J Immunol* 2004; 173: 145.

130. Tschopp J, Martinon F, Burns K. NALPs: a novel protein family involved in inflammation. *Nat Rev Mol Cell Biol* 2003; 4: 95.

131. Martinon F, Tschopp J. Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. *Cell* 2004; 117: 561.

132. Meylan E, Tschopp J, Karin M. Intracellular pattern recognition receptors in the host response. *Nature* 2006; 442: 39.

133. Inohara N, Nunez G. NODs: intracellualr proteins involved in inflammation and apoptosis. *Nat Rev Immunol* 2003; 3: 371.

134. Yoo NJ, Park WS, Kim SY, Reed JC, Son SG, Lee JY, Lee SH. Nod1, a CARD protein, enhances pro-interleukin-1beta processing through the interaction with pro-caspase-1. *Biochem Biophys Res Commun* 2002; 299: 652.

135. Cho DH, Hong YM, Lee HJ, Woo HN, Pyo JO, Mak TW, Jung YK. Induced inhibition of ischemic/hypoxic injury by APIP, a novel Apaf-1-interacting protein. *J Biol Chem* 2004; 279: 39942.

136. Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. *Immunity* 2004; 20: 319.

137. Damiano JS, Reed JC. CARD proteins as therapeutic targets in cancer. *Curr Drug Targets* 2004; 5: 367.

138. Razmara M, Srinivasula SM, Wang L, Poyet JL, Geddes BJ, DiStefano PS, Bertin J, Alnemri ES. CARD-8 protein, a new CARD family member that regulates caspase-1 activation and apoptosis. *J Biol Chem* 2002; 277: 13952.

139. Wang Y, Hasegawa M, Imamura R, Kinoshita T, Kondo C, Konaka K, Suda T. PYNOD, a novel Apaf-1/CED4-like protein is an inhibitor of ASC and caspase-1. *Int Immunol* 2004; 16: 777.

140. Gutierrez O, Pipaon C, Inohara N, Fontalba A, Ogura Y, Prosper F, Nunez G, Fernandez-Luna JL. Induction of Nod2 in myelomonocytic and intestinal epithelial cells via nuclear factor-kappa B activation. *J Biol Chem* 2002; 277: 41701.

141. Girardin SE, Boneca IG, Carneiro LA, Antignac A, Jehanno M, Viala J, Tedin K, Taha MK, Labigne A, Zahringer U, *et al.* Nod1 detects a unique muropeptide from gram-negative bacterial peptidoglycan. *Science* 2003; 300: 1584.

142. Chamaillard M, Hashimoto M, Horie Y, Masumoto J, Qiu S, Saab L, Ogura Y, Kawasaki A, Fukase K, Kusumoto S, *et al.* An essential role for NOD1 in host recognition of bacterial peptidoglycan containing diaminopimelic acid. *Nat Immunol* 2003; 4: 702.

143. Bonen DK, Ogura Y, Nicolae DL, Inohara N, Saab L, Tanabe T, Chen FF, Foster SJ, Duerr RH, Brant SR, *et al.* Crohn's disease-associated NOD2 variants share a signaling defect in response to lipopolysaccharide and peptidoglycan. *Gastroenterology* 2003; 124: 140.

144. Chamaillard M, Philpott D, Girardin SE, Zouali H, Lesage S, Chareyre F, Bui TH, Giovannini M, Zaehringer U, Penard-Lacronique V, *et al.* Gene-environment interaction modulated by allelic heterogeneity in inflammatory diseases. *Proc Natl Acad Sci USA* 2003; 100: 3455.

145. Girardin SE, Boneca IG, Viala J, Chamaillard M, Labigne A, Thomas G, Philpott DJ, Sansonetti PJ. Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection. *J Biol Chem* 2003; 278: 8869.

146. Tanabe T, Chamaillard M, Ogura Y, Zhu L, Qiu S, Masumoto J, Ghosh P, Moran A, Predergast MM, Tromp G, *et al.* Regulatory regions and critical residues of NOD2 involved in muramyl dipeptide recognition. *EMBO J* 2004; 23: 1587.

147. Kim JG, Lee SJ, Kagnoff MF. Nod1 is an essential signal transducer in intestinal epithelial cells infected with bacteria that avoid recognition by toll-like receptors. *Infect Immun* 2004; 72: 1487.

148. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, *et al.* Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001; 411: 599.

149. Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, *et al.* A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 2001; 411: 603.

150. Cuthbert AP, Fisher SA, Mirza MM, King K, Hampe J, Croucher PJ, Mascheretti S, Sanderson J, Forbes A, Mansfield J, *et al.* The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease. *Gastroenterology* 2002; 122: 867.

151. Girardin SE, Hugot JP, Sansonetti PJ. Lessons from Nod2 studies: towards a link between Crohn's disease and bacterial sensing. *Trends Immunol* 2003; 24: 652.

152. Russell RK, Wilson DC, Satsangi J. Unravelling the complex genetics of inflammatory bowel disease. *Arch Dis Child* 2004; 89: 598.

153. Behr MA, Semret M, Poon A, Schurr E. Crohn's disease, mycobacteria, and NOD2. *Lancet Infect Dis* 2004; 4: 136.

154. Elson CO. Genes, microbes, and T cells - new therapeutic targets in Crohn's disease. *N Engl J Med* 2002; 346: 614.

155. Inohara N, Ogura Y, Fontalba A, Gutierrez O, Pons F, Crespo J, Fukase K, Inamura S, Kusumoto S, Hashimoto M, *et al.* Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn's disease. *J Biol Chem* 2003; 278: 5509.

156. Chamaillard M, Girardin SE, Viala J, Philpott DJ. Nods, Nalps and Naip: intracellular regulators of bacterial-induced inflammation. *Cell Microbiol* 2003; 5: 581.

157. Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, Hafner R, Chamaillard M, Zouali H, Thomas G, Hugot JP. CARD15 mutations in Blau syndrome. *Nat Genet* 2001; 29: 19.

158. Rosenbaum JT, Planck SR, Davey MP, Iwanaga Y, Kurz DE, Martin TM. With a mere nod, uveitis enters a new era. *Am J Ophthalmol* 2003; 136: 729.

159. Watanabe T, Kitani A, Murray PJ, Strober W. NOD2 is a negative regulator of Toll-like receptor 2-mediated T helper type 1 responses. *Nat Immunol* 2004; 5: 800.

160. Netea MG, Kullberg BJ, de Jong DJ, Franke B, Sprong T, Naber TH, Drenth JP, Van der Meer JW. NOD2 mediates anti-inflammatory signals induced by TLR2 ligands: implications for Crohn's disease. *Eur J Immunol* 2004; 34: 2052.

161. Aganna E, Martinon F, Hawkins PN, Ross JB, Swan DC, Booth DR, Lachmann HJ, Bybee A, Gaudet R, Woo P, *et al.* Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. *Arthritis Rheum* 2002; 46: 2445.

162. Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004; 50: 607.

163. Neven B, Callebaut I, Prieur AM, Feldmann J, Bodemer C, Lepore L, Derfalvi B, Benjaponpitak S, Vesely R, Sauvain MJ, *et al.* Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood* 2004; 103: 2809.

164. Hoffman HM, Rosengren S, Boyle DL, Cho JY, Nayar J, Mueller JL, Anderson JP, Wanderer AA, Firestein GS. Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. *Lancet* 2004; 364: 1779.

165. Jander S, Stoll G. Differential induction of interleukin-12, interleukin-18, and interleukin-1β converting enzyme mRNA in experimental autoimmune encephalomyelitis of the Lewis rat. *J Neuroimmunol* 1998; 91: 93.

166. Wildbaum G, Youssef S, Grabie N, Karin N. Neutralizing antibodies to IFN-γ-inducing factor prevent experimental autoimmune encephalomyelitis. *J Immunol* 1998; 161: 6368.

167. Ito A, Matejuk A, Hopke C, Drought H, Dwyer J, Zamora A, Subramanian S, Vandenbark AA, Offner H. Transfer of severe experimental autoimmune encephalomyelitis by IL-12 and IL-18-potentiated T cells is estrogen sensitive. *J Immunol* 2003; 170: 4802.

168. Shi FD, Takeda K, Akira S, Sarvetnick N, Ljunggren HG. IL-18 directs autoreactive T cells and promotes autodestruction in the central nervous system via induction of IFN-γ by NK cells. *J Immunol* 2000; 165: 3099.

169. Furlan R, Martino G, Galbiati F, Poliani PL, Smiroldo S, Bergami A, Desina G, Comi G, Flavell R, Su MS, *et al.* Caspase-1 regulates the inflammatory process leading to autoimmune demyelination. *J Immunol* 1999; 163: 2403.

170. Schif-Zuck S, Westermann J, Netzer N, Zohar Y, Meiron M, Wildbaum G, Karin N. Targeted overexpression of IL-18 binding protein at the central nervous system overrides flexibility in functional polarization of antigen-specific Th2 cells. *J Immunol* 2005; 174: 4307.

171. Balashov KE, Rottman JB, Weiner HL, Hancock WW. CCR5(+) and CXCR3(+) T cells are increased in multiple sclerosis and their ligands MIP-1alpha and IP-10 are expressed in demyelinating brain lesions. *Proc Natl Acad Sci USA* 1999; 96: 6873.

172. Furlan R, Filippi M, Bergami A, Rocca MA, Martinelli V, Poliani PL, Grimaldi LM, Desina G, Comi G, Martino G. Peripheral levels of caspase-1 mRNA correlate with disease activity in patients with multiple sclerosis; a preliminary study. *J Neurol Neurosurg Psychiatry* 1999; 67: 785.

173. Fassbender K, Mielke O, Bertsch T, Muehlhauser F, Hennerici M, Kurimoto M, Rossol S. Interferon-γ-inducing factor (IL-18) and interferon-γ in inflammatory CNS diseases. *Neurology* 1999; 53: 1104.

174. Boxel-Dezaire AH, Trigt-Hoff SC, Killestein J, Schrijver HM, van Houwelingen JC, Polman CH, Nagelkerken L. Contrasting responses to interferon β-1b treatment in relapsing-remitting multiple sclerosis: does baseline interleukin-12p35 messenger RNA predict the efficacy of treatment? *Ann Neurol* 2000; 48: 313.

175. Nicoletti F, Di Marco R, Mangano K, Patti F, Reggio E, Nicoletti A, Bendtzen K, Reggio A. Increased serum levels of interleukin-18 in patients with multiple sclerosis. *Neurology* 2001; 57: 342.

176. Losy J, Niezgoda A. IL-18 in patients with multiple sclerosis. *Acta Neurol Scand* 2001; 104: 171.

177. Boxel-Dezaire AH, Smits M, Trigt-Hoff SC, Killestein J, van Houwelingen JC, Polman CH, Nagelkerken L. Cytokine and IL-12 receptor mRNA discriminate between different clinical subtypes in multiple sclerosis. *J Neuroimmunol* 2001; 120: 152.

178. Karni A, Koldzic DN, Bharanidharan P, Khoury SJ, Weiner HL. IL-18 is linked to raised IFN-γ in multiple sclerosis and is induced by activated CD4(+) T cells via CD40-CD40 ligand interactions. *J Neuroimmunol* 2002; 125: 134.

179. Franciotta D, Martino G, Zardini E, Furlan R, Bergamaschi R, Gironi M, Bergami A, Angelini G, De Benedetti F, Pignatti P, *et al.* Caspase-1 levels in biological fluids from patients with multiple sclerosis and from patients with other neurological and non-neurological diseases. *Eur Cytokine Netw* 2002; 13: 99.

180. Ming X, Li W, Maeda Y, Blumberg B, Raval S, Cook SD, Dowling PC. Caspase-1 expression in multiple sclerosis plaques and cultured glial cells. *J Neurol Sci* 2002; 197: 9.

181. Huang WX, Huang P, Hillert J. Increased expression of caspase-1 and interleukin-18 in peripheral blood mononuclear cells in patients with multiple sclerosis. *Mult Scler* 2004; 10: 482.

182. Im SH, Barchan D, Maiti PK, Raveh L, Souroujon MC, Fuchs S. Suppression of experimental myasthenia gravis, a B cell-mediated autoimmune disease, by blockade of IL-18. *FASEB J* 2001; 15: 2140.

183. Souroujon MC, Maiti PK, Feferman T, Im SH, Raveh L, Fuchs S. Suppression of myasthenia gravis by antigen-specific mucosal tolerance and modulation of cytokines and costimulatory factors. *Ann N Y Acad Sci* 2003; 998: 533.

184. Shi FD, Wang HB, Li H, Hong S, Taniguchi M, Link H, Van Kaer L, Ljunggren HG. Natural killer cells determine the outcome of B cell-mediated autoimmunity. *Nat Immunol* 2000; 1: 245.

185. Jander S, Stoll G. Increased serum levels of the interferon-γ-inducing cytokine interleukin-18 in myasthenia gravis. *Neurology* 2002; 59: 287.

186. Aarli JA. Role of cytokines in neurological disorders. *Curr Med Chem* 2003; 10: 1931.

187. Joosten LA, van De Loo FA, Lubberts E, Helsen MM, Netea MG, Der Meer JW, Dinarello CA, van den Berg WB. An IFN-γ-independent proinflammatory role of IL-18 in murine streptococcal cell wall arthritis. *J Immunol* 2000; 165: 6553.

188. Tissi L, McRae B, Ghayur T, von Hunolstein C, Orefici G, Bistoni F, Puliti M. Role of interleukin-18 in experimental group B streptococcal arthritis. *Arthritis Rheum* 2004; 50: 2005.

189. Leung BP, McInnes IB, Esfandiari E, Wei XQ, Liew FY. Combined effects of IL-12 and IL-18 on the induction of collagen-induced arthritis. *J Immunol* 2000; 164: 6495.

190. Wei XQ, Leung BP, Arthur HM, McInnes IB, Liew FY. Reduced incidence and severity of collagen-induced arthritis in mice lacking IL-18. *J Immunol* 2001; 166: 517.

191. Canetti CA, Leung BP, Culshaw S, McInnes IB, Cunha FQ, Liew FY. IL-18 enhances collagen-induced arthritis by recruiting neutrophils via TNF-α and leukotriene B4. *J Immunol* 2003; 171: 10095.

192. Gracie JA, Forsey RJ, Chan WL, Gilmour A, Leung BP, Greer MR, Kennedy K, Carter R, Wei XQ, Xu D, *et al.* A proinflammatory role for IL-18 in rheumatoid arthritis. *J Clin Invest* 1999; 104: 1393.

193. Smeets RL, van De Loo FA, Arntz OJ, Bennink MB, Joosten LA, van den Berg WB. Adenoviral delivery of IL-18 binding protein C ameliorates collagen-induced arthritis in mice. *Gene Ther* 2003; 10: 1004.

194. Banda NK, Vondracek A, Kraus D, Dinarello CA, Kim SH, Bendele A, Senaldi G, Arend WP. Mechanisms of inhibition of collagen-induced arthritis by murine IL-18 binding protein. *J Immunol* 2003; 170: 2100.

195. Plater-Zyberk C, Joosten LA, Helsen MM, Sattonnet-Roche P, Siegfried C, Alouani S, van De Loo FA, Graber P, Aloni S, Cirillo R, *et al.* Therapeutic effect of neutralizing endogenous IL-18 activity in the collagen-induced model of arthritis. *J Clin Invest* 2001; 108: 1825.

196. Ye XJ, Tang B, Ma Z, Kang AH, Myers LK, Cremer MA. The roles of interleukin-18 in collagen-induced arthritis in the BB rat. *Clin Exp Immunol* 2004; 136: 440.

197. Santos LL, Milenkovski GP, Hall PH, Leech M, Sharma L, Takeda K, Akira S, Kitching AR, Morand EF. IL-18 is redundant in T cell responses and in joint inflammation in antigen-induced arthritis. *Immunol Cell Biol* 2006; 84: 166.

198. Murphy CA, Langrish CL, Chen Y, Blumenschein W, Mc Clanahan T, Kastelein RA, Sedgwick JD, Cua DJ. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. *J Exp Med* 2003; 198: 1951.

199. Tanaka M, Harigai M, Kawaguchi Y, Ohta S, Sugiura T, Takagi K, Ohsako-Higami S, Fukasawa C, Hara M, Kamatani N. Mature form of interleukin 18 is expressed in rheumatoid arthritis synovial tissue and contributes to interferon-γ production by synovial T cells. *J Rheumatol* 2001; 28: 1779.

200. Maury CP, Tiitinen S, Laiho K, Kaarela K, Liljestrom M. Raised circulating interleukin-18 levels in reactive AA-amyloidosis. *Amyloid* 2002; 9: 141.

201. Scola MP, Thompson SD, Brunner HI, Tsoras MK, Witte D, Van Dijk MA, Grom AA, Passo MH, Glass DN. Interferon-γ: interleukin 4 ratios and associated type 1 cytokine expression in juvenile rheumatoid arthritis synovial tissue. *J Rheumatol* 2002; 29: 369.

202. Yamamura M, Kawashima M, Taniai M, Yamauchi H, Tanimoto T, Kurimoto M, Morita Y, Ohmoto Y, Makino H. Interferon-γ-inducing activity of interleukin-18 in the joint with rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 275.

203. Maeno N, Takei S, Imanaka H, Yamamoto K, Kuriwaki K, Kawano Y, Oda H. Increased interleukin-18 expression in bone marrow of a patient with systemic juvenile idiopathic arthritis and unrecognized macrophage-activation syndrome. *Arthritis Rheum* 2004; 50: 1935.

204. Ogata A, Kitano M, Yamanaka J, Yamasaki T, Hashimoto N, Iwasaki T, Hamano T, Fujimoto J, Kakishita E. Interleukin 18 and hepatocyte growth factor in fulminant hepatic failure of adult onset Still's disease. *J Rheumatol* 2003; 30: 1093.

205. Sato M, Takemura M, Shinohe R, Koishi H, Morita T, Seishima M. [Clinical significance of serum IL-18 determination in rheumatoid arthritis]. *Rinsho Byori* 2004; 52: 109.

206. Sawayama Y, Nabeshima S, Taniai H, Furusyo N, Kashiwagi S, Hayashi J. A Japanese case of severe refractory adult Still's disease: serum interleukin-18 is a possible marker of the response to low-dose cyclosporin A therapy. *Fukuoka Igaku Zasshi* 2002; 93: 189.

207. Choi JH, Suh CH, Lee YM, Suh YJ, Lee SK, Kim SS, Nahm DH, Park HS. Serum cytokine profiles in patients with adult onset Still's disease. *J Rheumatol* 2003; 30: 2422.

208. Fujii T, Nojima T, Yasuoka H, Satoh S, Nakamura K, Kuwana M, Suwa A, Hirakata M, Mimori T. Cytokine and immunogenetic profiles in Japanese patients with adult Still's disease. Association with chronic articular disease. *Rheumatology (Oxford)* 2001; 40: 1398.

209. Munakata T, Uzuki M, Shimamura T, Sawai T. [Dynamics of interleukin (IL-18) in serum, synovial fluid and synovial membrane in the patients with rheumatoid arthritis]. *Ryumachi* 2001; 41: 625.

210. Joosten LA, Radstake TR, Lubberts E, van den Bersselaar LA, van Riel PL, van Lent PL, Barrera P, van den Berg WB. Association of interleukin-18 expression with enhanced levels of both interleukin-1β and tumor necrosis factor α in knee synovial tissue of patients with rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 339.

211. Mosaad YM, Metwally SS, Auf FA, Abd el-Samee ER, el-Deek B, Limon NI, el-Chennawi FA. Proinflammatory cytokines (IL-12 and IL-18) in immune rheumatic diseases: relation with disease activity and autoantibody production. *Egypt J Immunol* 2003; 10: 19.

212. Eriksson P, Andersson C, Ekerfelt C, Ernerudh J, Skogh T. Sjögren's syndrome with myalgia is associated with subnormal secretion of cytokines by peripheral blood mononuclear cells. *J Rheumatol* 2004; 31: 729.

213. Chen DY, Lan JL, Lin FJ, Hsieh TY, Wen MC. Predominance of Th1 cytokines in peripheral blood and pathological tissues of patients with active untreated adult onset Still's disease. *Ann Rheum Dis* 2004; 63: 1300.

214. Rooney R, Murphy E, Benito M, Roux-Lombard P, FitzGerald O, Dayer JM, Bresnihan B. Synovial tissue interleukin-18 and the response to treatment in patients with inflammatory arthritis. *Ann Rheum Dis* 2004; 63: 1393.

215. Chen DY, Lan JL, Lin FJ, Hsieh TY. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. *J Rheumatol* 2004; 31: 2189.

216. Okamura H, Kashiwamura S, Ueda H. [Interleukin 18 in pathogenesis of rheumatoid arthritis]. *Nippon Rinsho* 2005; 63: 175.

217. Miranda LA, Fischer RG, Sztajnbok FR, Johansson A, Figueredo CM, Gustafsson A. Increased interleukin-18 in patients with juvenile idiopathic arthritis and early attachment loss. *J Periodontol* 2005; 76: 75.

218. Chen DY, Lan JL, Lin FJ, Hsieh TY. Association of intercellular adhesion molecule-1 with clinical manifestations and interleukin-18 in patients with active, untreated adult-onset Still's disease. *Arthritis Rheum* 2005; 53: 320.

219. Arlet JB, Le Thi Houng DB, Pouchot J, Piette JC. [Current concepts on the physiopathology of adul onset Still's disease]. *Rev Int Med* 2005; 26: 549.

220. van Kuijk AW, Reinders-Blankert P, Smeets TJ, Dijkmans BA, Tak PP. Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthriris: implications for therapy. *Ann Rheum Dis* 2006; 65: 1551.

221. Hessian PA, Highton J, Kean A, Sun CK, Chin M. Cytokine profile of the rheumatoid nodule suggests that it is a Th1 granuloma. *Arthritis Rheum* 2003; 48: 334.

222. Sugiura T, Kawaguchi Y, Harigai M, Terajima-Ichida H, Kitamura Y, Furuya T, Ichikawa N, Kotake S, Tanaka M, Hara M, *et al.* Association between adult-onset Still's disease and interleukin-18 gene polymorphisms. *Genes Immun* 2002; 3: 394.

223. Sivalingam SP, Yoon KH, Koh DR, Fong KY. Single-nucleotide polymorphisms of the interleukin-18 gene promoter region in rheumatoid arthritis patients: protective effect of AA genotype. *Tissue Antigens* 2003; 62: 498.

224. Gracie JA, Koyama N, Murdoch J, Field M, McGarry F, Crilly A, Schobel A, Madhok R, Pons-Kuhnemann J, McInnes IB, Moller B. Disease association of two distinct interleukin-18 promoter polymorphisms in Caucasian rheumatoid arthritis patients. *Genes Immun* 2005; 6: 211.

225. Sugiura T, Maeno N, Kawaguchi Y, Takei S, Imanaka H, Kawano Y, Terajima-Ichida H, Hara M, Kamatani N. A promoter haplotype of the interleukin-18 gene is associated with juvenile idiopathic arthritis in the Japanese population. *Arthritis Res Ther* 2006; 8: R60.

226. Pawlik A, Kurzawski M, Czerny B, Gawronska-Szklarz B, Drozdzik M, Herczynska M. Interleukin-18 promoter polymorphism in patients with rheumatoid arthritis. *Tissue Antigens* 2006; 67: 415.

227. Bokarewa M, Hultgren O. Is interleukin-18 useful for monitoring rheumatoid arthritis? *Scand J Rheumatol* 2005; 34: 433.

228. Petrovic-Rackov L, Pejnovic N. Clinical significance of IL-12, IL-15, IL-18 and TNF-α measurement in rheumatoid arthritis. *Clin Rheumatol* 2006; 25: 448.

229. Aita T, Yamamura M, Kawashima M, Okamoto A, Iwahashi M, Yamana J, Makino H. Expression of interleukin 12 receptor (IL-12R) and IL-18R on CD4+ T cells from patients with rheumatoid arthritis. *J Rheumatol* 2004; 31: 448.

230. Dai SM, Shan ZZ, Nishioka K, Yudoh K. Implication of interleukin 18 in production of matrix metalloproteinases in articular chondrocytes in arthritis: direct effect on chondrocytes may not be pivotal. *Ann Rheum Dis* 2005; 64: 735.

231. Chabaud M, Lubberts E, Joosten L, van Den BW, Miossec P. IL-17 derived from juxta-articular bone and synovium contributes to joint degradation in rheumatoid arthritis. *Arthritis Res* 2001; 3: 168.

232. Lubberts E, Joosten LA, Oppers B, van den Bersselaer L, Coenen-de Roo CJ, Kolls JK, Schwarzenberger P, van De Loo FA, van den Berg WB. IL-1-independent role of IL-17 in synovial inflammation and joint destruction during collagen-induced arthritis. *J Immunol* 2001; 167: 1004.

233. Lubberts E, van den Bersselaer L, Oppers-Walgreen B, Schwarzenberger P, Coenen-de Roo CJ, Kolls JK, Joosten LA, van den Berg WB. IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF-κB ligand/osteoprotegerin balance. *J Immunol* 2003; 170: 2655.

234. Olee T, Hashimoto S, Quach J, Lotz M. IL-18 is produced by articular chondrocytes and induces proinflammatory and catabolic responses. *J Immunol* 1999; 162: 1096.

235. Tanaka F, Migita K, Kawabe Y, Aoyagi T, Ida H, Kawakami A, Eguchi K. Interleukin-18 induces serum amyloid A (SAA) protein production from rheumatoid synovial fibroblasts. *Life Sci* 2004; 74: 1671.

236. Ogata A, Kitano M, Yamanaka J, Yamasaki T, Hashimoto N, Iwasaki T, Hamano T, Fujimoto J, Kakishita E. Interleukin 18 and hepatocyte growth factor in fulminant hepatic failure of adult onset Still's disease. *J Rheumatol* 2003; 30: 1093.

237. Larroche C, Mouthon L. Pathogenesis of hemophagocytic syndrome (HPS). *Autoimmun Rev* 2004; 3: 69.

238. Pittoni V, Bombardieri M, Spinelli FR, Scrivo R, Alessandri C, Conti F, Spadaro A, Valesini G. Anti-tumour necrosis factor (TNF) α treatment of rheumatoid arthritis (infliximab) selectively down regulates the production of interleukin (IL) 18 but not of IL12 and IL13. *Ann Rheum Dis* 2002; 61: 723.

239. Dayer JM. Interleukin-18, rheumatoid arthritis, and tissue destruction. *J Clin Invest* 1999; 104: 1337.

240. Liew FY, Wei XQ, McInnes IB. Role of interleukin-18 in rheumatoid arthritis. *Ann Rheum Dis* 2003; 62(Suppl 2): ii48.

241. van den Berg WB. Lessons from animal models of arthritis. *Curr Rheumatol Rep* 2002; 4: 232.

242. Matsui K, Tsutsui H, Nakanishi K. Pathophysiological roles for IL-18 in inflammatory arthritis. *Expert Opin Ther Targets* 2003; 7: 701.

243. Taylor PC. Anti-cytokines and cytokines in the treatment of rheumatoid arthritis. *Curr Pharm Des* 2003; 9: 10956.

244. Braddock M, Quinn A, Canvin J. Therapeutic potential of targeting IL-1 and IL-18 in inflammation. *Expert Opin Biol Ther* 2004; 4: 847.

245. Dinarello CA. Interleukin-18 and the treatment of rheumatoid arthritis. *Rheum Dis Clin Nort Am* 2004; 30: 417.

246. Muhl H, Pfeilschifter J. Interleukin-18 bioactivity: a novel target for immunopharmacological anti-inflammatory intervention. *Eur J Pharmacol* 2004; 500: 63.

247. McInnes IB, Liew FY, Gracie JA. Interleukin-18: a therapeutic target in rheumatoid arthritis? *Arthritis Res Ther* 2005; 7: 38.

248. van Oosterhout M, Levarht EW, Sont JK, Huizinga TW, Toes RE, van Laar JM. Clinical efficacy of infliximab plus methotrexate in DMARD naive and DMARD refractory rheumatoid arthritis is associated with decreased synovial expression of TNF-α and IL-18 but not CXCL12. *Ann Rheum Dis* 2005; 64: 537.

249. McInnes IB, Gracie JA. Targeting cytokines beyond TNF-α and IL-1 in rheumatoid arthritis. *Curr Pain Headache Rep* 2005; 9: 405.

250. Sun B, Sun SH, Chan CC, Caspi RR. Evaluation of in vivo cytokine expression in EAU-susceptible and resistant rats: a role for IL-10 in resistance? *Exp Eye Re* 2000; 70: 493.

251. Jiang HR, Wei X, Niedbala W, Lumsden L, Liew FY, Forrester JV. IL-18 not required for IRBP peptide-induced EAU: studies in gene-deficient mice. *Invest Ophthalmol Vis Sci* 2001; 42: 177.

252. Su SB, Silver PB, Grajewski RS, Agarwal RK, Tang J, Chan CC, Caspi RR. Essential role of the MyD88 pathway, but nonessential roles of TLRs 2, 4, and 9 in the adjuvant effect promoting Th1-mediated autoimmunity. *J Immunol* 2005; 175: 6303.

253. Hamzaoui K, Hamzaoui A, Guemira F, Bessioud M, Hamza M, Ayed K. Cytokine profile in Behcet's disease patients. Relationship with disease activity. *Scand J Rheumatol* 2002; 31: 205.

254. Hamzaoui A, Ghrairi H, Ammar J, Zekri S, Guemira F, Hamzaoui K. IL-18 mRNA expression and IFN-γ induction in bronchoalveolar lavage from Behcet's disease. *Clin Exp Rheumatol* 2003; 21: S8.

255. Oztas MO, Onder M, Gurer MA, Bukan N, Sancak B. Serum interleukin 18 and tumour necrosis factor-α levels are increased in Behcet's disease. *Clin Exp Dermatol* 2005; 30: 61.

256. Nagafuchi H, Takeno M, Yoshikawa H, Kurokawa MS, Nara K, Takeda E, Masuda C, Mizoguchi M, Suzuki N. Excessive expression of Txk, a member of the Tec family of tyrosine kinases, contributes to excessive Th1 cytokine production by T lymphocytes in patients with Behcet's disease. *Clin Exp Immunol* 2005; 139: 363.

257. Jang WC, Park SB, Nam YH, Lee SS, Kim JW, Chang IS, Kim KT, Chang HK. Interleukin-18 gene polymorphisms in Korean patients with Behcet's disease. *Clin Exp Rheumatol* 2005; 23: S59.

258. Ohta Y, Hamada Y, Katsuoka K. Expression of IL-18 in psoriasis. *Arch Dermatol Res* 2001; 293: 334.

259. Gangemi S, Merendino RA, Guarneri F, Minciullo PL, DiLorenzo G, Pacor M, Cannavo SP. Serum levels of interleukin-18 and s-ICAM-1 in patients affected by psoriasis: preliminary considerations. *J Eur Acad Dermatol Venereol* 2003; 17: 42.

260. Pietrzak A, Lecewicz-Torun B, Rolinski J. Interleukin-18 serum concentration in patients with psoriasis triggered by infection. *Ann Univ Mariae Curie Sklodowska [Med]* 2002; 57: 484; [Med].

261. Pietrzak A, Lecewicz-Torun B, Chodorowska G, Rolinski J. Interleukin-18 levels in the plasma of psoriatic patients correlate with the extent of skin lesions and the PASI score. *Acta Derm Venereol* 2003; 83: 262.

262. Mee JB, Alam Y, Groves RW. Human keratinocytes constitutively produce but do not process interleukin-18. *Br J Dermatol* 2000; 143: 330.

263. Zepter K, Haffner A, SooHoo LF, De Luca D, Tang HP, Fisher P, Chavinson J, Elmets CA. Induction of biologically active IL-1β-converting enzyme and mature IL-1β in human keratinocytes by inflammatory and immunologic stimuli. *J Immunol* 1997; 159: 6203.

264. Naik SM, Cannon G, Burbach GJ, Singh SR, Swerlick RA, Wilcox JN, Ansel JC, Caughman SW. Human keratinocytes constitutively express interleukin-18 and secrete biologically active interleukin-18 after treatment with pro-inflammatory mediators and dinitrochlorobenzene. *J Invest Dermatol* 1999; 113: 766.

265. Cho D, Kang JS, Park JH, Kim YI, Hahm E, Lee J, Yang Y, Jeon J, Song H, Park H, *et al.* The enhanced IL-18 production by UVB irradiation requires ROI and AP-1 signaling in human keratinocyte cell line (HaCaT). *Biochem Biophys Res Commun* 2002; 298: 289.

266. Niyonsaba F, Ushio H, Nagaoka I, Okumura K, Ogawa H. The human β-defensins (-1, -2, -3, -4) and cathelicidin LL-37 induce IL-18 secretion through p38 and ERK MAPK activation in primary human keratinocytes. *J Immunol* 2005; 175: 1776.

267. Kong J, Grando SA, Li YC. Regulation of IL-1 family cytokines IL-1α, IL-1 receptor antagonist, and IL-18 by 1,25-dihydroxyvitamin D3 in primary keratinocytes. *J Immunol* 2006; 176: 3780.

268. Ariizumi K, Kitajima T, Bergstresser OR, Takashima A. Interleukin-1β converting enzyme in murine Langerhans cells and epidermal-derived dendritic cell lines. *Eur J Immunol* 1995; 25: 2137.

269. Wang B, Feliciani C, Howell BG, Freed I, Cai O, Watanabe H, Sauder DN. Contribution of Langerhans cell-derived IL-18 to contact hypersensitivity. *J Immunol* 2002; 168: 3303.

270. Matos TJ, Jaleco SP, Goncalo M, Duarte CB, Lopes MC. Release of IL-1α via IL-1β-converting enzyme in a skin dendritic cell line exposed to 2,4-dinitrofluorobenzene. *Mediators Inflamm* 2005; 113: 131.

271. Wittmann M, Purwar R, Hartmann C, Gutzmer R, Werfel T. Human keratinocytes respond to interleukin-18: implication for the course of chronic inflammatory skin diseases. *J Invest Dermatol* 2005; 124: 1225.

272. Piskin G, Tursen U, Sylva-Steenland RM, Bos JD, Teunissen MB. Clinical improvement in chronic plaque-type psoriasis lesions after narrow-band UVB therapy is accompanied by a decrease in the expression of IFN-γ inducers -- IL-12, IL-18 and IL-23. *Exp Dermatol* 2004; 13: 764.

273. Companjen A, van der Wel L, van der Fits L, Laman J, Prens E. Elevated interleukin-18 protein expression in early active and progressive plaque-type psoriatic lesions. *Eur Cytokine Netw* 2004; 15: 210.

274. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-α, IFN-α, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm* 2005; 5: 273.

275. Flisiak I, Klepacki A, Chodynicka B. Plasma and scales levels of interleukin 18 in comparison with other possible clinical and laboratory biomarkers of psoriasis activity. *Biomarkers* 2006; 11: 194.

276. Konishi H, Tsutsui H, Murakami T, Yumikura-Futatsugi S, Yamanaka K, Tanaka M, Iwakura Y, Suzuki N, Takeda K, Akira S, *et al.* IL-18 contributes to the spontaneous development of atopic dermatitis-like inflammatory skin lesion independently of IgE/stat6 under specific pathogen-free conditions. *Proc Natl Acad Sci USA* 2002; 99: 11340.

277. Kawase Y, Hoshino T, Yokota K, Kuzuhara A, Kirii Y, Nishiwaki E, Maeda Y, Takeda J, Okamoto M, Kato S, *et al.* Exacerbated and prolonged allergic and non-allergic inflammatory cutaneous reaction in mice with targeted interleukin-18 expression in the skin. *J Invest Dermatol* 2003; 121: 502.

278. Numerof RP, Dinarello CA, Asadullah K. Cytokines as potential therapeutic targets for inflammatory skin diseases. *Eur Cytokine Netw* 2005; 16: 101.

279. Numerof RP, Asadullah K. Cytokine and anti-cytokine therapies for psoriasis and atopic dermatitis. *BioDrugs* 2006; 20: 93.

280. Kaiser P, Rothwell L, Vasicek D, Hala K. A role for IL-15 in driving the onset of spontaneous autoimmune thyroiditis? *J Immunol* 2002; 168: 4216.

281. Zaccone P, Fehervari Z, Cooke A. Tumour necrosis factor-α is a fundamental cytokine in autoimmune thyroid disease induced by thyroglobulin and lipopolysaccharide in interleukin-12 p40 deficient C57BL/6 mice. *Immunology* 2003; 108: 50.

282. Miyauchi S, Matsuura B, Onji M. Increased levels of serum interleukin-18 in Graves' disease. *Thyroid* 2000; 10: 815.

283. Takiyama Y, Miyokawa N, Tokusashi Y, Ito K, Kato S, Kimura S, Sato K, Katagiri M. Thyroid-stimulating hormone induces interleukin-18 gene expression in FRTL-5 cells: immunohistochemical detection of interleukin-18 in autoimmune thyroid disease. *Thyroid* 2002; 12: 935.

284. Mysliwiec J, Kretowski A, Stepien A, Mironczuk K, Kinalska I. Interleukin 18 and transforming growth factor β1 in the serum of patients with Graves' ophthalmopathy treated with corticosteroids. *Int Immunopharmacol* 2003; 3: 549.

285. Zhang JA, Zhang J, Xu L, Mar H, Wu XY. [Measurement of IL-12 and IL-18 in sera of patients with autoimmune thyroid disease.]. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2006; 22: 630.

286. Wakelkamp IM, Bakker O, Baldeschi L, Wiersinga WM, Prummel MF. TSH-R expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. *Clin Endocrinol (Oxf)* 2003; 58: 280.

287. Wakelkamp IM, Prummel MF, Wiersinga WM. Serum IL-18 levels are not increased in patients with untreated Graves' ophthalmopathy. *Horm Metab Res* 2004; 36: 44.

288. Phenekos C, Vryonidou A, Gritzapis AD, Baxevanis CN, Goula M, Papamichail M. Th1 and Th2 serum cytokine profiles characterize patients with Hashimoto's thyroiditis (Th1) and Graves' disease (Th2). *Neuroimmunomodulation* 2004; 11: 209.

289. Ide A, Kawasaki E, Abiru N, Sun F, Fukushima T, Ishii R, Takahashi R, Kuwahara H, Fujita N, Kita A, *et al.* Association of interleukin-18 gene promoter polymorphisms in type 1 diabetes and autoimmune thyroid disease. *Ann N Y Acad Sci* 2003; 1005: 436.

290. Neumann D, Del Giudice E, Ciaramella A, Boraschi D, Bossù P. Lymphocytes from autoimmune MRL lpr/lpr mice are hyperresponsive to IL-18 and overexpress the IL-18 receptor accessory chain. *J Immunol* 2001; 166: 3757.

291. Esfandiari E, McInnes IB, Lindop G, Huang FP, Field M, Komai-Koma M, Wei X, Liew FY. A proinflammatory role of IL-18 in the development of spontaneous autoimmune disease. *J Immunol* 2001; 167: 5338.

292. Faust J, Menke J, Kriegsmann J, Kelley VR, Mayet WJ, Galle PR, Schwarting A. Correlation of renal tubular epithelial cell-derived interleukin-18 up-regulation with disease activity in MRL-Faslpr mice with autoimmune lupus nephritis. *Arthritis Rheum* 2002; 46: 3083.

293. Bossù P, Neumann D, Del Giudice E, Ciaramella A, Gloaguen I, Fantuzzi G, Dinarello CA, Di Carlo E, Musiani P, Meroni PL, *et al.* IL-18 cDNA vaccination protects mice from spontaneous lupus-like autoimmune disease. *Proc Natl Acad Sci USA* 2003; 100: 14181.

294. Bossù P, Del Giudice E, Ciaramella A, Neumann D, Boraschi D. IL-18 and IL-18 receptors in the development of autoimmunity. *Eur Cytokine Netw* 2000; 11: 515.

295. Kinoshita K, Yamagata T, Nozaki Y, Sugiyama M, Ikoma S, Funauchi M, Kanamaru A. Blockade of IL-18 receptor signaling delays the onset of autoimmune disease in MRL-Faslpr mice. *J Immunol* 2004; 173: 5312.

296. Lin L, Peng SL. Interleukin-18 receptor signaling is not required for autoantibody production and end-organ disease in murine lupus. *Arthritis Rheum* 2005; 52: 984.

297. Wong CK, Li EK, Ho CY, Lam CW. Elevation of plasma interleukin-18 concentration is correlated with disease activity in systemic lupus erythematosus. *Rheumatology (Oxford)* 2000; 39: 1078.

298. Wong CK, Ho CY, Li EK, Lam CW. Elevation of proinflammatory cytokine (IL-12, IL-17, IL-18) and Th2 cytokine (IL-4) concentrations in patients with systemic lupus erythematosus. *Lupus* 2000; 9: 589.

299. Wong CK, Ho CY, Li EK, Tam LS, Lam CW. Elevated production of interleukin-18 is associated with renal disease in patients with systemic lupus erythematosus. *Clin Exp Immunol* 2002; 130: 345.

300. Amerio P, Frezzolini A, Abeni D, Teofoli P, Girardelli CR, De Pita O, Puddu P. Increased IL-18 in patients with systemic lupus erythematosus: relations with Th-1, Th-2, pro-inflammatory cytokines and disease activity. IL-18 is a marker of disease activity but does not correlate with pro-inflammatory cytokines. *Clin Exp Rheumatol* 2002; 20: 535.

301. Robak E, Wozniacka A, Sysa-Jedrzejowska A, Stepien H, Robak T. Circulating angiogenesis inhibitor endostatin and positive endothelial growth regulators in patients with systemic lupus erythematosus. *Lupus* 2002; 11: 348.

302. Robak E, Robak T, Wozniacka A, Zak-Prelich M, Sysa-Jedrzejowska A, Stepien H. Proinflammatory interferon-γ-inducing monokines (interleukin-12, interleukin-15, interleukin-18) - serum profile in patients with systemic lupus erythematosus. *Eur Cytokine Netw* 2002; 13: 364.

303. Crispin JC, Alcocer-Varela J, de Pablo P, Martinez A, Richaud-Patin Y, Alarcon-Segovia D. Immunoregulatory defects in patients with systemic lupus erythematosus in clinical remission. *Lupus* 2003; 12: 386.

304. Park MC, Park YB, Lee SK. Elevated interleukin-18 levels correlated with disease activity in systemic lupus erythematosus. *Clin Rheumatol* 2004; 23: 225.

305. Calvani N, Richards HB, Tucci M, Pannarale G, Silvestris F. Up-regulation of IL-18 and predominance of a Th1 immune response is a hallmark of lupus nephritis. *Clin Exp Immunol* 2004; 138: 171.

306. Pan ZX, Liu HF, Tang DS, Liang D, Chen XW. [IL-18 expression in whole blood cell cultures from active lupus nephritis and the inhibitory effects of FK506, cyclosporin A and dexamethasone]. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2004; 20: 741.

307. Wong CK, Lit LC, Tam LS, Li EK, Lam CW. Elevation of plasma osteopontin concentration is correlated with disease activity in patients with systemic lupus erythematosus. *Rheumatol* 2005; 44: 602.

308. Lesiak A, Sysa-Jedrzejowska A, Narbutt J, Lukamowicz J, Robak E, Wozniacka A. [Proinflammatory cytokines in inactive lupus erythematosus patients]. *Przegl Lek* 2005; 62: 838.

309. Maczynska I, Millo B, Ratajczak-Stefanska V, Maleszka R, Szych Z, Kurpisz M, Giedrys-Kalemba S. Proinflammatory cytokine (IL-1β, IL-6, IL-12, IL-18 and TNF-α) levels in sera of patients with subacute cutaneous lupus erythematosus (SCLE). *Immunol Lett* 2006; 102: 79.

310. Lit LC, Wong CK, Tam LS, Li EK, Lam CW. Raised plasma concentration and ex vivo production of inflammatory chemokines in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2006; 65: 209.

311. Tso TK, Huang WN, Huang HY, Chang CK. Relationship of plasma interleukin-18 concentrations to traditional and non-traditional cardiovascular risk factors in patients with systemic lupus erythematosus. *Rheumatology* 2006; 1145: 1148.

312. Tso TK, Huang WN, Huang HY, Chang CK. Elevation of plasma interleukin-18 concentration is associated with insulin levels in patients with systemic lupus erythematosus. *Lupus* 2006; 15: 207.

313. Wozniacka A, Lesiak A, Narbutt J, McCauliffe DP, Sysa-Jedrzejowska A. Chloroquine treatment influences proinflammatory cytokine levels in systemic lupus erythematosus patients. *Lupus* 2006; 15: 268.

314. Liang D, Mao WF, Yao CW, Liu HF, Chen XW. Imbalance of interleukin 18 and interleukin 18 binding protein in patients with lupus nephritis. *Cell Mol Immunol* 2006; 3: 303.

315. Aringer M, Smolen JS. Tumour necrosis factor and other proinflammatory cytokines in systemic lupus erythematosus: a rationale for therapeutic intervention. *Lupus* 2004; 13: 344.

316. Aringer M, Smolen JS. Cytokine expression in lupus kidneys. *Lupus* 2005; 14: 13.

317. Smolen JS, Steiner G, Aringer M. Anti-cytokine therapy in systemic lupus erythematosus. *Lupus* 2005; 14: 189.

318. Tucci M, Calvani N, Richards HB, Quatraro C, Silvestris F. The interplay of chemokines and dendritic cells in the pathogenesis of lupus nephritis. *Ann N Y Acad Sci* 2005; 1051: 421.

319. Calvani N, Tucci M, Richards HB, Tartaglia P, Silvestris F. Th1 cytokines in the pathogenesis of lupus nephritis: the role of IL-18. *Autoimmun Rev* 2005; 4: 542.

320. Kolkowski EC, Reth P, Pelusa F, Bosch J, Pujol-Borrell R, Coll J, Jaraquemada D. Th1 predominance and perforin expression in minor salivary glands from patients with primary Sjögren's syndrome. *J Autoimmun* 1999; 13: 155.

321. Bombardieri M, Barone F, Pittoni V, Alessandri C, Conigliaro P, Blades C, Priori R, McInnes IB, Valesini G, Pitzalis C. Increased circulating levels and salivary gland expression of interleukin-18 in patients with Sjögren's syndrome: relationship with autoantibody production and lymphoid organization of the periductal inflammatory infiltrate. *Arthritis Res Ther* 2004; 6: R447.

322. Kimura-Shimmyo A, Kashiwamura S, Ueda H, Ikeda T, Kanno S, Akira S, Nakanishi K, Mimura O, Okamura H. Cytokine-induced injury of the lacrimal and salivary glands. *J Immunother* 2002; 25: S42.

323. Tucci M, Quatraro C, Dammacco F, Silvestris F. Interleukin-18 overexpression as a hallmark of the activity of autoimmune inflammatory myopathies. *Clin Exp Immunol* 2006; 146: 21.

324. Nakamura S, Otani T, Ijiri Y, Motada R, Kurimoto M, Orita K. IFN-γ-dependent and -independent mechanisms in adverse effects caused by concomitant administration of IL-12 and IL-18. *J Immunol* 2000; 164: 3330.

325. Chikano S, Sawada K, Shimoyama T, Kashiwamura SI, Sugihara A, Sekikawa K, Terada N, Nakanishi K, Okamura H. IL-12 and IL-18 induce intestinal inflammation and fatty liver in mice in an IFN-γ dependent manner. *Gut* 2000; 47: 779.

326. Raqib R, Ekberg C, Sharkar P, Bardhan PK, Zychlinsky A, Sansonetti PJ, Andersson J. Apoptosis in acute shigellosis is associated with increased production of Fas/Fas ligand, perforin, caspase-1, and caspase-3 but reduced production of Bcl-2 and interleukin-2. *Infect Immun* 2002; 70: 3199.

327. Ishikura T, Kanai T, Uraushihara K, Iiyama R, Makita S, Totsuka T, Yamazaki M, Sawada T, Nakamura T, Miyata T, *et al.* Interleukin-18 overproduction exacerbates the development of colitis with markedly infiltrated macrophages in interleukin-18 transgenic mice. *J Gastroenterol Hepatol* 2003; 18: 960.

328. Camoglio L, te Velde AA, de Boer A, ten Kate FJ, Kopf M, van Deventer SJ. Hapten-induced colitis associated with maintained Th1 and inflammatory responses in IFN-γ receptor-deficient mice. *Eur J Immunol* 2000; 30: 1486.

329. Sartor RB. Colitis in HLA-B27/β2 microglobulin transgenic rats. *Int Rev Immunol* 2000; 19: 39.

330. ten Hove T, Corbaz A, Amitai H, Aloni S, Belzer I, Graber P, Drillenburg P, van Deventer SJ, Chvatchko Y, te Velde AA. Blockade of endogenous IL-18 ameliorates TNBS-induced colitis by decreasing local TNF-α production in mice. *Gastroenterology* 2001; 121: 1372.

331. Siegmund B, Fantuzzi G, Rieder F, Gamboni-Robertson F, Lehr HA, Hartmann G, Dinarello CA, Endres S, Eigler A. Neutralization of interleukin-18 reduces severity in murine colitis and intestinal IFN-γ and TNF-α production. *Am J Physiol Regul Integr Comp Physiol* 2001; 281: R1264.

332. Kanai T, Watanabe M, Okazawa A, Sato T, Yamazaki M, Okamoto S, Ishii H, Totsuka T, Iiyama R, Okamoto R, *et al.* Macrophage-derived IL-18-mediated intestinal inflammation in the murine model of Crohn's disease. *Gastroenterology* 2001; 121: 875.

333. Sivakumar PV, Westrich GM, Kanaly S, Garka K, Born TL, Derry JM, Viney JL. Interleukin 18 is a primary mediator of the inflammation associated with dextran sulphate sodium induced colitis: blocking interleukin 18 attenuates intestinal damage. *Gut* 2002; 50: 812.

334. Lochner M, Forster I. Anti-interleukin-18 therapy in murine models of inflammatory bowel disease. *Pathobiology* 2002; 70: 164.

335. Camoglio L, Juffermans NP, Peppelenbosch M, te Velde AA, ten Kate FJ, van Deventer SJ, Kopf M. Contrasting roles of IL-12p40 and IL-12p35 in the development of hapten-induced colitis. *Eur J Immunol* 2002; 32: 261.

336. Siegmund B. Interleukin-1beta converting enzyme (caspase-1) in intestinal inflammation. *Biochem Pharmacol* 2002; 64: 1-8.

337. Wirtz S, Becker C, Blumberg R, Galle PR, Neurath MF. Treatment of T cell-dependent experimental colitis in SCID mice by local administration of an adenovirus expressing IL-18 antisense mRNA. *J Immunol* 2002; 168: 411.

338. Takagi H, Kanai T, Okazawa A, Kishi Y, Sato T, Takaishi H, Inoue N, Ogata H, Iwao Y, Hoshino K, *et al.* Contrasting action of IL-12 and IL-18 in the development of dextran sodium sulphate colitis in mice. *Scand J Gastroenterol* 2003; 38: 837.

339. Maerten P, Shen C, Colpaert S, Liu Z, Bullens DA, van Assche G, Penninckx F, Geboes K, Vanham G, Rutgeerts P, *et al.* Involvement of interleukin 18 in Crohn's disease: evidence from in vitro analysis of human gut inflammatory cells and from experimental colitis models. *Clin Exp Immunol* 2004; 135: 310.

340. Singh JC, Cruickshank SM, Newton DJ, Wakenshaw L, Graham A, Lan J, Lodge JP, Felsburg PJ, Carding SR. Toll-like receptor-mediated responses of primary intestinal epithelial cells during the development of colitis. *Am J Physiol Gastrointest Liver Physiol* 2005; 288: G514.

341. Abad C, Juarranz Y, Martinez C, Arranz A, Rosignoli F, Garcia-Gomez M, Leceta J, Gomariz RP. cDNA array analysis of cytokines, chemokines, and receptors involved in the development of TNBS-induced colitis: homeostatic role of VIP. *Inflamm Bowel Dis* 2005; 11: 674.

342. Hultgren OH, Berglund M, Bjursten M, Hultgren Hornquist E. Serum interleukin-1 receptor antagonist is an early indicator of colitis onset in Gαi2-deficient mice. *World J Gastroenterol* 2006; 12: 621.

343. Ishikura T, Kanai T, Uraushihara K, Iiyama R, Makita S, Totsuka T, Yamazaki M, Sawada T, Nakamura T, Miyata T, *et al.* Interleukin-18 overproduction exacerbates the development of colitis with markedly infiltrated macrophages in interleukin-18 transgenic mice. *J Gastroenterol Hepatol* 2003; 18: 960.

344. Shen C, Bullens D, Kasran A, Maerten P, Boon L, Aerts JM, Van Assche G, Geboes K, Rutgeerts P, Ceuppens JL. Inhibition of glycolipid biosynthesis by N-(5-adamantane-1-yl-methoxy-pentyl)-deoxynojirimycin protects against the inflammatory response in hapten-induced colitis. *Int Immunopharmacol* 2004; 4: 939.

345. Hanawa T, Suzuki K, Kawauchi Y, Takamura M, Yoneyama H, Han GD, Kawachi H, Shimizu F, Asakura H, Miyazaki J, *et al.* Attenuation of mouse acute colitis by naked hepatocyte growth factor gene transfer into the liver. *J Gene Med* 2006; 8: 623.

346. Siegmund B, Lehr HA, Fantuzzi G, Dinarello CA. IL-1β-converting enzyme (caspase-1) in intestinal inflammation. *Proc Natl Acad Sci USA* 2001; 98: 13249.

347. Loher F, Bauer C, Landauer N, Schmall K, Siegmund B, Lehr HA, Dauer M, Schoenharting M, Endres S, Eigler A. The interleukin-1β-converting enzyme inhibitor pralnacasan reduces dextran sulfate sodium-induced murine colitis and T helper 1 T-cell activation. *J Pharmacol Exp Ther* 2004; 308: 583.

348. Siegmund B, Sennello JA, Lehr HA, Senaldi G, Dinarello CA, Fantuzzi G. Interferon regulatory factor-1 as a protective gene in intestinal inflammation: role of TCR γδ T cells and interleukin-18-binding protein. *Eur J Immunol* 2004; 34: 2356.

349. Eaton AD, Xu D, Garside P. Administration of exogenous interleukin-12 and interleukin-18 prevents the induction of oral tolerance. *Immunology* 2003; 108: 196.

350. Pizarro TT, Michie MH, Bentz M, Woraratanadharm J, Smith-Jr. MF, Foley E, Moskaluk CA, Bickston SJ, Cominelli F. IL-18, a novel immunoregulatory cytokine, is up-regulated in Crohn's disease: expression and localization in intestinal mucosal cells. *J Immunol* 1999; 162: 6829.

351. Monteleone G, Trapasso F, Parrello T, Biancone L, Stella A, Iuliano R, Luzza F, Fusco A, Pallone F. Bioactive IL-18 pression is up-regulated in Crohn's disease. *J Immunol* 1999; 163: 143.

352. Kanai T, Watanabe M, Okazawa A, Nakamaru K, Okamoto M, Naganuma M, Ishii H, Ikeda M, Kurimoto M, Hibi T. Interleukin 18 is a potent proliferative factor for intestinal mucosal lymphocytes in Crohn's disease. *Gastroenterology* 2000; 119: 1514.

353. Pages F, Lazar V, Berger A, Danel C, Lebel-Binay S, Zinzindohoue F, Desreumaux P, Cellier C, Thiounn N, Bellet D, *et al.* Analysis of interleukin-18, interleukin-1 converting enzyme (ICE) and interleukin-18-related cytokines in Crohn's disease lesions. *Eur Cytokine Netw* 2001; 12: 97.

354. Furuya D, Yagihashi A, Komatsu M, Masashi N, Tsuji N, Kobayashi D, Watanabe N. Serum interleukin-18 concentrations in patients with inflammatory bowel disease. *J Immunother* 2002; 25(Suppl 1): S65-S67.

355. Salvati VM, MacDonald TT, Bajaj-Elliott M, Borrelli M, Staiano A, Auricchio S, Troncone R, Monteleone G. Interleukin 18 and associated markers of T helper cell type 1 activity in coeliac disease. *Gut* 2002; 50: 186.

356. Merendino RA, Di Pasquale G, Sturniolo GC, Ruello A, Albanese V, Minciullo PL, Di Mauro S, Gangemi S. Relationship between IL-18 and sICAM-1 serum levels in patients affected by coeliac disease: preliminary considerations. *Immunol Lett* 2003; 85: 257.

357. Zhang B, Lu Y, Hong T, Pei F, Li F, Wang X. [Expression of interleukin 18 in intestinal mucosa of patients with inflammatory bowel disease and its implications]. *Beijing Da Xue Xue Bao* 2003; 35: 150.

358. Lettesjo H, Hansson T, Bergqvist A, Gronlund J, Dannaeus A. Enhanced interleukin-18 levels in the peripheral blood of children with coeliac disease. *Clin Exp Immunol* 2005; 139: 138.

359. Wiercinska-Drapalo A, Flisiak R, Jaroszewicz J, Prokopowicz D. Plasma interleukin-18 reflects severity of ulcerative colitis. *World J Gastroenterol* 2005; 11: 605.

360. Ludwiczek O, Kaser A, Novick D, Dinarello CA, Rubinstein M, Tilg H. Elevated systemic levels of free interleukin-18 (IL-18) in patients with Crohn's disease. *Eur Cytokine Netw* 2005; 16: 27.

361. Towers R, Naftali T, Gabay G, Carlebach M, Klein A, Novis B. High levels of glucocorticoid receptors in patients with active Crohn's disease may predict steroid resistance. *Clin Exp Immunol* 2005; 141: 357.

362. Hanai H, Iida T, Yamada M, Sato Y, Takeuchi K, Tanaka T, Kondo K, Kikuyama M, Maruyama Y, Iwaoka Y, *et al.* Effects of adacolumn selective leukocytapheresis on plasma cytokines during active disease in patients with active ulcerative colitis. *World J Gastroenterol* 2006; 12: 3393.

363. te Velde AA, van Kooyk Y, Braat H, Hommes DW, Dellemijn TA, Slors JF, van Deventer SJ, Vyth-Dreese FA. Increased expression of DC-SIGN+IL-12+IL-18+ and CD83+IL-12-IL-18- dendritic cell populations in the colonic mucosa of patients with Crohn's disease. *Eur J Immunol* 2003; 33: 143.

364. Kanai T, Watanabe M, Okazawa A, Nakamaru K, Okamoto M, Naganuma M, Ishii H, Ikeda M, Kurimoto M, Hibi T. Interleukin 18 is a potent proliferative factor for intestinal mucosal lymphocytes in Crohn's disease. *Gastroenterology* 2000; 119: 1514.

365. Okazawa A, Kanai T, Watanabe M, Yamazaki M, Inoue N, Ikeda M, Kurimoto M, Ishii H, Hibi T. Th1-mediated intestinal inflammation in Crohn's disease may be induced by activation of lamina propria lymphocytes through synergistic stimulation of interleukin-12 and interleukin-18 without T cell receptor engagement. *Am J Gastroenterol* 2002; 97: 3108.

366. Tamura K, Fukuda Y, Sashio H, Takeda N, Bamba H, Kosaka T, Fukui S, Sawada K, Tamura K, Satomi M, *et al.* IL18 polymorphism is associated with an increased risk of Crohn's disease. *J Gastroenterol* 2002; 37: 111.

367. Glas J, Torok HO, Tonenchi L, Kapser J, Schiemann U, Muller-Myhsok B, Folwaczny M, Folwaczny C. Association of polymorphisms in the interleukin-18 gene in patients with Crohn's disease depending on the CARD15/NOD2 genotype. *Inflamm Bowel Dis* 2005; 11: 1031.

368. Takagawa T, Tamura K, Takeda N, Tomita T, Ohda Y, Fukunaga K, Hida N, Ohnishi K, Hori K, Kosaka T, *et al.* Association between IL-18 gene promoter polymorphisms and inflammatory bowel disease in a Japanese population. *Inflamm Bowel Dis* 2005; 11: 10383.

369. Haas SL, Koch WA, Schreiber S, Reinhard I, Koyama N, Singer MV, Bocker U.-137 (G/C) IL-18 promoter polymorphism in patients with inflammatory bowel disease. *Scand J Gastroenterol* 2005; 40: 1438.

370. Aizawa Y, Sutoh S, Matsuoka M, Negishi M, Torii A, Miyakawa Y, Sugisaka H, Nakamura M, Toda G. Association of interleukin-18 gene single-nucleotide polymorphisms with susceptibility to inflammatory bowel disease. *Tissue Antigens* 2005; 65: 88.

371. Mc Alindon ME, Hawkey CJ, Mahida YR. Expression of interleukin 1β and interleukin 1β converting enzyme by intestinal macrophages in health and inflammatory bowel disease. *Gut* 1998; 42: 214.

372. McAlindon ME, Galvin A, McKaig B, Gray T, Sewell HF, Mahida YR. Investigation of the expression of IL-1β converting enzyme and apoptosis in normal and inflammatory bowel disease (IBD) mucosal macrophages. *Clin Exp Immunol* 1999; 116: 251.

373. Zhang Z, Wang L, Seydel KB, Li E, Ankri S, Mirelman D, Stanley Jr. SL. Entamoeba histolytica cysteine proteinases with interleukin-1β converting enzyme (ICE) activity cause intestinal inflammation and tissue damage in amoebiasis. *Mol Microbiol* 2000; 37: 542.

374. O'Connell J, Bennett MW, Nally K, O'Sullivan GC, Collins JK, Shanahan F. Interferon-γ sensitizes colonic epithelial cell lines to physiological and therapeutic inducers of colonocyte apoptosis. *J Cell Physiol* 2000; 185: 331.

375. Avivi-Green C, Polak-Charcon S, Madar Z, Schwartz B. Different molecular events account for butyrate-induced apoptosis in two human colon cancer cell lines. *J Nutr* 2002; 132: 1812.

376. McDermott MF, Aksentijevich I. The autoinflammatory syndromes. *Curr Opin Allergy Clin Immunol* 2002; 2: 511.

377. Ferrero-Miliani L, Seidelin JB, Nielsen OH. Toll-like receptor-mediated responses of primary intestinal epithelial cells during the development of colitis. *Am J Physiol Gastrointest Liver Physiol* 2005; 288: G514-G524.

378. Di Sabatino A, Ciccocioppo R, Cinque B, Millimaggi D, Morera R, Ricevuti L, Cifone MG, Corazza GR. Defective mucosal T cell death is sustainably reverted by infliximab in a caspase dependent pathway in Crohn's disease. *Gut* 2004; 53: 70.

379. Akita K, Ohtsuki T, Nukada Y, Tanimoto T, Namba M, Okura T, Takakura-Yamamoto R, Torigoe K, Gu Y, Su MS, *et al.* Involvement of caspase-1 and caspase-3 in the production and processing of mature human interleukin 18 in monocytic THP. 1 cells. *J Biol Chem* 1997; 272: 26595.

380. Kanai T, Uraushihara K, Totsuka T, Okazawa A, Hibi T, Oshima S, Miyata T, Nakamura T, Watanabe M. Macrophage-derived IL-18 targeting for the treatment of Crohn's disease. *Curr Drug Inflamm Allergy* 2003; 2: 131.

381. Siegmund B, Zeitz M. Therapeutic approaches in inflammatory bowel disease based on the immunopathogenesis. *Rocz Akad Med Bialymst* 2004; 49: 22.

382. Gordon JN, Di Sabatino A, Macdonald TT. The pathophysiologic rationale for biological therapies in inflammatory bowel disease. *Curr Opin Gastroenterol* 2005; 21: 431.

383. Monteleone G, Fina D, Caruso R, Pallone F. New mediators of immunity and inflammation in inflammatory bowel disease. *Curr Opin Gastroenterol* 2006; 22: 361.

384. Rothe H, Hibino T, Itoh Y, Kolb H, Martin S. Systemic production of interferon-gamma inducing factor (IGIF) versus local IFN-γ expression involved in the development of Th1 insulitis in NOD mice. *J Autoimmun* 1997; 10: 251.

385. Rothe H, Jenkins NA, Copeland NG, Kolb H. Active stage of autoimmune diabetes is associated with the expression of a novel cytokine, IGIF, which is located near Idd2. *J Clin Invest* 1997; 99: 469.

386. Rothe H, Kolb H. The APC1 concept of type I diabetes. *Autoimmunity* 1998; 27: 179.

387. Rothe H, Hausmann A, Casteels K, Okamura H, Kurimoto M, Burkart V, Mathieu C, Kolb H. IL-18 inhibits diabetes development in nonobese diabetic mice by counterregulation of Th1-dependent destructive insulitis. *J Immunol* 1999; 163: 1230.

388. Andre-Schmutz I, Hindelang C, Benoist C, Mathis D. Cellular and molecular changes accompanying the progression from insulitis to diabetes. *Eur J Immunol* 1999; 29: 245.

389. Rothe H, Itoh Y, Kolb H. Disease resistant, NOD-related strains reveal checkpoints of immunoregulation in the pancreas. *J Mol Med* 2001; 79: 190.

390. Hayashi T, Morimoto M, Iwata H, Onodera T. Possible involvement of IL-12 in reovirus type-2-induced diabetes in newborn DBA/1 mice. *Scand J Immunol* 2001; 53: 572.

391. Frigerio S, Hollander GA, Zumsteg U. Functional IL-18 is produced by primary pancreatic mouse islets and NIT-1 β cells and participates in the progression towards destructive insulitis. *Horm Res* 2002; 57: 94.

392. Rothe H, Hausmann A, Kolb H. Immunoregulation during disease progression in prediabetic NOD mice: inverse expression of arginase and prostaglandin H synthase 2 vs. interleukin-15. *Horm Metab Res* 2002; 34: 7.

393. Oikawa Y, Shimada A, Kasuga A, Morimoto J, Osaki T, Tahara H, Miyazaki T, Tashiro F, Yamato E, Miyazaki J, *et al.* Systemic administration of IL-18 promotes diabetes development in young nonobese diabetic mice. *J Immunol* 2003; 171: 5865.

394. Lukic ML, Mensah-Brown E, Wei X, Shahin A, Liew FY. Lack of the mediators of innate immunity attenuate the development of autoimmune diabetes in mice. *J Autoimmun* 2003; 21: 239.

395. Nicoletti F, Di Marco R, Papaccio G, Conget I, Gomis R, Bernardini R, Sims JE, Shoenfeld Y, Bendtzen K. Essential pathogenic role of endogenous IL-18 in murine diabetes induced by multiple low doses of streptozotocin. Prevention of hyperglycemia and insulitis by a recombinant IL-18-binding protein: Fc construct. *Eur J Immunol* 2003; 33: 2278.

396. Zaccone P, Phillips J, Conget I, Cooke A, Nicoletti F. IL-18 binding protein fusion construct delays the development of diabetes in adoptive transfer and cyclophosphamide-induced diabetes in NOD mouse. *Clin Immunol* 2005; 115: 74.

397. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 is a unique cytokine that stimulates both Th1 and Th2 responses depending on its cytokine milieu. *Cytokine Growth Factor Rev* 2001; 12: 53.

398. Hong TP, Andersen NA, Nielsen K, Karlsen AE, Fantuzzi G, Eizirik DL, Dinarello CA, Mandrup-Poulsen T. Interleukin-18 mRNA, but not interleukin-18 receptor mRNA, is constitutively expressed in islet β-cells and up-regulated by interferon-γ. *Eur Cytokine Netw* 2000; 11: 193.

399. Krook H, Wallstrom J, Sandler S. Function of rat pancreatic islets exposed to interleukin-18 in vitro. *Autoimmunity* 1999; 29: 263.

400. Ingelsson E, Saldeen J, Welsh N. Islet expression of perforin, Fas/Apo-1 and interleukin-1 converting enzyme (ICE) in non-obese diabetic (NOD) mice. *Immunol Lett* 1998; 63: 125.

401. Mohr S, Xi X, Tang J, Kern TS. Caspase activation in retinas of diabetic and galactosemic mice and diabetic patients. *Diabetes* 2002; 51: 1172.

402. Mohr S. Potential new strategies to prevent the development of diabetic retinopathy. *Expert Opin Invest Drugs* 2004; 13: 189.

403. Stephens LA, Thomas HE, Ming L, Grell M, Darwiche R, Volodin L, Kay TW. Tumor necrosis factor-α-activated cell death pathways in NIT-1 insulinoma cells and primary pancreatic β cells. *Endocrinology* 1999; 140: 3219.

404. Zhang S, Liu J, Dragunow M, Cooper GJ. Fibrillogenic amylin evokes islet β-cell apoptosis through linked activation of a caspase cascade and JNK1. *J Biol Chem* 2003; 278: 52810.

405. Schott WH, Haskell BD, Tse HM, Milton MJ, Piganelli JD, Choisy-Rossi CM, Reifsnyder PC, Chervonsky AV, Leiter EH. Caspase-1 is not required for type 1 diabetes in the NOD mouse. *Diabetes* 2004; 53: 99.

406. Nicoletti F, Conget I, Di Marco R, Speciale AM, Morinigo R, Bendtzen K, Gomis R. Serum levels of the interferon-γ-inducing cytokine interleukin-18 are increased in individuals at high risk of developing type I diabetes. *Diabetologia* 2001; 44: 309.

407. Hanifi-Moghaddam P, Schloot NC, Kappler S, Seissler J, Kolb H. An association of autoantibody status and serum cytokine levels in type 1 diabetes. *Diabetes* 2003; 52: 1137.

408. Sarvetnick N. IFN-γ, IGIF, and IDDM. *J Clin Invest* 1997; 99: 371.

409. Hoshino T, Wiltrout RH, Young HA. IL-18 is a potent coinducer of IL-13 in NK and T cells: a new potential role for IL-18 in modulating the immune response. *J Immunol* 1999; 162: 5070.

410. Yoshimoto T, Mizutani H, Tsutsui H, Noben-Trauth N, Yamanaka K, Tanaka M, Izumi S, Okamura H, Paul WE, Nakanishi K. IL-18 induction of IgE: dependence on CD4+ T cells, IL-4 and STAT6. *Nat Immunol* 2000; 1: 132.

411. Yoshimoto T, Tsutsui H, Tominaga K, Hoshino K, Okamura H, Akira S, Paul WE, Nakanishi K. IL-18, although antiallergic when administered with IL-12, stimulates IL-4 and histamine release by basophils. *Proc Natl Acad Sci USA* 1999; 96: 13962.

412. Yoshimoto T, Okamura H, Tagawa YI, Iwakura Y, Nakanishi K. Interleukin 18 together with interleukin 12 inhibits IgE production by induction of interferon-γ production from activated B cells. *Proc Natl Acad Sci USA* 1997; 94: 3948.

413. Hofstra CL, Van AI, Hofman G, Kool M, Nijkamp FP, Van AJ. Oosterhout: Prevention of Th2-like cell responses by coadministration of IL-12 and IL-18 is associated with inhibition of antigen-induced airway hyperresponsiveness, eosinophilia, and serum IgE levels.
J Immunol 1998; 161: 5054.

414. Kodama T, Matsuyama T, Kuribayashi K, Nishioka Y, Sugita M, Akira S, Nakanishi K, Okamura H. IL-18 deficiency selectively enhances allergen-induced eosinophilia in mice. *J Allergy Clin Immunol* 2000; 105: 45.

415. Campbell E, Kunkel SL, Strieter RM, Lukacs NW. Differential roles of IL-18 in allergic airway disease: induction of eotaxin by resident cell populations exacerbates eosinophil accumulation. *J Immunol* 2000; 164: 1096.

416. Kumano K, Nakao A, Nakajima H, Hayashi F, Kurimoto M, Okamura H, Saito Y, Iwamoto I. Interleukin-18 enhances antigen-induced eosinophil recruitment into the mouse airways. *Am J Respir Crit Care Med* 1999; 160: 873.

417. Wild JS, Sigounas A, Sur N, Siddiqui MS, Alam R, Kurimoto M, Sur S. IFN-γ-inducing factor (IL-18) increases allergic sensitization, serum IgE, Th2 cytokines, and airway eosinophilia in a mouse model of allergic asthma. *J Immunol* 2000; 164: 2701.

418. Hoshino T, Yagita H, Ortaldo JR, Wiltrout RH, Young HA. In vivo administration of IL-18 can induce IgE production through Th2 cytokine induction and up-regulation of CD40 ligand (CD154) expression on CD4+ T cells. *Eur J Immunol* 2000; 30: 1998.

419. Puren AJ, Fantuzzi G, Dinarello CA. Gene expression, synthesis, and secretion of interleukin 18 and interleukin 1β are differentially regulated in human blood mononuclear cells and mouse spleen cells. *Proc Natl Acad Sci USA* 1999; 96: 2256.

420. Netea MG, Joosten LA, Lewis E, Jensen DR, Voshol PJ, Kullberg BJ, Tack CJ, van Krieken H, Kim SH, Stalenhoef AF, *et al.* Deficiency of interleukin in mice leads to hyperphagia, obesity and insulin resistance. *Nat Med* 2006; 12: 650.

421. Lewis EC, Dinarello CA. Responses of IL-18 and IL-18 Receptor deficient pancreatic islets differ with convergence of positive and negative signals for the IL-18 Receptor. *Proc Natl Acad Sci USA* 2006; (in press).

422. Tamura T, Ueda S, Yoshida M, Matsuzaki M, Mohri H, Okubo T. Interferon-γ induces Ice gene expression and enhances cellular susceptibility to apoptosis in the U937 leukemia cell line. *Biochem Biophys Res Commun* 1996; 229: 21.

423. Neumann D, Tschernig T, Popa D, Schmiedl A, Pérez de Lema G, Resch K, Martin MU. Injection of IL-12 and IL-18 encoding plasmids ameliorates the autoimmune pathology of MRL/Mp-^{Tnfrsf6lpr} mice: synergistic effect on autoimmune symptoms. *Int Immunol* 2006; (in press).

424. Kinoshita K, Yamagata T, Nozaki Y, Sugiyama M, Ikoma S, Funauchi M, Kanamaru A. Blockade of IL-18 receptor signaling delays the onset of autoimmune disease in MRL-Fas^{lpr} mice. *J Immunol* 2004; 173: 5312.

425. Lin L, Peng SL. Interleukin-18 receptor signaling is not required for autoantibody production and end-organ disease in murine lupus. *Arthritis Rheum* 2005; 52: 984.

426. Faggioni R, Cattley RC, Guo J, Flores S, Brown H, Qi M, Yin S, Hill D, Scully S, Chen C, *et al.* IL-18-binding protein protects against lipopolysaccharide-induced lethality and prevents the development of Fas/Fas ligand-mediated models of liver disease in mice. *J Immunol* 2001; 167: 5913.

427. Faggioni R, Jones-Carson J, Reed DA, Dinarello CA, Feingold KR, Grunfeld C, Fantuzzi G. Leptin-deficient (ob/ob) mice are protected from T cell-mediated hepatotoxicity: role of TNF-α and IL-18. *Proc Natl Acad Sci USA* 2000; 97: 2367.

428. Randle JC, Harding MW, Ku G, Schonharting M, Kurrle R. ICE/Caspase-1 inhibitors as novel anti-inflammatory drugs. *Expert Opin Investig Drugs* 2001; 10: 1207.

429. Siegmund B. Interleukin-1β converting enzyme (caspase-1) in intestinal inflammation. *Biochem Pharmacol* 2002; 64: 1-8.

430. Faubel S, Edelstein CL. Caspases as drug targets in ischemic organ injury. *Curr Drug Targets Immune Endocr Metabol Disord* 2005; 5: 269.

431. Linton SD. Caspase inhibitors: a pharmaceutical industry perspective. *Curr Top Med Chem* 2005; 5: 1697.

432. Stack JH, Beaumont K, Larsen PD, Straley KS, Henkel GW, Randle JCR, Hoffman HM. IL-converting enzyme/caspase-1 inhibitor VX-765 blocks the hypersensitive response to an inflammatory stimulus in monocytes from Familial Cold Autoinflammatory Syndrome patients. *J Immunol* 2005; 175: 2630.

433. Dinarello CA. Anti-cytokine therapeutics and infections. *Vaccine* 2003; 21(Suppl 2): S24-S34.

434. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; 345: 1098.

435. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003; 48: 2122.

436. Nahar IK, Shojania K, Marra CA, Alamgir AH, Anis AH. Infliximab treatment of rheumatoid arthritis and Crohn's disease. *Ann Pharmacother* 2003; 37: 1256.

437. Campbell IK, Roberts LJ, Wicks IP. Molecular targets in immune-mediated diseases: the case of tumour necrosis factor and rheumatoid arthritis. *Immunol Cell Biol* 2003; 81: 354.

438. Zhang Y. Persistent and dormant tubercle bacilli and latent tuberculosis. *Front Biosci* 2004; 9: 1136.

439. Toussirot E, Wendling D. The use of TNF-α blocking agents in rheumatoid arthritis: an overview. *Expert Opin Pharmacother* 2004; 5: 581.

440. Mobley JL. Is rheumatoid arthritis a consequence of natural selection for enhanced tuberculosis resistance? *Med Hypotheses* 2004; 62: 839.

441. Rychly DJ, DiPiro JT. Infections associated with TNF-α antagonists. *Pharmacotherapy* 2005; 25: 1181.

442. Botsios C. Safety of tumour necrosis factor and interleukin-1 blocking agents in rheumatic diseases. *Autoimmun Rev* 2005; 4: 162.

443. Calabrese L. The yin and yang of TNF inhibitors. *Cleve Clin J Med* 2006; 73: 251.

444. Furst DE, Wallis R, Broder M, Beenhouwer DO. TNF antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. *Semin Arthritis Rheum* 2006; (Epub ahead of print).

445. Jo EK, Park JK, Dockrell HM. Dynamics of cytokine generation in patients with active pulmonary tuberculosis. *Curr Opin Infect Dis* 2003; 16: 205.

446. Salgame P. Host innate and Th1 responses and the bacterial factors that control Mycobacterium tuberculosis infection. *Curr Opin Immunol* 2005; 17: 374.

447. Sugawara I. Interleukin-18 (IL-18) and infectious diseases, with special emphasis on diseases induced by intracellular pathogens. *Microbes Infect* 2000; 2: 1257.

448. Biet F, Locht C, Kremer L. Immunoregulatory functions of interleukin 18 and its role in defense against bacterial pathogens. *J Mol Med* 2002; 80: 147.

449. Yamada G, Shijubo N, Shigehara K, Okamura H, Kurimoto M, Abe S. Increased levels of circulating interleukin-18 in patients with advanced tuberculosis. *Am J Respir Crit Care Med* 2000; 161: 1786.

450. Vankayalapati R, Wizel B, Weis SE, Samten B, Girard WM, Barnes PF. Production of interleukin-18 in human tuberculosis. *J Infect Dis* 2000; 182: 234.

451. Morosini M, Meloni F, Marone BA, Paschetto E, Uccelli M, Pozzi E, Fietta A. The assessment of IFN-γ and its regulatory cytokines in the plasma and bronchoalveolar lavage fluid of patients with active pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2003; 7: 994.

452. Inomata S, Shijubo N, Kon S, Maeda M, Yamada G, Sato N, Abe S, Uede T. Circulating interleukin-18 and osteopontin are useful to evaluate disease activity in patients with tuberculosis. *Cytokine* 2005; 30: 203.

453. Kwiatkowska S, Szkudlarek U, Luczynska M, Nowak D, Zieba M. Elevated exhalation of hydrogen peroxide and circulating IL-18 in patients with pulmonary tuberculosis. *Respir Med* 2006; (Epub ahead of print).

454. Kim SH, Cho D, Kim TS. Induction of in vivo resistance to Mycobacterium avium infection by intramuscular injection with DNA encoding interleukin-18. *Immunology* 2001; 102: 234.

455. Kremer L, Dupre L, Wolowczuk I, Locht C. In vivo immunomodulation following intradermal injection with DNA encoding IL-18. *J Immunol* 1999; 163: 3226.

456. Chung SW, Choi SH, Kim TS. Induction of persistent in vivo resistance to Mycobacterium avium infection in BALB/c mice injected with interleukin-18-secreting fibroblasts. *Vaccine* 2004; 22: 398.

457. Kinjo Y, Kawakami K, Uezu K, Yara S, Miyagi K, Koguchi Y, Hoshino T, Okamoto M, Kawase Y, Yokota K, *et al.* Contribution of IL-18 to Th1 response and host defense against infection by Mycobacterium tuberculosis: a comparative study with IL-12p40. *J Immunol* 2002; 169: 323.

458. Kobayashi K, Nakata N, Kai M, Kasama T, Hanyuda Y, Hatano Y. Decreased expression of cytokines that induce type 1 helper T cell/interferon-γ responses in genetically susceptible mice infected with Mycobacterium avium. *Clin Immunol Immunopathol* 1997; 85: 112.

459. Takeda K, Tsutsui H, Yoshimoto T, Adachi O, Yoshida N, Kishimoto T, Okamura H, Nakanishi K, Akira S. Defective NK cell activity and Th1 response in IL-18-deficient mice. *Immunity* 1998; 8: 383.

460. Sugawara I, Yamada H, Kaneko H, Mizuno S, Takeda K, Akira S. Role of interleukin-18 (IL-18) in mycobacterial infection in IL-18-gene-disrupted mice. *Infect Immun* 1999; 67: 2585.

461. Fantuzzi G, Banda NK, Guthridge C, Vondracek A, Kim SH, Siegmund B, Azam T, Sennello JA, Dinarello CA, Arend WP. Generation and characterization of mice transgenic for human IL-18-binding protein isoform a. *J Leukoc Biol* 2003; 74: 889.

462. Netea MG, Fantuzzi G, Kullberg BJ, Stuyt RJ, Pulido EJ, McIntyre Jr. RC, Joosten LA, Van der Meer JW, Dinarello CA. Neutralization of IL-18 reduces neutrophil tissue accumulation and protects mice against lethal Escherichia coli and Salmonella typhimurium endotoxemia. *J Immunol* 2000; 164: 2644.

463. Melnikov VY, Ecder T, Fantuzzi G, Siegmund B, Lucia MS, Dinarello CA, Schrier RW, Edelstein CL. Impaired IL-18 processing protects caspase-1-deficient mice from ischemic acute renal failure. *J Clin Invest* 2001; 107: 1145.

464. Pomerantz BJ, Reznikov LL, Harken AH, Dinarello CA. Inhibition of caspase 1 reduces human myocardial ischemic dysfunction via inhibition of IL-18 and IL-1β. *Proc Natl Acad Sci USA* 2001; 98: 2871.

465. Dinarello CA. Novel targets for interleukin 18 binding protein. *Ann Rheum Dis* 2001; 60(Suppl 3): iii18.

466. Raeburn CD, Dinarello CA, Zimmerman MA, Calkins CM, Pomerantz BJ, McIntyre Jr. RC, Harken AH, Meng X. Neutralization of IL-18 attenuates lipopolysaccharide-induced myocardial dysfunction. *Am J Physiol Heart Circ Physiol* 2002; 283: H650.

467. Dai C, Krantz SB. Interferon γ induces upregulation and activation of caspases 1, 3, and 8 to produce apoptosis in human erythroid progenitor cells. *Blood* 1999; 93: 3309.