ACTA ABP BIOCHIMICA POLONICA

Vol. 63, No 1/2016
59–63
http://dx.doi.org/10.18388/abp.2015_1153

Minireview

Interleukin 18 (IL-18) as a target for immune intervention*

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Interleukin 18 (IL-18) is a pleiotropic cytokine involved in the regulation of innate and acquired immune response. In the milieu of IL-12 or IL-15, IL-18 is a potent inducer of IFN-gamma in natural killer (NK) cells and CD4 T helper (Th) 1 lymphocytes. However, IL-18 also modulates Th2 and Th17 cell responses, as well as the activity of CD8 cytotoxic cells and neutrophils, in a host microenvironment-dependent manner. It is produced by various hematopoietic and nonhematopoietic cells, including dendritic cells and macrophages. In an organism, bioactivity of the cytokine depends on the intensity of IL-18 production, the level of its natural inhibitory protein — IL-18BP (IL-18 binding protein) and the surface expression of IL-18 receptors (IL-18R) on the responding cells. This review summarizes the biology of the IL-18/IL-18BP/IL-18R system and its role in the host defense against infections. The prospects for IL-18 application in immunotherapeutic or prophylactic interventions in infectious and non-infectious diseases are discussed.

Key words: interleukin-18 (IL-18), IL-18 receptor, IL-18 binding protein

Received: 31 July, 2015; revised: 26 October, 2015; accepted: 03 January, 2016; available on-line: 17 February, 2016

INTERLEUKIN-18

Interleukin 18 (IL-18) was first described in the serum of mice inoculated intraperitoneally with endotoxin and was called the "IFN-gamma inducing factor" (Nakamura *et al.,* 1989). The name was changed to IL-18 after isolation of this cytokine from the liver extracts of mice treated with *Propionibacterium acnes* and subsequently challenged with lipopolysacharide, after molecular cloning (Okamura *et al.,* 1995). Although originally described as a factor capable of inducing IFN-gamma production by murine splenocytes, the effector role of IL-18 rapidly expanded. IL-18 is currently classified as one of the members of the IL-1 cytokine superfamily- that acts as an important regulator of innate and acquired immune responses (Garcie *et al.,* 2003; Dinarello *et al.,* 2013). This cytokine is a potent activator of polarized T helper 1 (Th1) cells for IFN-gamma production and lymphocyte proliferation (Lebel-Binay *et al.,* 2000). Some studies have shown a functionally pleiotropic and complex functioning of IL-18, depending on the host environment. This cytokine plays effector and regulatory roles in a variety of early inflammatory responses. It is also expressed at the sites of chronic inflammation, in autoimmune diseases, in a variety of cancers, and in the context of numerous infectious diseases (Lebel-Binay *et al.,* 2000; Diakowska *et al.,* 2006; Kinjo *et al.,* 2002; Fabbi *et al.,* 2015).

THE PRODUCTION AND ACTIVATION OF IL-18

In the body, IL-18 is constitutively expressed by several cell types, including macrophages, Kupffer cells, keratinocytes, osteoblasts, adrenal cortex cells, intestinal epithelial cells, microglial cells and synovial fibroblasts (Garcie *et al.,* 2003). This cytokine is produced by activated immune cells, dendritic cells, monocytes and macrophages, T and B lymphocytes, natural killer cells (NK) and neutrophils. IL-18 is produced as a 24 kDa inactive precursor (pro IL-18) lacking a signal peptide required for secretion (Okamura *et al.,* 1995). In order to be activated, it must be processed by the intracellular cysteine protease caspase-1, which cleaves the precursor into an active mature molecule of 17 200 Da (Dinarello *et al.,* 2013; Wei *et al.,* 2014). Cleavage of pro IL-18 into mature IL-18 allows this molecule to be released from the cell, although a significant amount of the IL-18 precursor remains unprocessed inside the cell. A signal, which is supplied by IL-18 to the interior of the cell, needs binding of the mature cytokine to its ligand, which is the IL-18 receptor alpha chain (IL-18Rα). However, the low affinity of binding between IL-18 and IL-18Rα prevents initialization of the signal transduction pathway and immune cell activation (Schneider *et al.,* 2010). Full activation of cells by IL-18 requires interaction between the interleukin IL-18Rα receptor and the IL-18 beta chain co-receptor (IL-18Rβ). This complex is functionally and structurally similar to other members of the IL-1 family, with the IL-1RAcP co-receptor (IL-1 receptor accessory protein). The cytoplasmic fragment of the IL-18 receptor and other receptors of the IL-1 family have a TIR domain (Toll IL-1 receptor), belonging to the Toll-like (TLR) receptors. The activation of IL-18 results in a cascade of reactions in which the Toll-IL-1 receptor (TIR) recruits and binds to the myeloid differentiation factor 88 (MyD88), which mediates signal transduction to the TNF receptor associated factor 6 (TRAF6) and IL-1 receptor associated kinases (IRAKs). That reaction causes activation of the NF-κB transcription factor, which stimulates gene transcription leading to the production of pro-inflammatory cytokines (Dinarello *et al.,* 2013; Kali-

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*The results were presented at the 6th International Weigl Conference on Microbiology, Gdańsk, Poland (8–10 July, 2015).

Abbreviations: BCG, Bacillus Calmette-Guérin; GM-CSF, granulocyte macrophage colony stimulating factor; IL-18, Interleukin 18; IL-18BP, IL-18 binding protein; IL-18R, IL-18 receptor; IL-1RAcP, IL-1 receptor accessory protein; IRAKs, IL-1 receptor-associated kinases; MyD88, myeloid differentiation factor 88; NFκβ, nuclear factor κβ; rBCGmIL-18, recombinant BCG strain producing murine IL-18; TIR, Toll-IL1 receptor domain; TRAF-6, tumor necrosis factor receptor-associated factor-6

na *et al.,* 2000; Wei *et al.,* 2014). The IL-18 signal transduction pathway is illustrated in Fig. 1. IL-18 modulates numerous immune reactions mainly by stimulating the IFN-γ production and its modulatory effects depend on the co-existence of IL-18 with IL-12 or IL-15 in the microenvironment (Robinson *et al.,* 2012) These cytokines can increase the expression of the IL-18Rβ receptor, which is crucial for IL-18 signal transduction.

The proinflammatory activity of IL-18 is balanced by a constitutively secreted IL-18 binding protein (IL-18BP) with an extremely high affinity to IL-18, which is significantly higher than that of IL-18Rα. IL-18BP is a member of the Ig superfamily (Novick *et al.,* 2013). By binding IL-18, IL-18BP diminishes the production of IFN-gamma and other proinflammatory cytokines in order to reduce triggering autoimmune responses to infections (Nakanishi *et al.,* 2001). In humans, an increase in disease severity can be associated with an imbalance between IL-18 and IL-18BP, which yields to elevation of the levels of free IL-18 in the circulation (Dinarello *et al.,* 2013). The increase in the levels of IL-18 and/or IL-18BP has been implicated in severity of systemic juvenile idiopathic arthritis, systemic lupus erythematous, myocardial infarction, Crohn's disease, acute kidney injury, inflammatory bowel disease, sepsis and other diseases. The IL-18BP as well as IL-18 neutralizing antibodies, have been used safely in clinical trials in humans. However, it cannot be forgotten that in some models of disease, IL-18 plays a protective role. The broad spectrum of IL-18 functions, as well as the differing levels of the cytokine and IL-18BP that occur in numerous diseases, indicate that both, IL-18 and IL-18BP, can also be useful as the biomarkers in diagnostics (Dinarello *et al.,* 2013).

IL-18 is regarded as a potent regulator of innate and acquired immune responses (Garcie *et al.,* 2003; Dinarello *et al.,* 2013). With the participation of IL-12 or IL-15, IL-18 induces NK activity and directs immunity towards Th1 cell response, characterized by the profound IFN-gamma production. Without IL-12 or IL-15, IL-18 does not induce IFN-gamma production because these two cytokines increase the expression of IL-18Rβ, which is essential for the IL-18 signal transduction (Dinarello *et al.,* 2013). It has been also shown that IL-18 promotes IFN-gamma production in synergy with other Th-1-related cytokines, IL-2 and IL-23 (Okamoto *et al.,* 2002, Nakahira *et al.,* 2002, Okazawa *et al.,* 2004). In the absence of IL-12, IL-18 can induce the Th2 response. In *E. coli*-infected mice, IL-18 promoted both, Th1 and Th2 responses (Kinoshita, Kuranaga *et al.,* 2006). Studies performed in double knockout mice of IL-12p40 and IL-18, have shown that IL-18 plays a role in the induction of Th17 cell responses (Lim *et al.,* 2013). It has been suggested that IL-18 activates and enhances IL-17 production in already polarized Th17 cells, in a TCR-independent manner in synergy with IL-23 (Weaver *et al.,* 2006). The IL-18-driven increase in IFN-gamma production is accompanied by the enhancement in T cell proliferation and production of various cytokines (IFN-γ, TNF-α, GM-CSF, IL-14, IL-5, IL-13) by T helper (CD4+) lymphocytes and in activation of cytotoxic T (CD8+) lymphocytes. Multiple intraperitoneal IL-18 injections, but not just a single injection, enhanced both Th1 and Th2 response, humoral immunity, as well as neutrophil phagocytic activity in immunocompromised mice infected with pathogens, such as *E. coli, Listeria monocytogenes, Staphylococcus aureus, Cryptococcus neoformans* (Kinoshita *et al.,* 2013). However, exogenous IL-18 may sometimes induce exaggerated inflammatory reactions that are harmful to the host, because of its potent IFN-gamma inducing capability. The excessive IL-18-driven reaction sometimes causes multiorgan injures and lethality.

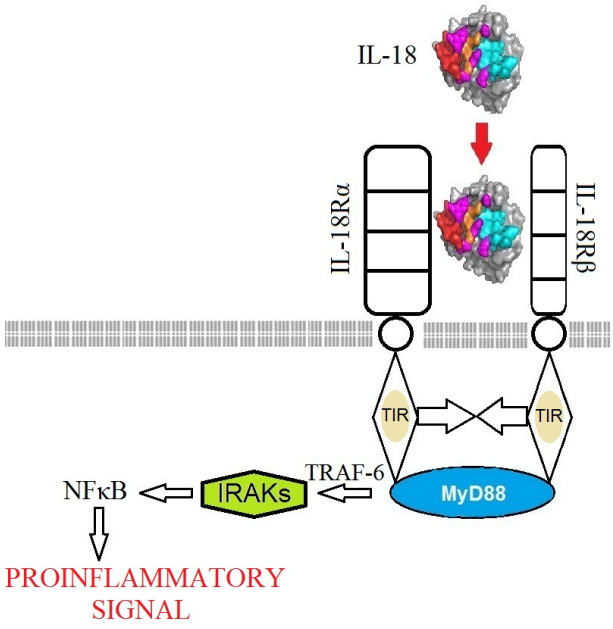

Figure 1. IL-18 signal transduction pathway (Dinarello *et al.*, 2003, modified).
IL-18R, IL-18 receptor; TIR, Toll-IL1 receptor domain; MyD88, myeloid differentiation factor 88; TRAF-6, tumor necrosis factor receptor-associated factor-6; IRAKs, IL-1 receptor-associated kinases; NFκB, nuclear factor κB.

PROSPECTS FOR THE IL-18 APPLICATION IN IMMUNE INTERVENTIONS

The IL-18 driven intensification of IFN-gamma production is accompanied by an increase in nitrogen oxide synthase and killing ability of macrophages. It suggests an important role of IL-18 in the resistance to intracellular pathogens- which are able to develop inside immune cells, including macrophages. *M.tb,* the causative agent of tuberculosis (TB), belongs to this group of bacterial pathogens. Recent epidemiological data clearly indicates that TB remains one of the most deadly infectious diseases. According to the WHO data from 2013, this disease was diagnosed in more than 9 million cases worldwide, and up to 2 million people die annually because of it. The control of TB is still difficult because of not fully effective diagnosis and insufficient protective effectiveness of the only currently used anti-tuberculosis BCG (Bacillus Calmette-Guerin) vaccine (WHO, Global Tuberculosis Report, 2014). A crucial role of IL-18 in the host protection against *M.tb* infection was shown by Kinjo *et al.* in studies using IL-18 knockout and IL-18 transgenic mice. IL-18 deficient mice were more prone to an *M.tb* infection and their sera, spleens, lungs and livers contained less IFN-γ than those of wild-type mice (Kinjo *et al.,* 2002). The IFN-γ production by spleen cells stimulated with mycobacterial antigens was also impaired in IL-18 knockout mice. In contrast, IL-18 transgenic mice were more resistant to an *M.tb* infection than control wild mice, and the levels of IFN-γ in their serum and its production by mycobacterial antigen stimulated spleen cells were increased. These data suggested a significant contribution of IL-18 to the development of Th1 immunity (Kinjo *et al.,* 2002). The pronounced

role of IL-18 in the defense against TB was confirmed by Schneider *et al.* (Schneider *et al.,* 2010). The protective Th1 response to *M.tb* was decreased in IL-18 deficient mice, which constituted a privilege for mycobacterial propagation. Neutrophil driven lung immunopathology, concomitant with unrestricted growth of *M.tb* bacteria, was most probably responsible for the premature death of IL-18 knockout mice infected with *M.tb.* In humans, IL-18 promoter gene –607C/A polymorphism was found to be a risk factor for TB in the Chinese population, but not for the south Indian population (Li *et al.,* 2013, Harishankar *et al.,* 2007). A large case-control study revealed that polymorphisms in the IL-18 receptor alpha chain gene *IL-18R1* were associated with the risk of TB in older Chinese people (over 46 years old) (Zhang *et al.,* 2014). In addition, SNPs (Single Nucleotide Polymorphism) in the *IL-18R1* promoter were associated with the genotype-specific methylation status and genotype-specific *IL-18R1* expression, which suggests that increased DNA methylation and decreased mRNA expression of *IL-18R1* might partially mediate the increased susceptibility to TB.

Extraordinary susceptibility to infections' complications, such as sepsis in patients with severe surgical stress, i.e. trauma injury, burn injury or major surgery, is a frequent and unresolved problem (Kinoshita *et al.,* 2013). The loss of the physical skin barrier, as well as bacterial translocation from the gut, can cause sepsis in such patients. Bacterial infection can lead to lethal multi-organ injuries, as the host defense system is significantly weakened, which promotes microbial growth. Mice studies suggest a possible medical application for IL-18 in the treatment of post-burn *E. coli* infection. Multiple injections of IL-18 to the burn injured mice remarkably increased the IFN-γ production by mononuclear liver cells, thus improving bacterial clearance and mouse survival after *E. coli* infection (Kinoshita *et al.,* 2004; Kinoshita, Kuranaga *et al.,* 2006). Small doses of IL-18 also restored the development of specific antibacterial immune responses, preventing infections with *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus,* the most common bacteria in post-burn infections (Kinoshita *et al.,* 2004; Kinoshita, Shinomiva *et al.,* 2006; Kinoshita *et al.,* 2011). IL-18 driven activation of neutrophils was mostly responsible for improved elimination of these pathogens. Therapy involving administration of IL-18 also results in an up-regulation of IFN-γ production by NK cells and recruitment of neutrophils, monocytes and macrophages into infectious foci. IL-18 treatment for burn-injured mice strengthened the host defense against *P. aeruginosa* infection by the up-regulation of natural IgM production in the liver B1 cells, which were characterized as $CD43^{+}CD5^{-}CD23^{-}B220^{dim}$ cells (Kinoshita, Shinomiva *et al.,* 2006). Such antibodies may opsonize bacteria and facilitate their ingestion by phagocytes before specific antibacterial antibodies are produced. Multiple IL-18 injections activate natural IgM-producing B-1 cells in the liver and restore the humoral immunity against bacterial infections after a burn injury. Such activity of IL-18 may also be helpful in preventing the serious complications in pneumococcal respiratory infections in immunocompromised patients (Kinoshita *et al.,* 2013). Altogether, these data suggest that IL-18 treatment may be recognized as an alternative and useful therapeutic tool against infections caused by intracellular and extracellular pathogens, even in individuals with an immunodeficiency.

In some preclinical models IL-18 has been found to have an antitumor activity (Srivastava *et al.,* 2013, Fabbi *et al.,* 2015). It has been shown that systemic administration of IL-18 enhances the regression of a well-established primary tumor by a mechanism that depends on CD8+ T cells, Fas (CD95)/FasL (Fas ligand) interaction and endogenous IFN-γ, particularly in a combination with other cytokines (Robertson *et al.*, 2008). In a combination with monoclonal antibodies (mAB) recognizing the CD20 antigen on B lymphocytes, IL-18 co-stimulates IFN-γ production and antibody-dependent cellular cytotoxicity (ADCC) of NK cells, which are activated through the surface receptors for Fc fragments of the antibody molecules. In this way, IL-18 augments the activity of mAB against B cell leukemias and lymphomas. In other experimental studies, synergistic effects of IL-18 and *M. bovis* BCG bacteria on the IFN-γ Th1 responses were observed in a mouse model of bladder cancer (Luo *et al.,* 2004). BCG has been applied in the treatment of superficial bladder cancer for years, however, 30–50% of patients did not respond to the BCG therapy. To improve the therapeutic efficacy of BCG, a recombinant BCG strain that functionally secretes murine IL-18 (rBCGmIL-18) was developed. BCG bacteria themselves are strong Th1 inducers. Small amounts of IL-18 released by rBCGmIL-18 augmented Th1 immunity in mice, which led to: a) reduced mycobacterial growth in spleen after infection, b) increased production of IFN-γ, TNF-α (tumor necrosis factor-α) and GM-CSF (granulocyte macrophage colony stimulating factor), and decreased secretion of IL-10, by spleen cells stimulated with BCG, c) augmented macrophage cytotoxicity against bladder cancer MBT-2 cells. It can be expected that this feature of recombinant BCG strains, capable of expressing IL-18, might be useful in immunotherapy and prophylaxis of diseases in which Th1 response is desirable (Dinarello *et al.,* 2013; Luo *et al.,* 2004; Novick *et al.*, 2013). This expectation seems to be confirmed by our recent demonstration of a remarkable advantage of recombinant rBCGhIL-18 producing human IL-18 over nonrecombinant BCG in the stimulation of dendritic cells to preferentially trigger strong IFN-γ secretion by naive CD4(+) T cells in healthy humans vaccinated with BCG (Szpakowski *et al.,* 2015). Previously, the rBCGmIL-18 strain producing murine IL-18 had been found to modify the Th2 type responses in a murine model of the ovalbumin-dependent allergic reaction. Following *in vitro* stimulation with an ovalbumin, lymph node cells from rBCGmIL-18-treated mice produced less IL-5 and more IFN-gamma than those of mice injected with nonrecombinant BCG (Biet *et al.,* 2005). After a challenge with ovalbumin, a strong reduction of bronchoalveolar eosinophilia was observed in rBCGmIL-18-injected mice. This activity of the rBCGhIL-18 strain might be helpful in alleviating the symptoms of allergic reactions. The polarized response of Th2 lymphocytes to an allergen is considered to be the main cause of the pathogenesis of asthma (Kowalski *et al.,* 2015).

Some data point to the crucial role of IL-18 in maintaining the homeostasis. A study group of IL-18 deficient mice indicated a predisposition of mice to obesity and other metabolic disorders. These mice were characterized by a significantly higher weight (by 40%) and an increase in the body fat content (over 100%) compared to wild-type animals. Individuals with a defect in the expression of the surface IL-18Rα receptor also showed a predisposition to obesity, diabetes and other metabolic disorders. These disorders were due to the inefficient functioning of the central nervous system region responsible for the regulation of the appetite, which might affect the depo-

sition of fat in the key blood vessels (Dinarello *et al.,* 2013; Novick *et al*., 2013).

The knowledge of the biology system including IL-18, its receptor IL-18R and inhibitor IL-18BP allows to suggest a possibility of alleviating the symptoms of diseases associated with the IFN-γ overproduction, such as systemic lupus erythematosus, Wagner's disease or Crohn's disease, by blocking the IL-18 activity. It is worth emphasizing that blocking the activity of IL-18 may also find applications in the treatment of multiple sclerosis, where IL-18 promotes the expression of a surface vascular cell adhesion molecule 1, attributed to play an important role in the development of the disease (Dinarello *et al.,* 2013; Novick *et al*., 2013; Wei *et al.,* 2014).

Despite all the potentially positive aspects of administration of exogenous IL-18 in preventing various complications in bacterial infections, immunostimulation of antitumor responses or diminishing allergic disorders, this cytokine can also cause an exaggerated inflammatory response due to its potent IFN-γ inducing capability. It limits a possibility of IL-18 therapy only to immunocompromised hosts, where this cytokine may effectively restore the host immune responses without evoking any exaggerated inflammatory processes. In order to overcome these limitations, new methods of IL-18 administration need to be developed to avoid the potential harmful effects of exogenous IL-18. Recombinant BCG mycobacteria producing IL-18 seem to be a good formula for the administration of IL-18 (Biet *et al.,* 2002, Luo *et al.,* 2004).

Acknowledgements

Supported by a grant from the Polish Ministry of Science and Higher Education, 2013/11/B/NZ6/01304.

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