Interleukin-18: Biological properties and role in disease pathogenesis

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Summary
Initially described as an interferon (IFN)γ-induced factor, interleukin (IL)-18 is indeed involved in Th1 and NK cell activation, but also in Th2, IL-17-producing γδ T cells and macrophage activation. IL-18, a member of the IL-1 family, is similar to IL-1β for being processed by caspase 1 to an 18 kDa-biologically active mature form. IL-18 binds to its specific receptor (IL-18Rα, also known as IL-1R7) forming a low affinity ligand chain. This is followed by recruitment of the IL-18Rβ chain. IL-18 then uses the same signaling pathway as IL-1 to activate NF-κB and induce inflammatory mediators such as adhesion molecules, chemokines and Fas ligand. IL-18 also binds to the circulating high affinity IL-18 binding protein (BP), such as only unbound free IL-18 is active. IL-18Rα may also bind IL-37, another member of the IL-1 family, but in association with the negative signaling chain termed IL-1R8, which transduces an anti-inflammatory signal. IL-18BP also binds IL-37 and this acts as a sink for the anti-inflammatory properties of IL-37. There is now ample evidence for a role of IL-18 in various infectious, metabolic or inflammatory diseases such as influenza virus infection, atheroma, myocardial infarction, chronic obstructive pulmonary disease, or Crohn’s disease. However, IL-18 plays a very specific role in the pathogenesis of hemophagocytic syndromes (HS) also termed Macrophage Activation Syndrome. In children affected by NLRC4 gain-of-function mutations, IL-18 circulates in the range of tens of nanograms/mL. HS is treated with the IL-1 Receptor antagonist (anakinra) but also specifically with IL-18BP. Systemic juvenile idiopathic arthritis or adult-onset Still’s disease are also characterized by high serum IL-18 concentrations and are treated by IL-18BP.

KEYWORDS
hemophagocytic syndromes, inflammatory diseases, interferon γ, interleukin-1, interleukin-18, interleukin-18 binding protein

1 INTRODUCTION

IL-18 was first identified as "IFNγ-inducing factor" isolated in the serum of mice after an intraperitoneal endotoxin, following pretreatment with Propionibacterium acnes, which stimulates liver’s Kupffer cells. With purification from mouse livers and molecular cloning of "IFNγ-inducing factor" in 1995, the name was changed to IL-18 which unexpectedly, appears to be related to IL-1 family and particularly to IL-1β in several ways. Human IL-18 and IL-1β although sharing only 15% sequence homology, share a common β-pleated sheet structure. IL-18 similarly to IL-1β is synthesized as an inactive precursor to become biologically active. Despite binding to different receptors, IL-1β and IL-18 use the same signaling pathways. However, apart from these important similarities, IL-18 and IL-1β appear to have a different biology.
2 | IL-18 BIOLOGY

2.1 | Cell origin and processing

IL-18 gene is located on chromosome 11 in humans and chromosome 9 in mice whose gene contains 7 exons with two distinct promoters on exon 1 and 2 including an interferon consensus sequence binding protein and a PU.1 binding sites. In contrast to other cytokine genes, IL-18 gene has few RNA-stabilizing elements, resulting in an unusually stable cytokine expression. Transcription of IL-18 precursor can be induced after TLR binding of PAMPs and activation of the NF-κB pathway. IL-18 gene encodes for a 193 amino acids precursor, first synthesized as an inactive 24-kDa precursor with no signal peptide, which accumulates in cell cytoplasm. In contrast with IL-1β, the IL-18 precursor is constitutively present in blood monocytes, macrophages, dendritic cells from healthy subjects. Similarly to IL-1α and IL-33, the IL-18 precursor is constitutively expressed in endothelial cells, keratinocytes or intestinal epithelial cells throughout the gastrointestinal tract and remains in the intracellular compartment of mesenchymal cells.

Similarly to IL-1β, the IL-18 precursor is processed intracellularly by caspase 1 into its mature biologically molecule of 18 kDa. For IL-18, the consensus is I-N-D at amino acid 50 but the N-terminus generated by caspase-1 is 14 amino acids before the consensus sequence, rather than 9 amino acids for IL-1β. Caspase 1 can be activated by various canonical inflammasomes belonging to the Nod-like receptors, AIM2-like receptors or TRIM family containing either a CARD or a PYD domain. Among the best known inflammasomes are NLRP-3, NLRC4, NLRP-1 and AIM2 which sense various danger signals. Caspase 1 activation also results in a cell-death program termed pyroptosis, which induces membrane pores and mature IL-1β and IL-18 release. Mature IL-1β can also be released from the cells by lysosome exocytosis or membrane microvesicles, but it is not clear whether IL-18 used the same pathways. Caspase 1-independent mechanisms of IL-18 cleavage have also been described. Notably, Fas Ligand activation of Fas-expressing Kupffer cells or splenic macrophages from Propiobacterium acnes-infected mice, can process active IL-18 in a caspase 1-independent but caspase 8-mediated fashion. Alternatively, caspase 3 cleaves IL-18 precursor and mature forms in inactive fragments. In addition, granzyme B from cytotoxic cells, chymase from mast cells or meprin β from intestinal and kidney epithelial cells can cleave IL-18 precursor in biologically active forms. IL-18 can also be released in its precursor form from dying cells and processed extracellularly in an active form by neutrophil proteases such as proteinase 3.

2.2 | IL-18 receptor and signaling pathways

IL-18 forms a signaling complex by binding to the IL-18 alpha chain (IL-18Ra), which is the ligand binding chain for mature IL-18; however, this binding is of low affinity (Figure 1). In cells that express the co-receptor, termed IL-18 receptor beta chain (IL-18Rb), a high affinity complex is formed, which then signals. The complex of IL-18 with the IL-18Ra and IL-18Rb chains is similar to that formed by other members of the IL-1 family with the co-receptor, the IL-1R accessory chain IL-1RAcP (also termed IL-1R3). Although nearly all cells express the IL-1R1, not all cells express IL-1RAcP. Similarly, most cells express the IL-18Ra but not all cells express the IL-18Rb. IL-18Rb is expressed on T-cells and dendritic cells but not commonly expressed in mesenchymal cells. Following the formation of the heterodimer, the Toll-IL-1 receptor (TIR) domains approximate and it appears that the cascade of sequential recruitment of MyD88, the four IRAKs and TRAF-6 followed by the degradation of IκB and release of NF-κB are nearly identical as that for IL-1. However, there are differences between IL-1 and IL-18 signaling. With few exceptions, IL-1α or IL-1β are active on cells in the low nanogram/mL range and often in the picogram/mL range. In contrast, IL-18 activation of cells expressing the two IL-18 receptor chains requires 10 to 20 ng/mL and sometimetime higher levels.

In addition to NF-κB, the IL-18/IL-18Ra/IL-18Rb complex has been shown to induce phosphorylation of STAT3 in an NK and hippocampal cell lines and the p38 MAP kinase pathway in neutrophils.

2.3 | IL-37 and IL-1R8

The tertiary structure of IL-18 is closely related to IL-37 and the intron-exon borders of the IL-18 and IL-37 genes suggest a close...
IL-37 is an inhibitor of the innate immune response. IL-37 binds to the IL-18Rα but does not recruit IL-18Rβ. Moreover, silencing of IL-18Rα in mice has been shown to result in a surprising paradoxical increase in inflammation, suggesting the presence of an anti-inflammatory ligand and of a co-receptor that delivers an inhibitory signal. In fact, IL-37 binds to an orphan receptor of the IL-1 family formerly known as SIGIRR, now designated as IL-1R8, which forms a tripartite complex with IL-18Rα and induces an anti-inflammatory response (Figure 1). The IL-37/IL-18Rα/IL-1R8 activates the STAT-3 signaling pathway, decreases NF-κB and AP-1 activation and reduces IFNγ production. Thus, IL-37 and IL-18 have opposing effects on cells, and IL-37 may naturally modulate IL-18 inflammatory functions.

### 2.4 Biological functions in adaptive immunity

IL-18 is a unique cytokine involved in activation and differentiation of various T cell populations (Figure 2). Together with IL-12, IL-18 participates in the Th1 paradigm. This property of IL-18 is due to its ability to induce IFNγ either with IL-12 or IL-15, since IL-12 or IL-15 increases the expression of IL-18Rα. IL-18 in combination with IL-12 acts on CD4, CD8 T cells and NK cells to induce IFNγ production, via the simultaneous activation of NF-κB by IL-18 and STAT-4 by IL-12. Interestingly, most of the effects of IL-12 concerning IFNγ induction by T cells, appears dependent on caspase 1 and are therefore mediated via IL-18 processing. IL-18 also directly upregulates perforin- and FasL-dependent cytotoxicity in NK cell and CD8 T cells. A population of M-CSF-primed macrophages expresses a membrane form of IL-18 which after shedding, may activate NK cells. Macrophages can also produce IFNγ, when activated by IL-18 and IL-12.

Importantly, without IL-12 or IL-15, IL-18 does not induce IFNγ production, but plays an important role in the differentiation of naive T cells into Th2 cells, producing IL-13 and IL-4. Furthermore, basophils and mast cells, which express IL-18Rα, produce large amounts of IL-13 and IL-4 in response to IL-18 stimulation. In addition, whereas IL-18 in combination with IL-12 inhibits IgE production in an IFNγ-dependent mechanism, IL-18 alone induces IgE accumulation in vivo.

It is not clear whether IL-18 itself, similar to IL-1β, has a role in Th17 CD4-positive T cell differentiation, but via the induction of IFNγ by Th1 cells or macrophages, IL-18 may in fact negatively influence Th17 differentiation. IL-18, however, induces IL-17 production by γδ T cells which express IL-18Rα and this mechanism may be involved in diseases such as auto-immune encephalomyelitis, systemic JIA or neonatal sepsis. In the Helicobacter pylori chronic infection, IL-18 has been shown to play a role in FoxP3-positive Tregs differentiation.

### 2.5 Proinflammatory properties of IL-18

Independently of IFNγ or other cytokines, IL-18 exhibits characteristics of other proinflammatory cytokines, such as increases in cell adhesion molecules, nitric oxide synthesis, and chemokine production.
IL-18 induces ICAM-1 expression on myeloid cells, and also VCAM-1 expression on micro-endothelial cells or synovial fibroblasts in vitro and in vivo via NF-κB activation.\(^{45,46}\) Blocking IL-18 activity reduces metastasis in a mouse model of melanoma due to a reduction in IL-18-induced expression of VCAM-1.\(^{47}\) IL-18 also induces CXC chemokines by macrophages or synovial fibroblasts as well as angiogenic factors in rheumatoid arthritis tissues.\(^{48-50}\) A unique property of IL-18 is the induction of Fas ligand (FasL), which may account for severe hepatic damages in several pathogenic conditions.\(^{12,51}\) The induction of fever, a well-studied property of IL-1β is not a property of IL-18 since injection of IL-18 into mice, rabbits or humans does not produce fever.\(^{52}\)

### 2.6 IL-18 binding protein

The discovery of the IL-18BP took place during the search for the soluble receptors for IL-18.\(^{53,54}\) IL-18BP is a constitutively secreted protein, with an exceptionally high affinity for IL-18 (400 pM). Present in the serum of healthy humans at a 20-fold molar excess compared to IL-18, IL-18BP may contribute to a default mechanism by which a Th1 response to foreign organisms is blunted in order to reduce triggering an autoimmune responses to a routine infection.\(^{55}\) Although IL-18BP is readily secreted, it falls into the functional category of being a shed soluble receptor. As shown in Figure 1, IL-18BP contains only one IgG domain whereas the Type II IL-1 receptor contains three domains. In this regard, the single IgG domain of IL-18BP is similar to IL-1R8 (SIGIRR), which also has a single IgG domain. The salient property of IL-18BP in immune responses is in downregulating Th1 responses by binding to IL-18 and thus reducing the induction of IFNγ. Since IL-18 also affects Th2 responses, IL-18BP also has properties controlling a Th2 cytokine response. Harboring a classic signal peptide, IL-18BP is readily secreted. Serum levels in healthy subjects are in the range of 2,000-4,000 pg/mL compared to the levels of IL-18 in the same sera of 80-120 pg/mL.\(^{55}\) Moreover, IL-18BP binds IL-18 with an affinity of 400 pM, an affinity significantly higher than that of IL-18Ra. Because a single IL-18BP molecule binds a single IL-18 molecule, one can calculate bound vs free IL-18 in a mixture of both molecules.\(^{55}\) This balance and the concentrations of free IL-18 may be more relevant than total IL-18 when interpreting the concentrations of IL-18 in patients. For example, in Wegener's granulomatosis and systemic lupus erythematosus, both IL-18BP and IL-18 are high, but the level of IL-18BP is not sufficiently high enough to neutralize IL-18 and therefore, the level of free IL-18 is higher than in healthy subjects. The same observation has been made in situations such as sepsis, SJIA and macrophage activation syndrome.\(^{55,56}\)

A unique property of IL-18BP is that the molecule also binds the anti-inflammatory cytokine, IL-37. Thus, in any pathological condition, the outcome is the result of the concentrations of active IL-18, the surface level of IL-18Ra, the presence of IL-1R8 and the level of IL-18BP (Figure 1).\(^{26}\) Hence, the anti-inflammatory property of IL-37 can be affected by the concentration of IL-18BP. As the concentration of IL-18BP increases and binds IL-37, there is the possibility that IL-37 becomes less available as an anti-inflammatory cytokine. Indeed this has been observed in mice injected with IL-18BP. At low dosing of IL-18BP, there is reduced inflammation in a model of rheumatoid arthritis but as the doing of IL-18BP increases, the anti-inflammatory properties of IL-18BP are lost.\(^{57}\)

IL-18BP is highly regulated at the level of gene expression and unexpectedly, IFNy increases gene expression and synthesis of IL-18BP.\(^{58,59}\) Therefore, IFNy driving an increase in the natural and potent inhibitor of IL-18 falls into the category of a negative feedback loop. The concept is supported by clinical data showing that patients being treated with IFNy for hepatitis have elevated levels of IL-18BP.\(^{60}\)

### 3 IL-18 IN PATHOLOGICAL CONDITIONS

Several autoimmune diseases are associated with elevated production of IFNy and IL-18. Diseases such as systemic lupus erythematosus, rheumatoid arthritis, Type-1 diabetes, Crohn's disease, psoriasis and graft vs host disease are thought to be mediated in part, by IL-18 and has been previously reviewed.\(^{4-7}\) In this review, we will discuss the role of IL-18 in the pathogenesis of inflammatory bowel diseases, metabolic syndrome and cardiovascular diseases, lung inflammatory diseases, sepsis, hemophagocytic syndromes and systemic juvenile idiopathic arthritis.

#### 3.1 IL-18 in inflammatory bowel diseases

Innate immunity and inflammasome activation, notably NLRP3, are implicated in the earlier phases of Crohn's disease.\(^{61}\) Increased total IL-18 (in the order of 400 pg/mL) and IL-18BP have been found in the serum of adult and pediatric patients with Crohn's disease and mature IL-18 has been detected in the digestive tissues from patients with active Crohn's disease, but not in ulcerative colitis.\(^{62-65}\) IL-18 co-localized with lamina propria cells in active lesions, whereas it appears located in epithelial cells in inactive areas.\(^{65}\) Furthermore patients harboring an NLRC4 mutation have both high serum IL-18 concentrations and severe digestive tract inflammation, and IL-18 transgenic mice have more severe colitis.\(^{66,67}\) In agreement, several studies have reported the beneficial effects of IL-18 inhibition using neutralizing anti-IL-18 antibodies or IL-18BP. In DSS or TNSB-induced models of inflammatory bowel diseases,\(^{68-71}\) Using conditional IL-18 and IL-18R-deficient mice affecting intestinal epithelial or hematopoietic cells in the DSS model, it was possible to show that IL-18 may be produced by both cell sources, but that intestinal epithelial cells were the major targets of IL-18 pathogenic action.\(^{72}\) Similarly IL-18BP-deficient mice demonstrated a more severe form of DSS colitis, due to decreased maturation of mucus-producing goblet cells.\(^{72}\) These data involving IL-18 in inflammatory bowel diseases pathogenesis are related to others showing the pathogenic roles of NLRP3, caspase 1, mIR223 and IL-1β in the DSS model.\(^{73-75}\)

Therefore, a surprising finding was the association of Crohn's disease susceptibility with NLRP3 or IL-18 gene polymorphisms known to decrease NLRP3 and IL-18 expression.\(^{76-78}\) Subsequently, several groups reported that NLRP3-, caspase 1- or ASC-deficient mice developed a more severe form of DSS colitis due to a rupture
of the intestinal barrier associated with proliferation of commensal bacteria, increased chemokine production and leukocyte infiltration in the colon.\textsuperscript{79,80} These phenomena are due to decreased IL-18 (more than IL-1\textbeta) production by intestinal epithelial cells and can be reversed by injection of IL-18.\textsuperscript{79,80} Another inflammasome, NLRP6 is highly expressed in the large and small intestine, especially in the intestinal epithelium and appears to be involved in IL-18 production in the digestive tract.\textsuperscript{81} NLRP6 is involved in the response to viral pathogens and bacterial components of the commensal microbiome, and microbiome-derived modulators of NLRP6 activity have been identified, such as the bile acid derivative taurine as a positive regulator of IL-18 production, or spermin and histamine as negative regulators.\textsuperscript{82} NLRP6 activation induces protective mucus production by goblet cells, as well as IL-18-dependent anti-microbial peptides production by epithelial cells and plays a role in the maintenance of a normal microbiota in the lumen. Indeed NLRP6 KO mice developed a dysbiotic microbiota, notably increased of prevotellacae.\textsuperscript{83} The dysbiotic microbiota is transferrable to wildtype mice in which it suppresses NLRP6 activation, dampens IL-18 production, decreases antimicrobial peptide production, and increases the severity of DSS colitis.\textsuperscript{83,84} Interestingly, this phenotype can be reversed by IL-18 injection.\textsuperscript{82,83}

The digestive tract is a complex organ since it tolerates millions of commensal bacteria yet the intestine rapidly recognizes pathogenic microorganisms and eliminates them. This is due to the different barriers composing the intestinal mucosa. First, an anatomical barrier consisting in an epithelial cell and mucus layer associated with an antimicrobial barrier including antimicrobial peptides and immunoglobulin A, then an immunological barrier in the lamina propria containing cells of the innate and adaptive immune system constituting the gut-associated lymphoid tissue, GALT.\textsuperscript{85,86} In this context, IL-18 may play a dichotomous role (Figure 3). In homeostatic conditions, IL-18 is protective. NLRP6 and NLRP3 inflammasomes activation in epithelial cells may induce IL-18 production, which in turn, induces the maturation of goblet cells, mucus and production of antimicrobial peptides which maintained both an intact intestinal barrier and normal microbiota in the lumen. In addition, IL-18 may also decrease Th-17 differentiation and modulate Treg cell function, since these cells in the lamina propria

\begin{figure}
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\caption{Role of IL-18 in inflammatory bowel diseases. In homeostatic conditions (A), IL-18 is produced by intestinal epithelial cells (IEC) after processing by NLRP3 or NLRP6 inflammasomes. IL-18 has a protective role on intestinal barrier through mucus synthesis by goblet cells (green triangles) or secretion of anti-microbial peptides (AMP) by IEC. In this way, IL-18 maintains a normal microbiota in the digestive tract. In case commensal bacteria enter the mucosa (pink arrow), macrophages from the lamina propria secrete IL-18 which controls infection and IL-1\textbeta which has healing properties. In pathogenic conditions (B), the epithelial barrier is disrupted and bacteria enter massively in the lamina propria where they induce local macrophages to produce IL-18 which is detrimental (purple) and IL-1\textbeta (pink) which is protective. Disrupted IEC also release IL-1\textalpha which is highly proinflammatory in this setting (purple) and activates macrophages. This leads to chemokine secretion and leukocyte recruitment from the peripheral blood into the lamina propria. In the meantime, IL-18 inhibits mucus production by goblet cells and modify microbiota favoring dysbiosis.}
\end{figure}
express the IL-18R. In case of chronic inflammation with anatomical barrier rupture and dysbiosis on the contrary, IL-18 is detrimental. NLRP3 and other inflammasomes may be activated in mononuclear cells from the lamina propria inducing large concentrations of pathogenic IL-18, leukocyte recruitment and severe inflammation. In this setting, IL-1α constitutively present in intestinal epithelial cells is released by injured cells and has an important pro-inflammatory role, whereas IL-1β secreted by mononuclear cells from the lamina propria has been shown to play a rather protective healing role. Anti-TNFα and anti-IL-12/23 are efficient treatments in inflammatory bowel diseases, likely via the decrease in IFN-γ. Since TNFα can induce IL-18, it is possible that part of the action of anti-TNFα may in fact be due to IL-18 inhibition.

3.2 | IL-18 in metabolic syndrome and diabetes type 2

The metabolic syndrome is characterized by central obesity, acquired insulin resistance, high blood triglycerides, low HDL, blood hypertension and increases the risk of type 2 diabetes (5-7 fold), and that of cardiovascular disease by twofold. Obesity, type 2 diabetes and atherogenesis are characterized by low-grade underlying inflammation. NLRP3, caspase 1 and IL-1β play an important role in type 2 diabetes pathogenesis since IL-1β mediates obesity-induced inflammation, increases insulin resistance and destroys β-cells. Thus high IL-18 levels in obese patients, metabolic syndrome or type 2 diabetes is not unexpected. In addition, a polymorphism of IL-18 gene associated with increased serum IL-18 levels has been linked to insulin resistance and metabolic syndrome. The visceral rather than subcutaneous adipose tissue from obese individuals produces more IL-18 than lean controls, and serum IL-18 concentrations decreased after bariatric surgery.

Despite these data suggesting a link between high IL-18 concentrations and metabolic syndrome or type 2 diabetes, studies in mice reveal paradoxical observations. IL-18 or IL-18Rα-deficient mice, far from being protected from metabolic syndrome, appeared to become obese and develop insulin-resistance after 6 months of normal chow diet, due to both hyperphagia and decrease energy consumption. Intravenous, intracerebral or intraperitoneal injection of exogenous IL-18 corrected hyperphagia, increased catabolism (possibly via IL-18-induced IFNγ production) and decreased insulin-resistance. IL-18 may increase insulin sensitivity via the phosphorylation of STAT3 in cells and possibly via activation of AMP-activated kinase (AMPK) in muscles. Insulin resistance despite high IL-18 levels is reminiscent of leptin resistance in obesity and type 2 diabetes, indeed PBMC of patients with obesity or type 2 diabetes were found to be resistant to the stimulating action of IL-18 on STAT3-mediated IFNγ production, due to decreased IL18Rα and IL-18Rβ expression. Thus it appears that IL-18, similar to leptin is an adipokine which controls both food intake and energy homeostasis. Increased IL-18 concentrations in patients with obesity and type 2 diabetes may in fact, constitute a retrocontrol mechanism in order to compensate insulin resistance induced by other pro-inflammatory cytokines. In agreement with this hypothesis, treatment with anti-IL-18 monoclonal antibodies demonstrated no improvement in patients with type 2 diabetes.

3.3 | IL-18 in atherosclerosis and myocardial infarction

NLRP3 inflammasome and IL-1β play important roles in early atherogenesis. Cholesterol crystals which accumulate in atherosclerotic lesions activate NLRP3 and induce caspase1 activation, leading to IL-1β and IL-18 secretion. In addition, irradiated atherogenic-prone LDLR-deficient mice were protected from atherosclerosis, when reconstituted with NLRP3 or ASC- deficient bone marrow. IL-18 and IL-18Rα are highly expressed in macrophages from atherogenic plaque, significantly more in unstable plaques. Alternatively, transfection with an expression-plasmid DNA encoding IL-18BP in atheroma-prone ApoE KO mice prevented plaque progression. Injection of IL-18 to ApoE KO mice increased the severity of the disease, an effect which was not observed in IFNγ KO mice, suggesting that the effects of IL-18 were mediated in a large part by IFNγ in this model. IL-18 may also play a long term pro-atherogenic role, since ApoE-deficient mice crossed with IL-18-deficient mice appeared protected, despite increased circulating cholesterol concentrations. Again, the effects of IL-18 may be mediated by IFNγ, since IL-18-deficient mice had a decreased IFNγ signature. In summary, IL-18 aggravates atherosclerosis by inducing IFNγ, which promotes the acceleration of the vascular disease. Despite these pro-atherogenic properties, IL-18 gave controversial results when used as a biomarker in cardiovascular diseases. Several studies suggest that IL-18 is increased (in the order 70 to 300 pg/mL) in the serum of patients with coronary diseases, with a predictive value for death occurrence and a good correlation with coronary atherosclerosis evaluated by coronaryography, but these results were not confirmed when carotid atheroma was evaluated by ultrasound.

IL-18 is, however, increased in patients at risk or with myocardial infarction as well as in patients with congestive heart failure. Increased serum IL-18 concentrations and tissue IL-18 expression were found in a murine model of acute myocardial infarction and IV injection of both anti-IL-18 or mesenchymal stem cells overexpressing IL-18BP into the coronary artery before ischemia, reduced infarct size. IL-18 may be involved in several aspects of myocardial infarction or congestive heart failure. Stimulation of a cardiomyocyte cell line with IL-18 induces cell hypertrophy and production of atrial natriuretic peptide, a marker of cardiac hypertrophy. Injection of IL-18 to WT mice induces atrial natriuretic peptide expression in the heart, as well as myocardial hypertrophy and contractile dysfunction. IL-18 has cardiodepressant effects and neutralization of IL-18 with either anti-IL-18 monoclonal antibodies or IL-18BP improved contractile function. Importantly, IL-18 may mediate some of the well-known cardiodepressant effects of IL-1β, since IL-18 blockade with IL-18BP has been shown to prevent the systolic dysfunction induced by IL-1β. Finally, IL-18 participates in extracellular remodeling and myocardial fibrosis. Indeed administration of IL-18 to WT mice induced cardiac tissue fibrosis after 7 days and IL-18 induced the...
synthesis of osteopontin by cardiac fibroblasts, which mediates cardiac fibrosis. 132,133

3.4 | IL-18 in lung diseases

3.4.1 | Asthma

Whereas IL-18 is a well-known inducer of the Th1-type immune response, as discussed earlier, several studies have shown that in absence of IL-12, IL-18 acts to induce Th2 functions. IL-18 is involved in the pathogenesis of allergic asthma, which is characterized by a Th2-type airway inflammation with eosinophils, IgE production, airway hyperresponsiveness, mucus metaplasia and cytokines such as IL-13 and IL-5. IL-18 gene polymorphisms have been associated with asthma severity in adults, notably the rs5744247C>G variants, which found increase IL-18 mRNA transcription and IL-18 secretion by LPS-stimulated monocytes. 134 Similarly, IL-18Rα polymorphisms have been associated with allergic asthma in three different North European populations. 135 Increased IL-18 concentrations have been transiently found in the serum of asthmatic patients, especially during asthma exacerbations with increased IL-18 expression in epithelial and smooth muscle cells from patients airway biopsies. 136,137 IL-18 concentrations correlate with the methacholine test, and inversely with the peak expiratory flow. In addition, in lung autopsies performed on 12 patients with fatal asthma, IL-18 and IL-18Rα were highly expressed and associated with increased eosinophils and CD8+ T lymphocytes. 138 In animal the common model of ovalbumin sensitized and challenged mice, intraperitoneal IL-18 injection increases eosinophil recruitment into the airways but not airway hyperresponsiveness. 139 More recently, ovalbumin sensitization/inhalation in IL-18 transgenic mice overproducing IL-18 in the lungs, demonstrated airway hyperresponsiveness and severe inflammation with leukocyte infiltration as well as IFNγ, eotaxin and IL-13 production. In addition, treatment with anti-CD4 decreased airway hyperresponsiveness, lymphocyte count, IL-13 and IFNγ concentrations in broncho-alveolar lavage fluids, whereas the same model in IL-13-deficient mice, the infiltrating eosinophils were less and airway hyperresponsiveness was reduced. 140 In summary, due to its Th-2 inducing functions, IL-18 may participate in airway inflammation and hyperresponsiveness in allergic asthma and may be an interesting therapeutic target in severe asthma resistant to steroids.

3.4.2 | Chronic obstructive pulmonary disease

Chronic obstructive pulmonary diseases (COPD) include lung emphysema and chronic bronchitis, both characterized by chronic inflammation, alveolar destruction, airway remodeling and fibrosis. 141 The main causes of COPD are cigarette smoking (primary or second-hand) and air pollution. Cigarette smoke contain more than 4500 chemical products, oxidants and free-radicals that activate the innate immune system and induce lung inflammation. 142 IL-18 has been shown to be highly expressed in alveolar macrophages, CD8 T lymphocytes as well as bronchial and alveolar epithelial cells from patient lungs, whereas circulating 18Rα-expressing T cells were higher in COPD patients. 143-145 Serum IL-18 concentrations are increased in COPD and smokers when compared to non-smokers healthy controls, correlated positively with disease severity and negatively with the forced expiratory volume tests. 144

In mice, chronic exposure to cigarette smoke induces emphysema, small-airway remodeling and even pulmonary hypertension thus mimicking COPD. After 2-week smoke exposure in this model, IL-18 was increased in lung biopsies and the broncho-alveolar lavage fluid, especially in alveolar macrophages, associated with increased levels of caspases 1 and 11. In IL-18Rα KO mice, alveolar cell apoptosis, protease and chemokine production significantly decreased, reducing both inflammation and lung emphysema. 144 Cigarette smoke exposure combined with poly (I:C) TLR activation to reproduce viral infection, acted synergistically to induce a more severe lung inflammation with alveolar remodeling, emphysema and airway fibrosis. IL-18 was highly increased in alveolar macrophages associated with IFNα, followed by IL-12 and IFNγ. Inflammation, epithelial and endothelial cell apoptosis were significantly decreased in IL-18Rα or IFNγ-deficient mice, demonstrating the important role of Th1-mediated inflammation in this model. 146

A second-hand smoke model has been created in Sprague–Dawley rats which after 2-month exposure, demonstrated emphysema associated with mild pulmonary hypertension, increased “foamy” macrophages, excess epithelial and endothelial cell apoptosis associated with decreased VEGFR1 and VEGFR2 expression. IL-18 was increased while IL-18BP was decreased, and free IL-18 induced endothelial cell apoptosis, increased endothelial permeability and decreased VEGFR expression. 147 Another interesting animal model appears to be lung-specific IL-18 transgenic mice which demonstrated typical COPD lesions such as emphysema, mucus metaplasia and fibrosis. Accumulation of inflammatory cells including macrophages, neutrophils, eosinophils and lymphocytes is observed in BAL fluids. All lymphocyte subpopulations are represented, notably CD4 which consists in both Th1, Th17 and Th2. 148 Notably Th1 lymphocytes seem to have a rather protective role, since IFNγ-deficient animals have more severe inflammation and emphysema, and IFNγ decreases IL-18, IL-17 and IL-13. On the contrary IL-13 KO mice demonstrate decreased inflammation, emphysema and fibrosis. 149

3.4.3 | Acute lung injury

NLRP3 is expressed in lung epithelial cells as well as in monocytes and macrophages and NLRP3 activation is protective in various models of lung infection, however, excessive NLRP3 stimulation has been demonstrated to be detrimental and may cause acute lung injury. 150 The most severe form of acute lung injury is represented by acute respiratory distress syndrome (ARDS) with a 40%-mortality. 151 IL-18 concentrations have been found elevated in the serum and lung of patients with ARDS (in the order of 600 pg/mL), and correlated with severity score and death. 152,153 Among the most severe forms of ARDS are those induced by avian influenza virus. Seasonal influenzae RNA and M2 proteins are known to activate NLRP3 inflammasome in a protective way, since NLRP3- and caspase-1-deficient mice demonstrate...
more severe lung lesions as well as increased lethality.\textsuperscript{154,155} In this setting, although controversial, IL-18 but not IL-12, has been shown to be protective in the early defenses against influenza by inducing NK cell cytotoxicity and IFNγ production.\textsuperscript{156-158} On the contrary, avian influenza H5N1 and H7N9 contain a PB1-F2 protein which maintain both inhibits IFNα production and activates NLRP3 in a strong and prolonged way.\textsuperscript{159} This prolonged NLRP3 activation leads to excess IL-18 production and induces a very detrimental IFNγ-biased cytokine storm which appears to characterize ARDS pathogenesis.\textsuperscript{160-162}

Interestingly, this pathogenesis appears common to coronavirus-induced severe acute respiratory syndrome (SARS), another severe form of ARDS and possibly to the 1918 influenza virus.\textsuperscript{163-165} This dual role of NLRP3 in influenza infection and potentially in ARDS has been recently demonstrated by temporal inhibition of NLRP3 using MCC950, a specific NLRP3 activation inhibitor.\textsuperscript{166,167}

### 3.5 | IL-18 in sepsis

Sepsis is characterized by both excessive inflammation and immune suppression.\textsuperscript{168} IL-18 and IL-18BP concentrations are elevated in the serum of pediatric and adult patients with sepsis, are free IL-18 remains higher than in healthy individuals or in non-septic patients.\textsuperscript{43,55} In postoperative sepsis patients, high IL-18 serum levels during the 2 first days represent an early predictive factor for a lethal outcome, possibly suggesting a role for IL-18 in the pathogenesis of sepsis.\textsuperscript{169}

Interestingly, caspase 1 KO mice are protected against LPS-induced septic shock, whereas IL-1β KO mice are not.\textsuperscript{170} In agreement, anti-IL-18 monoclonal antibody treatment appears to be protective in two models of \textit{E. coli} or \textit{Salmonella} LPS-induced septic shock, decreasing neutrophils in the liver and lungs, and IFNγ, TNFα or chemokine serum concentrations.\textsuperscript{170} Also, combined IL-1β and IL-18 inhibition has been shown to be protective in models induced by LPS injection or cecal ligation.\textsuperscript{171} IL-18 appears to be especially important in mediating endotoxin-induced liver and lung injuries.\textsuperscript{172,173}

The presence of free IL-18 in sepsis serum due to an imbalance of IL-18/IL-18BP ratio, lead to the use of IL-18BP in a murine model of cecal ligation. However, IL-18BP injection 8 hours after sepsis onset appeared slightly protective in the more severe forms, but not in those with a low predicted mortality rate.\textsuperscript{174}

Similar to what is observed in influenza, in the LPS-induced model of sepsis, there is a duality role for IL-18. Injection of low doses LPS seems to induce moderate and transient serum increase of IL-18 and IFNγ, which enhanced antibacterial host defenses and are protective. In contrast, after the administration of high doses of LPS, high concentrations of IL-18 and IFNγ are observed, which increased until death, associated with reduced antibacterial defenses. In the latter case, anti-IL-18 restores antibacterial defenses and is protective of a fatal outcome, whereas it decreased defenses in the former situation, suggesting an optimal range of IL-18 concentration is essential for host defenses.\textsuperscript{175} These data may be in part explained by a positive loop of induction of caspase 1 mRNA transcription by IFNγ, leading to sustained IL-18 and IFNγ levels.\textsuperscript{176} More recently, the role of IL-18 and its capacity to induce IL-17 in conjunction with IL-1 has been outlined in a model of neonatal sepsis.\textsuperscript{42} Premature infants have elevated serum concentrations of IL-18 which increases in sepsis, associated with an inverse correlation with the gestational age. In a lethal model of neonatal sepsis, IL-18-deficient mice were protected whereas the administration of IL-18 increased lethality. In this model, ablation of the adaptive immune system afforded no protection, whereas treatment with anti-IL-17 was protective, due to the fact that IL-18 induced IL-17 secretion by γδ T cells from injured digestive tract or the lungs. Interestingly, in this model IL-1R1- but not IL-1β-deficient mice were protected, suggesting a role for IL-1α which was found highly expressed in the gut of septic neonatal mice treated with IL-18. IL-17 is known to play a role in neutrophil-induced inflammation and IL-18 is known to increase PMN functions.\textsuperscript{25,177} Thus, despite a protective role of IL-18 and IL-17 in host defense against infection, their combined excessive actions during sepsis may become deleterious.

The duality of IL-18 in sepsis and possibly in other models of cytokine storm might be explained by different inflammasome and caspase involvement. Caspase 1-deficient mice which are resistant to endotoxic shock, are in fact deficient in both caspase 1 and caspase 11.\textsuperscript{11} Interestingly, NLRP3-deficient mice are not protected against sepsis, despite the fact that NLRP3 controls caspase 1 activation and both IL-1β and IL-18 secretion, suggesting that caspase 11, rather than caspase 1 may play an essential role in the protection of caspase 1/11-deficient mice toward sepsis.\textsuperscript{178} Caspase 11 is mainly involved in a non-canonical inflammasome in mice. Caspase 11 oligomerizes with CARD to sensor intra-cytoplasmic LPS, usually due to high serum concentrations of LPS, and induces pyroptosis-mediated cell death. This mechanism dominates over that of canonical inflammasomes, which activate caspase1, such as NLRP3.\textsuperscript{179} Excess of pyroptotic cell death may induce both strong IL-18 and DAMPS release inducing an “ecosanoid storm,” shock and death.\textsuperscript{11}

### 3.6 | IL-18 in hemophagocytic syndromes

Hemophagocytic syndromes or hemophagocytic lymphohistiocytosis (HLH) are characterized by the association of clinical and biological symptoms such as fever, hepatomegaly, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, intravascular coagulation and could result in multiseceral deficiency.\textsuperscript{180} The presence of hemophagocytosis in the bone marrow is not required for the diagnosis, but its presence in this clinical picture is highly suggestive of the disease. Noteworthy is the fact that hemophagocytosis may also be frequently observed in the bone marrow of sepsis patients.\textsuperscript{181}

HLH can be divided in two presentations. The primary form usually occurs early in life and is due to recessive mutations affecting proteins involved in lymphocyte cytotoxicity, such as perforin, Munc 13D, syntaxin 11, Munc 18-2, rab27 or Lyst.\textsuperscript{182} The other HLH syndrome, is also known as Secondary HLH or Macrophage Activation Syndrome, complicates infections, notably due to intracellular micro-organisms, lymphoma or rheumatic diseases, such as systemic lupus erythematosus or systemic juvenile idiopathic arthritis (sJIA) and its adult equivalent, adult-onset Still’s disease (AOSD).\textsuperscript{183} Animal models can mimick the two forms of HLH. Perforin-deficient mice
infected with lymphocyte choriomeningitis virus (LCMV) was the first published model of primary HLH, followed by models using Munc 13D- or Rab27-deficient mice, or murine cytomegalovirus (MCMV) infection. Another model mimicking secondary HLH is due to TLR-9 hyperstimulation by repeated CpG injections into wildtype mice. More recently, other models of secondary HLH have been reported, such as LPS stimulation in mice overexpressing IL-6, EBV, Salmonella typhimurium or murine cytomegalovirus (MCMV) infection in humanized or wildtype mice. In humans as well as in all these animal models, excess circulating inflammatory cytokines with a rather Th1 profile, designed as a “cytokine storm,” is the primary event. Among them, IFNγ seems to play the important pathogenic role, since inhibition of IFNγ appears protective in most murine models. It is not completely clear, however, since some models depend also on TNFα or other cytokines.

The role of IL-18 in HLH is likely due to its capacity to induce IFNγ and pro-inflammatory cytokines. Several reports have found elevated IL-18 concentrations in the serum of patients with both primary and secondary HLH as well as in animal models and IL-18 correlated with the biological criteria and evolution of the disease. Usually, the concentrations of IL-18 range from 0.6 to 3 ng/mL in HLH patients. There is the exception in two conditions, in which IL-18 concentrations are higher than 5 ng/mL, namely XLP type 2 due to XIAP mutations and sJIA/AOSD. In both situations, IL-18 concentrations do not return to normal levels even after recovery of the HLH. Such elevated concentrations are unusual for an inflammatory cytokine and question its significance, especially since in the majority of these studies, the distinction between total IL-18 and free IL-18 was not made. In a previous study of Secondary HLH complicating lymphoma, infections and AOSD, we observed an increase in free IL-18, IL-18BP concentrations being similar to those in control patients without HLH, perhaps suggesting a relative resistance of IL-18BP synthesis to IFNγ which was elevated in these patients. A resistance of mononuclear cells to produce IL-18BP in response to IFNγ stimulation, was indeed reported in a patient with a primary HLH. This relative imbalance between IL-18 and its natural inhibitor may favor IFNγ and TNFα excessive production. Thus, there was a study on the effect of recombinant human IL-18BP in a model of perforin-deficient mice infected with MCMV. Although there was no reduction in survival, IL-18BP demonstrated a significant protective effect on liver and spleen lesions due to the decrease in IFNγ, TNFα, and FasL concentrations. Noteworthy is the fact that in this animal model, no anti-cytokine strategy has been shown to increase survival probably due to the fact that concentrations of IFNγ and TNFα are found, respectively, 10-fold and 5-fold higher than in the LCMV-infected perforin-deficient model. However even in the perforin KO-LCMV model, anti-IL-18 treatment did not significantly influence animal survival.

Despite disappointing animal data, the role of IL-18 in HLH is valid. In 2014, two independent groups reported on two pediatric patients with severe refractory HLH and digestive tract lesions without mutations affecting cytotoxicity, but bearing gain-of-function mutations of the NLRC4 inflammasome. Ex vivo experiments showed that these mutations induced very high concentrations of IL-18 (10 ng/mL), whereas IL-1β was modestly affected. Interestingly, IL-18 concentrations in patients with NLRC4 mutations were significantly higher than in NOMID patients, the most severe form of disease associated with NLRC4 gain-of-function mutations, despite the fact that both inflammasomes activate caspase 1. Pyroptosis appears to be induced by mutant NLRC4, more than by NLRP3 mutations which are not commonly associated with HLH development in humans.

Moreover, there is the successful treatment with recombinant human IL-18BP (tadekinig) of a patient with severe and refractory HLH bearing a NLRC4 mutation. That report demonstrates that IL-18 inhibition is likely an effective strategy in HLH, at least in this particular genetic background.

### 3.7 IL-18 in systemic juvenile idiopathic arthritis/adult onset Still’s Disease

sJIA (and its adult homolog AOSD) constitutes a distinct group of patients among JIA. Systemic JIA is clinically characterized by high spiking fever, cutaneous rash, hepato/splenomegaly, serositis, whereas arthritis the main symptom in JIA, could be absent at least at the disease onset. Biologically, sJIA is characterized by severe generalized inflammation, neutrophilia, thrombocytosis, and hyperferritinemia. An unusually frequent complication of sJIA is macrophage activation syndrome (MAS), a form of secondary HLH, which occurs in 15% of the patients, whereas hemophagocytosis ("occult MAS") may be present in the bone marrow of almost 50% of the patients with active sJIA, suggesting a special pathogenic link between these 2 diseases.

Initial gene expression profile study discovered an IL-1 signature in sJIA, and other studies have found upregulation of a cluster of genes involved in innate immunity and IL-1R/TLR signaling. Nevertheless, treatments with anakinra (IL-1 Receptor antagonist) or canakinumab (anti-IL-1β monoclonal antibody) are effective in nearly 50% of the patients. Another group of patients, however, with a greater number of involved joints and lower neutrophil count may not or incompletely respond to anakinra, developing persistent synovitis. It is also possible to distinguish two different subgroups of sJIA patients depending on their serum cytokine profile, the group with more severe arthritis having higher concentrations of IL-6. Indeed IL-6 is markedly elevated in sJIA patients and correlates with the severity of joint involvement. Inhibition of IL-6 using the IL-6 receptor blocking antibody tocilizumab may be an effective treatment in sJIA patients not responding to IL-1β blockade.

IL-18 has been found highly elevated in the serum of active sJIA in numerous studies. The concentrations of IL-18 in sJIA range 5-10 ng/mL, close to those found in NLRC4 mutations. Elevated IL-18 concentrations correlate with ferritin concentrations and the occurrence of MAS, with a cut-off of 47 ng/mL predictive of MAS occurrence. All but one of these reports studied total IL-18, however, using a new ELISA able to directly detect free IL-18, elevation of free IL-18 was recently confirmed in the serum of sJIA patients. IL-18BP concentrations are increased in sJIA patients compared to...
healthy controls, but not differently than patients with other autoimmune diseases, thus out of proportion of IL-18 increase. The reason for this imbalance may involve epigenetic regulation. miRNA134 which inhibits IL-18BP synthesis is overexpressed in the PBMC of AOSD patients and miRNA134 concentrations are elevated in the serum of patients with active disease.\textsuperscript{217} Correcting IL-18/IL-18BP imbalance is a rationale strategy, and an open-label phase 2 trial using IL-18BP has recently been conducted. AOSD patients were treated and normalization of both CRP and ferritin levels were observed with a dose of 160 mg subcutaneously three times a week (Gabay C, personal communication 2017).

Despite high concentrations of IL-18, IFN\textsubscript{y} is rarely found in patients with active JIA and numerous studies of gene expression failed to detect an IFN\textsubscript{y}-signature in these patients.\textsuperscript{207,216,218,219} Moreover, in a recently described animal model of sJIA using complete Freund’s adjuvant, IFN\textsubscript{y} appeared rather protective, since IFN\textsubscript{y}-deficient mice developed a more severe phenotype which was dependent on IL-17.\textsuperscript{220} The authors considered IFN\textsubscript{y}-mediated inhibition of Th17 as a possible explanation of this protective effect. It should be noted that IL-17 has been found elevated in sJIA patients, due to increased IL-17 positive γδ cells expressing IL-18R\textsubscript{a}, whose proliferation is dependent on IL-17.\textsuperscript{220} Another explanation may be the long-term recognized negative effect of IFN\textsubscript{y} on Th17 production.\textsuperscript{214,221} On the contrary, IFN\textsubscript{y} may be found in the serum of sJIA patients complicated by MAS and a decrease IL-18/IFN\textsubscript{y} ratio may characterized MAS appearance.\textsuperscript{214} However, both IL-18, sCD163 and HO-1 concentrations are elevated in active sJIA as well as in MAS and ‘occult MAS’, corresponding to hemophagocytosis mediated by M2 macrophages expressing CD163. IL-18 is present in the bone marrow of patients with active sJIA, suggesting that the underlying proliferation of hemophagocytic M2 is part of sJIA and possibly linked to increased IL-18 concentrations.\textsuperscript{222}

In addition, the links of MAS with primary HLH leads to the search for a common pathogenic pathway. NK cell cytotoxicity was reported to be abnormal in patients with active sJIA with or without MAS, consisting in decreased circulating NK numbers, perforin expression and cytolysis.\textsuperscript{223-225} In addition, whole exome sequencing reported that heterozygous mutations affecting Munc13.4, Munc 18.2 or Lyst were present in 35% of sJIA patients with MAS, but only in 14% of patients with sJIA without MAS.\textsuperscript{226} Furthermore, in animal models of sJIA consisting in complete Freund’s adjuvant administration in IFN\textsubscript{y} KO mice or in LPS-stimulated mice overexpressing IL-6, NK cell lymphopenia as well as decreased cytolysis was observed.\textsuperscript{220,227} A more recent study, however, showed that after normalization of NK percentage, no cytotoxicity deficiency was observed in sJIA patients and only minor NK abnormalities such as increased surface NKp44 expression and decreased granzyme K expression were present.\textsuperscript{228} Despite these discrepancies, NK cells indeed are dysfunctional during sJIA, a surprising observation in view on the high concentrations of IL-18 present in this disease. Two reports demonstrated that in sJIA patients NK cells are resistant to the action of IL-18, due to an absence of phosphorylation of IL-18R\textsubscript{β}, rendering NK cells incapable to produce IFN\textsubscript{y} in response to IL-18.\textsuperscript{228,229} Moreover, some reports have suggested that high IL-18 concentrations may induce lymphocyte apoptosis and NK cell death possibly explaining the observed NK lymphopenia.\textsuperscript{230,231}

4 | CONCLUSION

As a member of the IL-1 family, IL-18 appears to share characteristics of IL-1β with caspase-1 processing of the inactive precursor to an active cytokine. But the IL-18 precursor also shares characteristics with the precursor IL-1α, as both are constitutively present in healthy mesenchymal tissues and are released following necrotic cell death. IL-18 acts differently than IL-1β notably due its effects on lymphocyte activation Through induction of IFN\textsubscript{y}, IL-18 participates in the defense against intracellular bacteria and some virus. Possibly, via IL-13 and IgE production, it may have a role in the immune response against helminths.

In some inflammatory diseases, it remains unclear whether IL-18 or IFN\textsubscript{y} is causative. Unusually high serum concentrations of free IL-18 (more than 10 ng/mL) such as NLRC4 mutations or systemic JIA/ AOSD implicate a dominant role for IL-18. Treatment with recombinant IL-18BP or anti-IL-18 is likely to be effective in the treatment of HLH syndrome associated with both of these diseases. In other diseases, such as avian flu, corticosteroid-resistant asthma, sepsis or other secondary HLH, an INF\textsubscript{γ}-biased cytokine storm is found, an imbalance between IL-18 and IL-18BP has been described, and the concentrations of free IL-18 are in the nanogram range. In these diseases, the role of pyroptosis, the levels and the role of IL-37 should probably be studied in the future, and IL-18-targeted therapy possibly considered. In addition, as shown in the heart, some of the pathogenic effects of IL-1β are mediated by IL-18, suggesting that IL-18 could be a target for therapy for heart diseases besides IL-1 and NLRP3. The presence of IL-18 in mesenchymal cells, notably keratinocytes and epithelial cells suggest an important role for IL-18 in local barrier defenses which in some chronic inflammatory diseases may be disrupted.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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