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Review Article

Interleukin-18 in Health and Disease

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Abstract

Interleukin-18 (IL-18) is a relatively newly discovered immunostimulatory cytokine, which is structurally similar to IL-1. IL-18 is produced mainly by activated macrophages, however; it may also be expressed by kupffer cells, T cells, B cells, keratinocytes, astrocytes, and osteoblasts. IL-18 can regulate both innate and adaptive immune responses through its effects on natural killer (NK) cells, monocytes, dendritic cells, T cells, and B cells. IL-18 has multiple biological activities via its capacity to stimulate innate immunity and both Th1 and Th2 mediated responses. IL-18 acts synergistically with other pro-inflammatory cytokines to promote interferon-γ (IFN-γ) production by NK cells, T cells, and possibly other cell types. It induces gene expression and synthesis of Tumor Necrosis Factor (TNF), IL-1, Fas Ligand, and several chemokines. It also exerts anti-tumor effects that are mediated by enhancement of Natural Killer (NK) cell activity, reduction of tumorigenesis, induction of apoptosis and inhibition of angiogenesis in tumor cells. IL-18 plays a critical role in the Th1 response required for host defense against viruses as well as plays a role in inflammatory liver disease. IL-18 was significantly upregulated in persons with chronic HCV infection compared to healthy persons or asymptomatic carriers. This upregulation correlated with hepatic injury, indicating a role for IL-18 in the pathogenesis of HCV infection. In addition, neutralization of IL-18 by administration of anti-IL-18 monoclonal antibodies (mAb) results in total prevention of liver injury. Raised levels of serum IL-18 was demonstrated in chronic HCV-patients before antiviral therapy with Pegylated IFN (PEG-IFN). A marked decline in IL-18 was associated with remission of hepatic inflammatory activity in responders, while persistent raised levels of IL-18 were associated with PEG-IFN treatment failure.

Keywords: HCV, cytokines, interleukins

Discovery of IL-18

In 1989, Nakamura and co-workers[1] described an endotoxin-induced serum activity that induced IFN-γ production from mouse spleen cells. This serum activity functioned not only as a direct inducer of IFN-γ but rather as a co-stimulant together with IL-2 or mitogens. An attempt to purify the activity from post-endotoxin mouse serum revealed an apparently homogeneous 50-55-kDa protein[2,3]. Because other cytokines can act as co-stimulants for IFN-γ production, the failure of antibodies to IL-1, IL-4, IL-5, IL-6, or TNF to neutralize the serum activity suggested that it was a distinct factor. In 1995, another report was published by Nakamura and co-workers demonstrating that the endotoxin-induced co-stimulant for IFN-γ production was present in extracts of livers from mice preconditioned with *P. acnes*[4]. In this model, the hepatic macrophage population (Kupffer cells) expanded dramatically, and the low dose of bacterial lip-

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opolysaccharide (LPS), which is not lethal in non-preconditioned mice, becomes lethal. A factor was purified from mouse livers and named IFN-γ -inducing factor (IGIF)[4]. IGIF purified from liver homogenates did not induce IFN-γ by itself, but functioned primarily as a co-stimulant with mitogens or IL-2. Neutralizing antibodies to mouse IGIF were shown to prevent liver damage induced by LPS in pre-conditioned mice. IFN-γ is an important mediator of LPS-induced toxicity in pre-conditioned mice[5]. IGIF, also called IL-18, is a cytokine which is synthesized by activated macrophages, T-cells, NK cells, Kupffer cells, dendritic cells (DCs), adrenal cortex cells, osteoblasts, Langerhans cells and intestinal epithelial cells[5].

Structure and production of IL-18

IL-18 is a proinflammatory cytokine of 18 kDa and 157 amino acids. It is synthesized as an inactive precursor (pro-IL-18) of a 24 kDa, which is cleaved by interleukin-1 β-converting enzyme (ICE or caspase-1) producing the mature, bioactive peptide that is readily released from the cells[6].

Molecular structure and gene expression
Human IL-18 genes are located on chromosome 11. Human IL-18 cDNAs encoding precursor IL-18 are composed of 193 amino acids. The genomic analysis of the promoter region demonstrated that for constitutive expression of IL-18 at least 92 base pairs of the promoter region are essential[7].

IL-18 receptors
The receptor for IL-18 (IL-18R) is a heterodimer composed of two chains: 1) a ligand-binding component (α chain) which is responsible for the extracellular binding of IL-18 *(was identified as IL-1 receptor-related protein, IL-1Rrp).* 2) A signaling component (β chain) which is responsible for the intracellular signal transduction *(also termed accessory protein-like, AcPL)* since it is related to the IL-1R accessory protein, both of which belong to the IL-1R family[8].

Interleukin-18 binding protein (IL-18BP)
IL-18BP is the natural inhibitor of IL-18, which negatively regulates its biologic effects. IL-18BP is a constitutively secreted protein with a high-affinity binding to IL-18 (400 pmol/L). Once IL-18 is secreted, it is bound and inactivated by IL-18BP. The production of IL-18BP is enhanced as a negative feedback mechanism in response to increased IL-18 production, to ensure protection from tissue damage due to the uncontrolled pro-inflammatory activity. IL-18BP is highly expressed in spleen and the intestinal tract, both of which are immunologically active tissues[9]. The promoter for IL-18BP contains two IFN-γ response elements, and constitutive gene expression for IL-18BP is dependent on IFN-γ, which suggests a compensatory feedback mechanism. Thus, elevated concentrations of IFN-γ stimulate more IL-18BP in an attempt to reduce IL-18-mediated IFN-γ production[10].

Processing of IL-18
The molecular mechanism for the production of IL-18 is mediated by TNF receptor associated factor 6 (TRAF-6). Interleukin receptor activates myeloid differentiation Factor-88 (MyD88) and IL-1 receptor-associated kinase (IRAK). This activation leads to the synthesis of proinflammatory genes, such as inducible nitric oxide (iNOS) and IFN-γ. IL-18 also enhances the pro-inflammatory activity by inducing matrix metalloproteinases, which are crucial for pathological chemotaxis of immune cells to target tissues (i.e. hepatic tissue)[11]. IL-18 binds to IL-18Rα and IL-18Rβ to form a high-affinity complex that induces signaling pathways together with other IL-1R family members. This involves recruitment and activation of MyD88 and IL-1R-associated kinase (IRAK) to the receptor complex[12]. IL-18 is processed into active forms by at least

two recognized proteases. One pathway involves the same enzyme that typically activates IL-1β, caspase-I, [also known as interleukin-1 converting enzyme (ICE)]. Alternatively, IL-18 is activated by the neutrophil-derived serine proteinase, proteinase 3 (PR3). These two activation pathways are differentially associated with cellular processes and pathologies[13].

Function and Biological Activity of IL-18

IL-18 and inflammatory process

IL-18 is evolving as a major pro-inflammatory cytokine with implications for a role in inflammatory and infectious diseases. IL-18 was first described as IGIF[14]; however, the ability of IL-18 to induce IFN-γ production is primarily in the context of a second stimulus in that it acts with IL-12, mitogens, or microbial agents to augment IFN-γ production[15]. Alone, IL-18 does not induce IFN-γ production from T lymphocytes. However, in vitro LPS and zymosan-induced IFN-γ production from murine spleen cells is strongly reduced using neutralizing antibodies to murine IL-18, confirming similar findings in vivo and suggesting that endogenous IL-18 is an essential for IFN-γ production by microbial agents. Because of its ability to induce tumor necrosis factor α, IL-1β, and both CXC and CC chemokines and because IL-18 induces Fas ligand as well as nuclear translocation of nuclear factor kB (NF-kB), IL-18 ranks with other pro-inflammatory cytokines as a likely contributor to systemic and local inflammation[16]. Consistent with stimulating TNF production, IL-18 upregulates Fas ligand-mediated cytotoxic activity of natural killer (NK), T cells, and the myelomonocytic cell line KG-1. In addition to macrophagic cells, keratinocytes produce functional IL-18 after stimulation with contact sensitizers and hence IL-18 may have a role in the inflammatory process after allergen contact. During endotoxin-induced liver damage in mice, neutralizing antibodies to IL-18 reduced tissue damage[17].

IL-18 and immunity

IL-18 plays roles equally in both the innate and the adaptive immune systems. It works together with IL-12 to induce cell-mediated immunity following infection with microbial products such as lipopolysaccharide (LPS). After stimulation with IL-18, NK cells and certain T-cells release IFN-γ or type II interferon that plays an important role in activating macrophages and other cells[18]. IL-18 induces both T_H1 and T_H2 responses. Thus, it is involved in the development of protective immunity against intracellular microbes, including viruses such as HCV[19]. In addition, the combination of IL-18 and IL-12 has been shown to inhibit IL-4 dependent IgE and IgG1 production, and enhance IgG2a production by B-cells[20].

IL-18 and IFN

IL-18 production is induced by stressful stimuli (*i.e.*, bacterial or neurogenic signals). In this context, it has been proposed that a stress-induced release of IL-18 can lead to a reinforcing cycle of IFN-γ/IL-18 production[21]. Following an initial wave of IL-18-induced IFN-γ production, newly secreted IFN-γ can now stimulate monocytes/ macrophages to increase their interleukin-1 converting enzyme (ICE) activity[15]. In the presence of continued IL-18 production, increased ICE activity probably results in more processed IL-18, which leads to more lymphocyte IFN-γ production, which leads to more macrophage ICE activity. Thus, IL-18 promotes not only IFN-γ synthesis, but also participates in its overall activities[13].

IL-18 and apoptosis

IL-18 has also been implicated in killing mediated by the Fas ligand (FasL). FasL is a tightly regulated 40 kDa member of the TNF superfamily of molecules. The binding of

FasL to its widely expressed receptor, Fas, usually leads to activation of an apoptotic program in the cell expressing Fas. Cells that are believed to mediate such activities are $CD4^+$ T_H1 cells and NK cells (two cell populations that express FasL under the influence of IL-18). In this respect, IL-18 again demonstrates a relationship to IFN-γ that appears as an upregulator of Fas antigen expression[22]. IL-18 upregulates both FasL and IFN-γ production in T-cells and the produced IFN-γ may induce Fas antigen on a variety of cell types. Thus IL-18, via IFN-γ induction, could be considered a molecule that provides both the means (FasL) and the opportunity (Fas) for instigating apoptotic cell death[22].

IL-18 and Tumors

IL-18 exerts anti-tumor effects, which are mediated by enhancement of NK cell activity, reduction of tumorigenesis, induction of apoptosis and inhibition of angiogenesis in tumor cells[5].

Pathological role of IL-18

Apart from its physiological role, IL-18 is also able to induce severe inflammatory reactions, which suggests its role in certain inflammatory disorders and autoimmune diseases. These include diseases that involve elevated IFN-γ such as graft-versus-host disease (GVHD); psoriasis, rheumatoid arthritis and Crohn's disease. IL-18 is also implicated in pathologies resulting from ischemia such as myocardial infarction, renal failure and liver damage[13].

IL-18 and Liver Diseases

IL-18 has been shown to play a key role in the pathogenesis of acute liver injury in mice that have been challenged with endotoxin after priming with Propionibacterium acnes and lipopolysaccharide (LPS). Concanavalin A (Con A)-induced hepatitis is an immune-mediated disease in which the interplay of $CD4^+$ T-cells and T_H1 cytokines causes Fas-mediated liver cell death[6]. In addition, FasL-activated macrophages cause liver damage in an IL-18-dependent, caspase-1-independent process; whereas, ischemia reperfusion-induced myocardial dysfunction is IL-18 and caspase-1-dependent[13]. In mice, IL-18 immuno-neutralization by administration of anti-IL-18 monoclonal antibodies (mAb) protects from liver injury induced by Con A[23]. In addition, IL-18 deficient mice are resistant to LPS-induced liver injury[24].

IL-18 and viral infections

Many reports suggest that IL-18 might play a role in viral infections. A positive effect of IL-18 has been shown in mouse models of herpes simplex and vaccinia virus infection, demonstrating that IL-18 inhibits human immunodeficiency virus (HIV) production in peripheral blood mononuclear cells (PBMC)[25]. However, the mechanism of this antiviral effect and its relationship to viral replication has not been determined. IL-18 has been shown to inhibit hepatitis B virus (HBV) replication in the livers of transgenic mice[26].

IL-18 and HCV infection

Immune response, essentially conducted by cytokines, plays an important role in the pathogenesis of HCV infection. A significant correlation between both intra-hepatic and circulating T_H1-type cytokines and the degree of liver injury has been reported[27]. The pathogenic role of IL-18 in liver disease is suggested by: (i) the up-regulation of IL-18 mRNA in CHC infection[28]; (ii) the elevated serum levels of IL-18 in patients with CHC, biliary atresia, primary biliary cirrhosis and autoimmune hepatitis[29]; and (c) the association between raised serum IL-18 and acute rejection in patients with liver transplantation[30]. Previous studies have shown an increased expression of proinflammatory cytokines, in particular IL-18, which corre-

lates with IFN-γ production in CHC and cirrhosis[28]. Abbate *et al*. revealed an up-regulated expression of the IFN-related genes (IFN-γ, IFN-α receptor-1, IFN regulatory factor-1, and IL-18), together with down-regulated expression of IFN-α and IFN-β in patients with HCV infection compared with non-alcoholic steatohepatitis[31]. Previous studies provided significant evidence indicating that IL-18 plays a prominent role in liver injury. In 2002, Ludwiczek and co-workers[32] reported elevated levels of plasma IL-18 and IL-18 binding protein (IL-18BP) in patients with chronic liver disease compared with healthy controls, which supports a possible role for IL-18 in the in the chronic cellular immune response against hepatocytes[33]. In CHC, the administration of IFN-γ exerts an anti-inflammatory action *in vivo* by induction of IL-18 binding protein and late suppression of IL-18[29].

IL-18 and IFN therapy

IFN-α exerts its anti-inflammatory action by induction of IL-18-binding protein production. In HCV infection, the increased IL-18 production is neutralized by IL-18BP. This neutralization is crucial for the regulation of inflammation and development of fibrosis[34]. IFN therapy increases plasma IL-18BP levels by 3- to 24-fold within 24 h following the institution of therapy[29]. Elevated serum IL-18 was demonstrated in chronic HCV-patients before the start of PEG-IFN therapy. A marked decline in IL-18 was associated with remission of hepatic inflammatory activity in responders, while persistent raised levels of IL-18 were associated with treatment failure. Effective IFN-α therapy reduces the IL-18 concentration[35] while, elevated level of IL-18 receptors was a significant predictor of poor outcome of IFN therapy in HCC[36].

IL-18 polymorphisms and HCV

Two single nucleotide polymorphisms (-607 C/A and -137 G/C) in the promoter region of the IL-18 gene have repeatedly been found to be associated with the IL-18 promoter transcription activity. Both SNPs disrupt transcription factors binding sites, and at least decrease the level of IL-18 mRNA[37]. Lower promoter activity was observed for the minor alleles -607A and -137C compared to the more common alleles -607C and -137G, respectively. Haplotypes carrying these alleles also correlated with IL-18 levels in peripheral blood mononuclear cells (PBMC) or plasma. Moreover, these haplotypes capture the majority of genetic variation of IL-18, due to the presence of strong linkage disequilibrium among polymorphisms in the gene[38]. The carriage of at least one allele C at position -607 or G at position -137 seems to be a risk factor for developing more severe forms of chronic hepatitis. IL-18 haplotype (AC) may play a protective role against chronic hepatitis progression. Patients who are homozygous for C at position - 607 and G at position -137 have higher levels of IL-18 mRNA compared to other genotypes[39].

IL-18 and Fungal infections

IL-18 in synergy with IL-12 promotes the antifungal response to *C. neoformans* by inducing IFN-γ from NK cells and NO from macrophages with a down-regulation of IL-4 production[40]. Thus, IL-18 administration during *C. neoformans* infection promotes the antifungal response. IL-18 appears effective even in the absence of IL-12. In a chronic fungal asthma model, IL-18 promotes innate responses, preventing the development of severe fungus-induced asthmatic disease[41]. In caspase-1-deficient mice, IL-18 restores defective Th1 responses during Candida albicans infection[42].

IL-18 and Bacterial infections

The intracellular pathogen Mycobacterium avium has been widely studied using a variety of murine strains including IL-18 and IL-18R-deficient mice. These studies showed

the requirement for a strong Th1 response and a critical role for IL-18 in expulsion of the pathogen. The contribution of IL-18 during a protective Th1 response is further demonstrated in human studies on patients with M. tuberculosis infection who displayed a decreased ability to produce IL-18 and IFN-γ in response to antigen compared with healthy PPD-responsive controls[43]. Similarly, Kinjo and colleagues[44]. have demonstrated an impaired IFN-γ production in IL-18-deficient mice following infection. However, patients with advanced disease appear to have raised plasma IL-18 levels[45]. In leprosy, the Th1/Th2 balance is key to disease outcome, but currently data on IL-18 are conflicting. In resistant tuberculoid leprosy (TL), protective IFN-γ production is associated with increased IL-18 mRNA expression within lesions, and monocytes from TL patients show increased IL-18 mRNA expression following in vitro challenge with bacterial antigen. Furthermore, such in vitro challenge of T and NK cells of TL patients resulted in increased IFN-γ production compared with cells from patients with susceptible lepromatous leprosy (LL). However, Yoshimoto et al[46] have shown that serum IL-18 levels were much higher in an LL cohort. IL-18 could therefore promote the development of the Th2 response, characteristic of LL. Further in vivo studies have shown the importance of IL-18 in the protective immune response to a number of bacterial infections including salmonella, yersinia, chlamydiae, and shigella[47,48].

IL-18 and Protozoan infections

A protective role of IL-18 during Leishmania major infection was reported. Wei and colleagues[49] reported increased susceptibility to Protozoan infections in IL-18-deficient mice. In severe combined immunodeficiency (SCID) mice, IL-18 augments NK cell-mediated immunity to Toxoplasma gondii[50]. Moreover, resistance to T. cruzi required the development of a successful IFN-γ response, which correlated with increased expression of IL-12 and IL-18. Finally, high levels of IL-18 were detected in mice infected with P. berghei, and neutralizing anti-IL-18 antibodies shortened survival times. Serum IL-18 rises in patients with uncomplicated Plasmodium falciparum malaria who mount an effective Th1 response[51].

IL-18 and immunotherapy

Systemic administration of IL-18 showed a significant antitumor activity in animal models. Phase I clinical trials of recombinant human IL-18 have established that it can be securely administered to patients with advanced cancer. Biologic effects of IL-18 therapy include activation of monocytes, NK cells, T cells and an increased production of IFN-γ. IL-18 acts mostly as a costimulatory cytokine, thus its best use for cancer immunotherapy is in combination with other immunostimulatory cytokines, vaccines, or monoclonal antibodies[52].

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