Interleukin-18 binding protein: Biological properties and roles in human and animal immune regulation (Review)

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Abstract. IL-18 binding protein (IL-18BP) is a natural regulatory molecule of the proinflammatory cytokine IL-18. It can regulate activity of IL-18 by high affinity binding. The present review aimed to highlight developments, characteristics and functions of IL-18BP. IL-18BP serves biological and anti-pathological roles in treating disease. In humans, it modulates progression of a number of chronic diseases, such as adult-onset Still's disease. The present review summarizes molecular structure, role of IL-18BP in disease and interaction with other proteins in important pathological processes.

Contents

1. Introduction

The proinflammatory cytokine interleukin-18 (IL-18) is involved in host inflammation responses to infections or injuries. It regulates both innate and adaptive immune responses. A protein with a molecular weight of 38 kDa isolated and purified from human urine was discovered to bind to IL-18. It was considered to be a soluble receptor but was proved to have no transmembrane region of a cytokine receptor (1). Following this, it was identified in 1999 as a protein factor that can specifically bind to IL-18 with high affinity and antagonize the biological function of IL-18 and named IL-18 binding protein (IL-18BP) (2). IL-18BP gene is expressed in numerous types of tissues and cells of humans and animals and its expression is regulated by interferon γ (IFN-γ) (3). IL-18BP is a glycoprotein belonging to the immune globulin superfamily. IL-18BP can effectively inhibit action of IL-18 *in vivo* and *in vitro* and is considered as a natural antagonist of IL-18 (4-10). Studies have shown that there is no homology between IL-18BP and two receptors of IL-18, IL-1 receptor-related protein (IL-1Rrp) and accessory protein (AcPL) (11). IL-1Rrp, a functional IL-18 receptor component (12,13), leads to activation of signaling pathways similar to those used by IL-1 (14). IL-1Rrp1) and IL-1R accessory protein-like (IL-1RAcPL) confer responsiveness to IL-18 in a highly specific and unique manner (no functional pairing with other IL-1Rs and IL-1R-like molecules). Co-transfection with both receptor components resulted in expression of both low and high affinity binding sites for IL-18 [K:(d) of 11 and 0.4 nM, respectively (15). Anti-IL-1RAcPL mAb can effectively inhibit IL-18-induced activation of NF-κB (15). IL-18 has weak affinity for IL-1Rrp1. However, binding of murine recombinant IL-18 (rIL-18) is not detected in T helper (Th)1-developing splenic $CD4^+$ T cells isolated from IL-1Rrp-deficient mice. This affects activation of NF-κB or c-Jun N-terminal kinase in Th1 cells and cytolytic activity of natural killer (NK) cells as well as IFN-γ production in response to IL-18. Expression of IL-18BP and IL-18 is balanced in human and animals (16). Studies on disease processes have found that there is a significant positive correlation between expression levels of IL-18 and IL-18BP in healthy people (3,11,17-21). In the progression of certain types of diseases, such as secondary hemophagocytic syndrome, sepsis, there is an imbalance in expression levels of IL-18 and IL-18BP. The ratio of IL-18 to IL-18BP increases, even though both proteins are present at higher levels compared with control. This imbalance leads to an increased disease severity (22). Although expression levels of both IL-18 and IL-18BP are high in the serum of patients with Wegener's granulomatosis, the amount of IL-18BP is insufficient to neutralize IL-18. As a result, levels of free IL-18 in the serum are higher compared with those in healthy individuals, leading to inflammatory reactions (4,23,24). This phenomenon has been observed in patients with inflammatory diseases such as sepsis (24,25), systemic juvenile congenital arthritis (26) and macrophage activation syndrome (27). Another feature

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of IL-18BP is its ability to bind to anti-inflammatory factor IL-37, thereby inhibiting its anti-inflammatory function (28). This dual role of IL-18BP helps maintain balance in the host immune system. IL-18BP provides a tipping point and once the amount of IL-18 exceeds this tipping point, IL-18BP is unable to prevent IL-18-mediated Th1 immune response. In a clinical setting, children with IL-18BP deficiency and hepatitis A ultimately die from severe viral hepatitis (29). A key factor is in this outcome is lack of IL-18 inhibition due to the IL-18BP defect, which leads to the progression of inflammation to a malignant state. The return of the normal balance of IL-18 and IL-18BP expression levels predicts the outcome of health. The role of IL-18BP in immune regulation (30,31), immunoprophylaxis (32-34) and disease recovery (35-37) in animals and humans provides broad application prospects in human and veterinary medicine.

2. IL-18BP biology

Cell origin and processing. IL-18BP mRNA is highly expressed in human heart, lung, placenta, spleen and colon tissue (38). IL-18BP is also strongly expressed in the hypothalamus of Sprague-Dawley rats (39). Only low levels of IL-18BP mRNA are found in unstimulated human keratinocytes and colon cancer and glomerular mesangial cells (3).

IL-18BP was discovered when searching for the soluble receptors for IL-18 (40). IL-18BP has a high affinity of 400 pM with IL-18. It is a constitutively secreted protein due to harboring a classic signal peptide (24). In terms of functional category, secreted IL-18BP is a shed soluble receptor. IL-18BP may indirectly decrease auto-immune responses to routine infection via a blunted Th1 response to foreign organisms. IL-18BP downregulates Th1 responses by binding to IL-18 in immune responses to decrease the induction of IFN-γ (41).

Serum levels in healthy mice show a 20-fold difference between IL-18BP and IL-18 (8). Due to the one-to-one binding characteristics of IL-18 and IL-18BP, the bound count vs. free IL-18 in a mixture of both molecules can be calculated. This balance and concentrations of free IL-18 predict whether subjects are healthy. IL-18BP A is elevated (21.9±1.44 ng/ml) in the serum and total IL-18 is elevated to 1.5±0.4 ng/ml in patients with sepsis upon admission. At these levels, most IL-18 is bound to IL-18BP A. However, the remaining free IL-18 levels are higher than in healthy individuals (64±17 pg/ml). IL-18BPa inhibits circulating IL-18 in sepsis and further decreases circulating IL-18 activity (24).

Molecular structure of IL-18BP. IL-18BP has an immunoglobulin (Ig) region that resembles the extracellular Ig structure of the cytokine receptor, which differs from the IL-1 and IL-18 receptor families in its three IgG domains (40). The Ig region of IL-18BP is necessary for the protein function and its binding and inhibition of IL-18 are associated with this region. Sequence analysis confirms that the human and mouse IL-18BP genes are 585 and 582 bp, respectively. Human IL-18BP consists of 164 amino acid residues. Its signal peptide contains 30 amino acid residues. There are four N glycosylation sites in human IL-18BP. The mature peptide contains 134 amino acids (42). Predictive analysis of hydrophilicity and hydrophobicity shows that IL-18BP has no transmembrane region (42). Mouse IL-18BP comprises 165 amino acid residues, including a signal peptide with 28 amino acid residues and four N glycosylation sites. The amino acid sequences are 60.8% homologous. IL-18BP gene in human is located in chromosome 11Q13, encoded by exon without a transmembrane region (43).

At least four IL-18BP isoforms are present in human cDNA libraries due to tissue specificity and mRNA shearing. IL-18BP sequences differ primarily in their carboxyl termini whereas the N-terminal is identical (44). The human IL-18BP A is abundant in cDNA libraries. IL-18BP B is found in monocytes and Jurkat libraries, IL-18BP C is found in spleen and Jurkat libraries, and IL-18BP D is only found in Jurkat cells. Libraries have different IL-18BP isoforms which are key for immune response. The amino acids of 1/3 to 2/3 of isoforms are the same. The difference mainly lies in the C terminal. A total of six IL-18BP isoforms have different functions due to different conformation of their c-terminal amino acid residues and Ig region. Human IL-18BP A and C differ only in the 29 amino acid residues at the c-terminal. IL-18BP A has a high affinity with human IL-18 with a dissociation constant of 399 nM. IL-18BP C can also bind to IL-18 with a dissociation constant of 2.94 nM. Since their Ig regions are similar, human IL-18BP A and C can inhibit biological activity of IL-18. However, human IL-18BP B and IL-18BP D lack a complete Ig region so they cannot bind to IL-18 or inhibit its activity. A total of two IL-18BP isoforms of mice are also found. Mouse IL-18BP C and IL-18BP D have a complete Ig region and interact with mice IL-18 to act as inhibitors. Moreover, mouse IL-18BP D and human IL-18BP A share the same C-terminal, so mouse IL-18BP D can also neutralize the effect of human IL-18, indicating the importance of the Ig region of IL-18BP for its function (44,45).

Role in human and animal immune regulation

IL-18BP and disease recovery. The serum IL-18BP A levels have a significant positive correlation with right ventricular systolic pressure estimated by echocardiography. The signaling inhibition due to interaction between IL-18 and IL-18BP A may be involved in development of pulmonary vascular involvement leading to pulmonary hypertension (46). It also modulates systemic inflammation in systemic sclerosis. In human skin cells, ultraviolet irradiation results in a dose-dependent increase of melanogenesis following treatment with IL-18. However, IFN-γ has the opposite effect (47). This is caused by IFN-γ markedly upregulating IL-18BP production in normal human foreskin-derived epidermal keratinocytes in a dose-dependent manner, indicating the balance between IL-18BP, IL-18 and IFN-γ. Once external forces disrupt this normal balance, the host inflammatory response and occurrence of disease is triggered. There is an imbalance between IL-18 and IL-18BP in the circulation of individuals with human immunodeficiency virus (HIV), which may explain why HIV-infected long-term non-progressors are able to delay autoimmune deficiency syndrome (AIDS) progression (48). Patients with autoinflammatory disorders also have high serum levels of IL-18, without a corresponding increase in IL-18BP or IL-1β (49). There are high serum levels of total and free IL-18, IL-18BP and IL-37 in patients with primary Sjögren's syndrome compared

with healthy controls (50). To inhibit the inflammatory storm caused by IL-18, small molecule inhibitors have been investigated to block the IL-18-induced production of IFN-γ, which is associated with inflammatory disease such as rheumatoid arthritis and Crohn's disease (51). The small molecules disrupt IL-18 binding to IL-18BP and its cognate receptors. In patients with allergic asthma, expression of IL-18, IL-18BP and IL-18R is increased (9). Similarly, enhanced expression of IL-18 and IL-18BP is observed in the plasma of patients with eczema (19). IL-18 and IL-18BP are present in narrow ratio in patients with non-allergic asthma and these cytokines exhibit a significant association with each other. However, the molar concentration ratio of plasma IL-18BP/IL-18 in skin mast cells of patients with eczema is decreased. Additionally, the expressions of IL-18BP exhibits a positive correlation in eosinophil-enriched cells (19). The concentrations of IL-18BP A and IL-36 receptor antagonist (IL-36RA) increase following peripheral blood mononuclear cell (PBMC) exposure to culture-derived hepatitis C virus (52). There are significant correlations between IL-18BP A and indices of liver inflammation and fibrosis (52). Furthermore, genetic variations in IL-18BP are linked to hepatitis A severity (53). C-C Chemokine receptor Type 2 (CCR2) antagonist RS504393 elevates the levels of IL-18BP and decreases the mRNA and/or protein levels of antinociceptive factors (54). CCR2 may be a promising target for decreasing neuropathic pain and augmenting the effects of opioid analgesia and overexpression IL-18BP can counteract the effects of IL-18 in asthma (9). Therapies that enhance IL-18BP activity or block IL-18R may be beneficial for treating asthma. Systemic juvenile idiopathic arthritis and adult-onset Still's disease (AOSD) are associated with high serum IL-18 concentration and can be treated with IL-18BP (55,56). As a treatment option for AOSD, recombinant human IL-18BP,tadekinig alfa, in patients receiving either 80 mg or 160 mg tadekinig alfa showed good safety profiles and early signs of efficacy (56). IL-18BP$^{-/-}$ mice display more severe manifestations of macrophage activation syndrome (MAS) than wild-type mice when persistently stimulated by toll-like receptor 9 (TLR9) with unmethylated cytosine guanine dinucleotide containing single-stranded DNA (CpG) (57). Endogenous IL-18BP provides a protective role against MAS induced by CpG. When exploring the effect of intrathecal administration of bovine lactoferrin, in combination with signal transduction pathway inhibition or an inflammatory cytokine production to allodynia/hyperalgesia in the whisker pad area following mental nerve transection (MNT) in rats, it was found that IL-18BP also attenuates allodynia/hyperalgesia and IL-18 upregulation, similar to bovine lactoferrin (58). Dysregulated production of cytokines has a significant effect on systemic lupus; higher levels of total IL-18, IL-18BP, IL-1Ra and soluble receptor sIL-1R4 are observed in systemic lupus erythematosus (SLE) (59), suggesting that IL-18 and IL-18BP are upregulated in SLE. Treatment of multiple sclerosis (MS) with IFN-β significantly downregulates IL-18 and IL-18BP to normal levels, suggesting that its therapeutic effect on MS may be, at least in part, due to its ability to slow progression of disease on multiple levels (60). IL-18BP as an inhibitor to neutralize IL-18 can inhibit the production of cytokines inducing injury such as IL-6, IFN-γ, TNF-α, C-X3-C motif chemokine ligand 1 (CX3CL1) and CXCL10 and improve allograft function (61). Therefore, IL-18BP may play an important role in organ transplantation.

A number of experimental data has demonstrated the positive role of IL-18BP in disease recovery (9,62-65). It has been reported that remifentanil can protect the liver against ischemia/reperfusion injury by upregulating hepatic expression of IL-18BP (66). The underlying mechanisms are hypothesized to be due to transcriptional activation of the IL-18BP promoter, which can upregulate hepatic IL-18BP expression (66). IL-18BP pretreatment has been observed to suppress the infiltration of inflammatory cells and release of inflammatory factors in acute lung injury (ALI) mice *in vivo* and in primary macrophages stimulated with lipopolysaccharide (LPS) *in vitro* (67-69). Additionally, IL-18BP decreases activation of NF-κB and upregulates Nrf2 (70). This indicates IL-18BP has potential pharmaceutical applications for ALI treatment (70). IL-18BP is able to provide a protective effect against renal fibrosis by neutralizing IL-18 biological activity (65). Neutralization between IL-18 and IL-18Bp improves survival rate and bleomycin (BLM)-induced pulmonary fibrosis (PF) in mice. IL-18BP suppress the BLM-induced epithelial mesenchymal transition *in vivo* (71). These findings indicate IL-18BP as a potential option for PF therapy. IL-18BP as an antagonist of IL-18 can neutralize the toxicity of human IL-18 in the liver. A 40-nucleotide deletion in IL18-BP results in loss of function. In the absence of IL-18BP, excessive NK cell activation by IL-18 leads to uncontrolled killing of human hepatocytes *in vitro* (29). Mouse (57,72) models have shown that IL-18BP has a restorative effect on albuminuria and histopathological injury of the kidney. It also restores induction of serum cytokines in mouse model of minimal change disease induced by Adriamycin (63). The relative expression of IL-18 and IL-18BP mRNA is significantly elevated in patients with active and latent tuberculosis. The significant increase in IL-18 and IL-18BP, as well as IFN-γ mRNA expression, is a manifestation of active tuberculosis disease (20). Administration of recombinant human IL-18BP enhances the survival rate of CD2F1 mice compared with vector control-treated group. Additionally, IL-18BP therapy inhibits expression of IFN-γ targeting IL-18 downstream in mouse bone marrow. It also decreases reactive oxygen species levels in irradiated mouse heart tissue, weakens expression of stress responsive factor growth differentiation factor-15 and improves the intestine protector citrulline levels in serum of total body irradiated mice (73). This implies that IL-18BP may defend multiple organs from radiation-induced inflammation and oxidative stress. Gene expression analysis of patients with idiopathic pulmonary fibrosis indicates that serum IL-18BP levels are significantly higher than in healthy volunteers; independent correlation between serum IL-18BP levels and idiopathic pulmonary fibrosis suggests a novel prognostic biomarker for idiopathic pulmonary fibrosis (74). Levels of nine circulating cytokines, including IL-18 and IL-18BP, are significantly higher in patients with proteinase 3-antineutrophil cytoplasmic antibody compared with myeloperoxidase-associated vasculitis (75). IL-18, IL-18BP and resistin are considered to be circulating markers of inflammation that explain seasonal variations in the morbidity and severity of immune-mediated diseases (76).

IL-18BP as a tool for disease treatment and recovery can be applied to patient care and potential drug development (77-80). By artificially injecting IL-18BP, the free IL-18 in the body can be neutralized, tissue damage caused by inflammation can be reduced and recovery accelerated (81-85).

Interaction between IL-18BP and other cytokines. IL-18BP, an endogenous inhibitor of IL-18, binds to circulating IL-18 with high affinity. It also interacts with other cytokines to play a biological function. IL-18BP binds IL-18 with a high affinity to inhibit IL-18-induced Th1 and other cells from producing IFN-γ and reduce the activation by IL-18 of NF-κB. IL-18BP disrupts NK cell maturation and contributes to sustaining steady-state levels of circulating IL-18. IL-18BP regulates Th1 responses via the IFN-γ pathway. Additionally, IL-18BP can regulate the activation of TLR3 by miR-134. (Fig. 1). Thus, unbound free IL-18 is active. IL-18, an inducer of IFN-γ in T lymphocytes, was discovered in 1996 (86). It is a pleiotropic cytokine with multiple biological functions, such as stimulating Th1 cells to secrete human IFN-γ, granulocyte macrophage-colony stimulating factor and IL-8, promoting Th1 cell proliferation, enhancing Fas-mediated cell cytotoxicity and NK cell cytotoxicity, leading to anti-infection, anti-tumor and other effects. However, IL-18 expression is significantly increased in certain types of autoimmune disease, like Lupus erythematosus (87,88), Rheumatoid arthritis (17,89,90). Expression levels of IL-18BP, IL-18 and IL-18 receptor in different tissues and the exact association between them have been investigated (8,11,18,91). IL-18BP has high affinity with IL-18, with a binding dissociation constant of 0.4 nM, which is higher than that of IL-18 and its receptor IL-1 Rrp (39 nM). This is due to the strong electrostatic interaction between IL-18 and IL-18BP, which can form two ionic bonds, E42/IL-18-K130/IL-18BP and K89/IL-18-E114/IL-18BP, as well as a large number of internal hydrophobic bonds. IL-18BP neutralizes IL-18 at equimolar concentration (92). IL-18BP neutralizes IL-18 activity by interacting with three residues (Leu5, Lys53 and Ser55) that are part of the binding site for hIL-18Rα (93). This is mediated by binding to IL-18 and inhibiting IL-18-induced Th1 and other cells from producing IFN-γ and decreasing the activation effect of IL-18 on NF-κB and LPS-induced IFN-γ synthesis. Therefore, IL-18BP is a natural antagonist of IL-18. The crystal structure of orthopoxvirus IL-18BP, ectromelia virus IL-18BP (ectvIL-18BP), in complex with hIL-18 showed that ectvIL-18BP adopts a canonical Ig fold and interacts via one edge of its β-sandwich with three cavities on the hIL-18 surface through extensive hydrophobic and hydrogen bonding interactions (94).

The pro-inflammatory effects of IL-1 family cytokines are determined by levels of transcription, expression of decoy receptors, enzymatic processing of precursors and release of soluble antagonists (95). IL-18BP binding to IL-18 can competitively inhibit binding from the protein products of the IL18R1 and IL18RAP genes (96). Additionally, IL-1R accessory protein-like 2 and IL-1R8 show a similar amino acid sequence to binding site A of human and viral IL-18BP (96). IL1R9 has similar structure to IL18BP with conserved intron/exon boundaries, protein structure, and key binding site amino acids by bioinformatics approaches. IL1R9, IL18R1, IL18RAP or IL1R9 all bind IL-18. Human platelets contain IL-18BP, which is present in pre-made form and is released irrespective of platelet activation. Plasma and Platelet-Poor Plasma (PPP) samples from healthy donors contains comparable amounts of IL-18BP, while the PPP from HIV-infected people contains notable amounts of IL-18. IL-18 and IL-18BP co-localize to alpha granules inside platelets and are secreted out with different kinetics (97).

IL-18 signaling is mediated by the inhibitory effects of IL-18BP. The reduced abundance of splenic NK cells in IL-18BP knockout mice, as well as, the increased abundance of immature NK cells and the reduced mature population of NK cells demonstrate that IL-18BP disrupts NK cell maturation and contributes to sustaining steady-state levels of circulating IL-18 (69). IL-18BP appears to function as a carrier protein, not just an inhibitor. The balance of IL-18/IL-18BP/IL-18R expression in inflammatory cells, such as monocytes, neutrophils and B cells, determines the role of IL-18 in asthma (9). IL-18BP inducibility is notable in human epithelial cells but weakened in monocytes. Epigenetic silencing by single CpG methylation causes differential IL18BP regulation in both types of cell. A specific CpG (coined CpG2) adjacent to a γ-activated site is responsible for IL18BP induction (98). In a mouse asthma model, lower IL-18BP$^+$ but increased IL-18R$^+$ basophils in blood and IL-18BP$^+$ mast cells in the bronchoalveolar lavage fluid as well as enhanced IL-18R$^+$ mast cells in the lung indicate that mast cells and basophils may be associated with asthma pathogenesis by an IL-18-associated mechanism (99). The persistent IL-18 inhibition via IL-18BP leads to diminished cardiac fibrosis and NF-κB phosphorylation, normalized electrical remodeling, reformative diastolic function and attenuated IL-18-mediated ventricular tachycardia (VT) in sickle cell disease mice. This indicates that IL-18 is a mediator of VT and sickle cell cardiomyopathy in mice, providing a novel therapeutic application for patients at risk of sudden cardiac death (100). The mRNA levels of IL-18BP, IL-18 and IL-18R are notably increased in clinical pituitary tumors compared with non-functional adenomas (101). This indicates that elevated expression of IL-18BP follows increased expression of IL-18. However, the mRNA and protein expression of IL-18BP, IL-18, IL-18Rα and IL-18Rβ in epithelial cells from subjects with asthma is different. IL-18 expression is decreased and the IL-18BP is absent. However, IL-18Rα expression is not different between healthy and asthmatic patients (21). A novel tetramer with 2:2 stoichiometry is exhibited in the crystal structure of the IL-18:IL-18BP complex. It has a higher-order assembly between IL-18 and IL-18BP harmonized by a disulfide-bond distal to the binding surface connecting two molecules (102).

IL-18BP binds cytokine IL-37 and serves as a sink for the anti-inflammatory IL-18 (103), potentially playing a crucial role in tumor escape from immune surveillance. The concurrent increase serum levels of IL-37 and IL-18BP and their positive correlation may promote disease progression in low- and high-grade brain tumors by suppressing antitumor immune responses (79).

Reznikov *et al* (32) found that IL-18 does not induce the synthesis of prostaglandin E2 (PGE2) in peripheral blood mononuclear cells (PBMCs). However, stimulation of PBMCs with IL-1β increases PGE2 production by a factor of 12 and the addition of IL-18 decreases PGE2 production by 40%. The effect of IL-18 is mediated by IFN-γ, as antibodies against

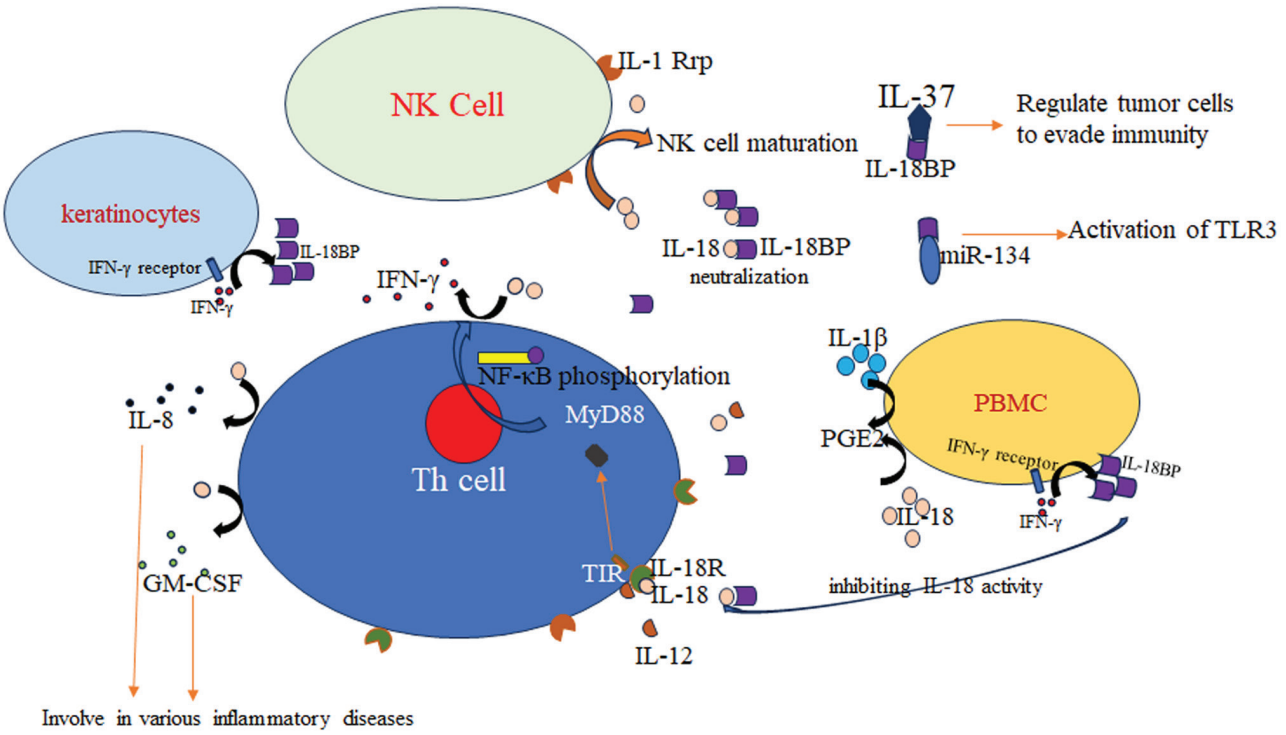

Figure 1. Biological functions of IL-18BP. IL-18BP binds IL-18 with a high affinity to inhibit IL-18-induced Th1 and other cells from producing IFN-γ and reduce the activation by IL-18 of NF-κB. IL-18BP disrupts NK cell maturation and contributes to sustaining steady-state levels of circulating IL-18. IL-18BP regulates Th1 responses via the IFN-γ pathway. IL-18 can induce T cells to produce GM-CSF, IL-8 and other cytokines, which are involved in immunomodulatory processes. IL-18 regulates the maturation of NK cells to expresses IL-1 Rrp, which is conducive to IL-1 binding. A complex with IL-18 and its receptor IL-18R, IL-12, and TIR involved in the MyD88-mediated IFN-γ production pathway. IFN-γ stimulates cells such as PBMC to produce IL-18BP through IFN-γ receptors. The pro-inflammatory factors IL-1β and IL-18 induce PBMC and other cells to produce PGE2, which is involved in biological activities such as inflammation, blood pressure, fertility and bone homeostasis. Additionally, IL-18BP can regulate the activation of TLR3 by miR-134. BP, binding protein; Th, helper T cells; NK, Natural kill; TLR, Toll-like receptors; miR, microRNA; GM-CSF, granulocyte-macrophage colony-stimulating factor; TIR, Toll/interleukin receptor; Rrp, receptor related protein; PGE2, prostaglandin E2; PBMC, peripheral blood mononuclear cell.

IFN-γ prevent IL-18 from inhibiting PGE2 synthesis. When recombinant IL-18BP is added to PBMC culture medium alone, spontaneous PGE2 synthesis is increased. Addition of IL-18BP to IL-1β-stimulated PBMCs also increases PGE2 synthesis. These results indicate that although IL-18 and IL-1 share similarities in structure, receptor and signal transduction, they are functionally different and IL-18BP inhibits IL-18 activity by decreasing the IFN-γ-mediated response. IL-18 is a key inducer of IFN-γ production and IFN-γ can stimulate high expression of IL-18BP in keratinocytes. Therefore, regulation by IL-18BP of biological activity of IL-18 may be realized through the IFN-γ-mediated negative feedback mechanism. IL-18 promotes production of IFN-γ and strongly induces a Th1 response. Therefore, IL-18BP is involved in regulation of Th1 responses in the form of early Th1 cytokine inhibitors (104). In addition, inhibition of IFN-γ increases production of natural and IL-1-induced PGE2, which promotes Th2 response of dendritic cells and Th0 cells and inhibits Th1-associated cytokine production (105,106).

IL-18BP, as the target of microRNA-134 (miR-134), participates in the regulation of the activation of TLR3. Expression of microRNA-134 (miR-134) has a negative correlation with IL-18BP mRNA levels in peripheral blood cells following TLR3 ligand treatment (107). Shi *et al* found that the activation of NLRP3 inflammasome induced by Baicalin, a type of Chinese herbal medicine, could result in increased hepatic expression of IL-18 and IL-1β, which alleviates liver regeneration in acetaminophen-intoxicated mice. MCC950, a NLRP3 inhibitor, and recombinant mouse IL-18BP can decrease this promotion (108).

IL-18BP and its homologs in pox viruses. Studies have shown that IL-18BP has a similar structure to certain virus-encoded proteins, such as MC53L and MC54L from molluscum contagiosum virus (MCV) (109,110). MCV produces small skin tumors in immunocompetent individuals and opportunistic infection in immunodeficient patients with AIDS (109,111). Despite the relatively low overall sequence identity, MC54L and hIL-18BP have similar hIL-18 binding sites and functional epitopes. MC54L shares the same five amino acids with seven high-affinity amino acids of hIL-18BP, contributing to its ability to bind hIL-18. When MC54L non-conserved valine is mutated to phenylalanine, making it more similar to hIL-18BP, its affinity for hIL-18 increases >10 times (112). The sequences encoded by these genes have high homology with the IL-18BP protein. They also have high affinity for IL-18 in humans and mice and inhibit the activity of IL-18-induced production of IFN-γ (112). Additionally, a 32-amino-acid segment that is C-terminal to the IL-18 binding domain cleaves MC54L by cellular furin. MC54L can simultaneously bind heparin and IL-18, which inactivates IL-18 near the site of infection and at more distal locations (110).

Homologs of IL18-BP are also encoded by many pox viruses including MCV and orthopox viruses (113), such as variola virus (114), the causative agent of smallpox (94). A previous report indicated that IL-18BP of variola virus prevents IL-18 from binding to IL-18R by interacting with three residues: Lys53, Ser55 and Leu5, which are part of the binding site for hIL-18Rα (93). Yaba-like disease virus IL-18BP forms a disulfide bonded homo-dimer that engages IL-18 in a 2:2 stoichiometry, with the absence of the key lysine-phenylalanine interaction (115). A 14L protein from Yaba monkey tumor virus, which is similar to orthopoxvirus IL-18BPs, can bind both human and murine IL-18 with high affinity, at 4.1 and 6.5 nM, respectively (116). It is also reported that the genes of several poxviruses, including vaccinia (117), ectromelia and cowpox viruses (118), encode proteins with sequence similarity to IL-18BPs. The ectromelia virus protein blocks NF-κB activation and induction of IFN-γ in response to IL-18. An attenuated vaccinia virus, Ankara, encodes IL-18-binding activity to improve the safety and immunogenicity of this promising human vaccine candidate (118). The dissociation constants of viral proteins for murine IL-18 are 12-50-fold lower than that for human IL-18. ectvIL-18BP adopts a canonical Ig fold and interacts via one edge of its β-sandwich with three cavities on the hIL-18 surface through extensive hydrophobic and hydrogen bonding interactions. This blocks a putative receptor-binding site on IL-18, preventing IL-18 from engaging its receptor (94). Variola virus protein D7L and ectromelia virus protein P13 both have a higher affinity for murine than human IL-18. D7L interacts with glycosaminoglycans (GAGs) via the C terminus, while P13 does not. D7L interacts with both GAG and IL-18 simultaneously, indicating that the binding sites are distinct (114). A total of three mutations (F49A, E77A and E69A) significantly affect binding with both species of IL-18, leading to the complete abrogation of binding affinity, to different extents. However, mutant H70A shows reduced affinity for human IL-18, while binding to murine IL-18 is not affected (119). These proteins antagonize the inflammatory response to infection, which is one of the mechanisms by which pox viruses evade immune defense. IL-18BP is predicted to have putative functions involving immune evasion in a pathogenic fowlpox virus (120).

IL-18BP in other animal species. Expression of IL-18BP is significantly increased when IFN-γ is added to cell culture medium. Additionally, LPS can increase IL-18BP levels, suggesting that inflammatory factors or pathways may upregulate IL-18BP expression. The mouse IL-18BP, ~163 amino acids in size, was discovered and cloned from cDNA of body cells (43). IL-18BP in giant panda (AmIL-18BP) had been cloned and characterized from the spleen in China (121). Mouse spleen lymphocytes treated with recombinant protein AmIL-18 and AmIL-18BP show substantially decreased expression levels of IFN-γ. The spliced chicken IL-18BP (chIL-18BP) isoform is predicted to be intracellular. However, certain divergent vertebrate species (humans and mice) are deficient in similar variants with the same exon. Full-length and intracellular chIL-18BPs are similarly effective at inhibiting IL-18-induced IFN-γ release from an avian B cell line. Inhibition of IL-18BP from different species has a similar inhibitory effect on IL-18-mediated IFN-γ release. The two conserved key residues in the chIL-18BP protein sequence account for 50% of the binding affinity between IL-18 and IL-18BP (122). To the best of our knowledge, the amplified swine IL-18BP splice mRNA has not been reported; only a predicted gene sequence has been searched in GenBank (GenBank No. XM_003129618.5; ncbi.nlm.nih.gov/nuccore/XM_003129618.5). Unpublished data of Key Laboratory for Clinical Diagnosis and Treatment of Animal Disease at the Ministry of Agriculture, Inner Mongolia Agricultural University, Huhhot, China) show that porcine IL-18BP has at least five transcription mutants amplified from porcine alveolar macrophages. To the best of our knowledge, this has not been reported in GenBank or any public reference platform. Whether IL-18BP serves an important role in animal immune defense and disease recovery requires further investigation.

3. Conclusion

IL-18BP is a glycoprotein with an Ig region, a member of the immunoglobulin superfamily. A total of six isoproteins of IL-18BP have been found. IL-18BP can effectively inhibit the action of IL-18 *in vivo* and *in vitro* and is a natural antagonist of IL-18. The development of many types of inflammatory disease is accompanied by changes in the expression of IL-18BP and IL-18. In addition, proteins encoded by several pox viruses have high homology with IL-18BP, and their viral products attenuate the IL-18-induced Th1 response. Gene therapy utilizing the antagonistic effect of IL-18BP against IL-18 may provide novel treatment for certain types of autoimmune disease. IL-18BP has a promising role in immune regulation and immunoprophylaxis and potentially in disease recovery in animals and humans.

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Authors' contributions

FXW wrote and edited the manuscript. Data authentication is not applicable. The author has read and approved the final manuscript.

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Competing interests

The author declares that he has no competing interests.

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