Interleukin 18 – a pleiotropic cytokine involved in the Th1 and Th2 immunological response

Magdalena Trzeciak, Małgorzata Sokołowska-Wojdyło, Wioletta Barańska-Rybak, Agata Maciejewska, Igor Michajłowski, Jadwiga Roszkiewicz

Department of Dermatology, Venereology and Alergology, Medical University of Gdansk, Poland
Head: Prof. Jadwiga Roszkiewicz MD, PhD

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Abstract

Interleukin 18 (IL-18) is a pleiotropic cytokine that plays a crucial role in the control of the balance between the Th1 and Th2 response. Synergistically with IL-12, IL-18 promotes an immunological response of the TH1 type, by enhancing INF-γ synthesis and inhibition of IgE production. On the other hand, IL-18 can enhance IL-4 and IL-13 production and stimulates IgE synthesis. Moreover, in the presence of IL-3, IL-18 can directly stimulate basophils and mast cells to produce their mediators. The gene of IL-18 is located on chromosome 11q22.2-22.3, which was identified as an important candidate region for susceptibility to atopy. The aim of this paper is to characterize IL-18, the evolution of views on it and to emphasize the influence of IL-18 on the development of infectious, inflammatory, autoimmune diseases and malignancies with a special consideration of atopic diseases.

Key words: interleukin 18, immunoglobulin E, lymphocytes Th1 and Th2.

Characteristics

Interleukin 18 (IL-18) was identified in 1989 as the INF-γ inducing factor. It was discovered in mouse's serum, after having injected *Propionobacterium acne* endotoxin. Six years later, in 1995, IL-18 was cloned and recognized as a single peptide chain of molecular weight 18 000 Da [1, 2]. In the natural environment IL-18 is synthesized as an inactive precursor – polypeptide of molecular weight 24 kDa (pro-IL-18) [3] – and subsequently is activated by intracellular cysteine-caspase 1 protease (enzyme converting IL-1β) [3-5]. Interleukin 18 is secreted by keratinocytes, monocytes, macrophages, dendritic cells, epithelial cells and osteoblasts [4-6]. Moreover, it can be produced by ependymal cells and microglia [7].

Mechanism of action

The receptor for IL-18 is located on numerous cells [2, 6, 8] specified in Table 1. It is a hetero dimer composed of two subunits: α and β. Chain α binds IL-18 and chain β is responsible for the transduction of the signal [1, 2, 4]. The structure of IL-18 receptor and the transduction of the signal are presented in Figure 1.

Binding of IL-18 with the receptor's α subunit activates β chain and Toll domains located in the cytoplasmic fragment of the chain. The Toll domain binds IL-18 with Toll-like receptor, which recognizes microorganisms' antigens too. Intracellular protein – MyD88 adapter protein – which is a fragment of the TLR (Toll-like receptor) transduction pathway, is activated and leads to the phosphorylation of protein kinase IRAK (IL-1 receptor-associated kinase), which then activates TRAF 6 protein (TNF-R associated factor 6). Subsequently, through the protein kinase system, which is activated by MAP (mitogen activated protein kinases) mitogen, whose final cascade's elements include c-Jun N-terminal kinases (JNK), transcription factors activating protein 1 (AP-1) and nuclear factor κB (NFκB) are activated. As a result of this activation, transcription of IL-4, IL-13 and other effectors increases. Furthermore, the increase of the IL-4 and IL-13 concentration, acting through STAT 6, induces allergic inflammation [1, 2, 5, 9, 10].

Interleukin-18 has an additional receptor/inhibitor: IL-18 binding protein (IL-18 BP) [1, 2, 4]. Clinical studies concerning its use in rheumatoid arthritis [2] and psoriasis [2, 11] are ongoing.

Address for correspondence: Magdalena Trzeciak MD, PhD, Department of Dermatology, Venereology and Alergology, Medical University of Gdansk, 7 Dębinki, 80-211 Gdańsk, Poland, tel.: 501 188 586, fax: +48 58 349 25 86, e-mail: mtrzeciak@gumed.edu.pl

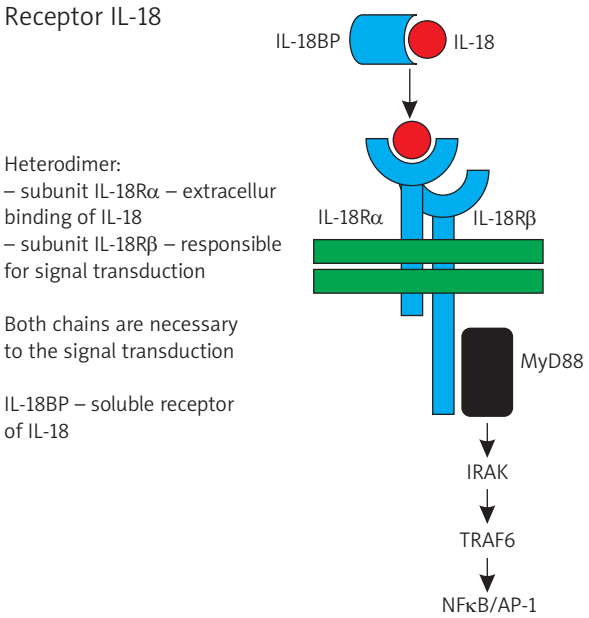
Table 1. Cells with the receptor for IL-18

T lymphocytes [2, 8]
Dendritic cells [2, 8]
Mast cells [6]
Basophils [6]
Macrophages [8]
Neutrophils [2]
NK cells [3, 8]

Clinical applications

As mentioned before, IL-18 used to be called a factor inducing INF-γ from Th, CD8 and NK cells [1, 6, 8, 12, 13]. Considering this activity, IL-18 is a basic cytokine taking part in defence against bacterial, fungal, parasitic and viral infections [3]. It is one of the first to inform the immunological system about emerging infection [4]. Moreover, it was considered that through the induction of INF-γ, IL-18 suppress the synthesis of IgE and demonstrates anti-allergic properties. Currently, it is known that it presents such activity in synergy with IL-12 by increasing the expression of IL-18 receptor on T-cells [8, 14].

Breakthrough studies in recent years [3, 4, 6, 14-16] have proved that IL-18 influences the production of IL-4 and IL-13 and, through this, stimulates the synthesis of IgE. Those results have presented IL-18 in a completely different light and have caused a hail of studies on the role of this cytokine in the development of allergic diseases. Interleukin 18 activates T-cells and mastocytes to secrete IL-13 and IL-4 [6, 14, 16]. In combination with IL-2, it increases the production of IL-13 [17]. Besides, what was scientifically proved, in the presence of IL-3 it is able to directly stimulate basophils and mastocytes to secrete inflammatory reaction mediators such as histamine, serotonin, IL-4 and IL-13 without IgE participation. Under the influence of this direct activation, *in vitro*, basophils produce IL-4 and IL-13, whereas mastocytes produce only IL-13 [6]. It was proved that IL-18 induces skin lesions typical for atopic dermatitis independently of the level of cytokines [16, 18]. A thesis was advanced that it was strictly IL-18, not IgE, that plays a significant role in the development of dermatitis through the activation of mastocytes and T-cells [16]. In transgenic mice, deprived of the STAT6 gene which is responsible for the signal transduction in the development of the allergic reaction and for IgE production, undetectable levels of IgE, and reduced level of histamine and mastocytes were noted. Still, pruritus and skin lesions typical for atopic dermatitis were present in mice. Transgenic mice, deprived of IL-18, did not present any signs of



IL-18Rα, β – subunit α, β of receptor IL-18, IL-18BP – IL-18 binding protein-soluble receptor IL-18 (protein binding IL-18), MyD88 (Myeloid differentiation factor88) – adaptor protein MyD88, IRAK (IL-1 receptor- associated kinase) – kinase IRAK, TRAF6 (TNF-R associated factor 6) – factor associated with TNFR, AP-1 – activator protein 1, NFκB (nuclear factor κB) – transcription factor κB

Fig. 1. The IL-18 receptor and the signal pathway (according to [1, 4])

Table 2. Diseases and conditions with elevated concentration of IL-18 in serum

Malignancies [20]
Diabetes type 1 [1]
Rheumatoid arthritis [1]
Multiple sclerosis (SM) [1, 21]
Crohn's disease [1, 22]
Graft versus host disease (GVHD) [1, 23]
Systemic lupus erythematosus (SLE) [24]
Hepatitis [25]
Inflammation of central nervous system [26]
Sepsis [27]
Helicobacter pyroli infection [28]
Viral infection [29]
Pregnancy [30]
Stress (concentration of IL-18 in blood serum is increased by the activation of hypothalamic-pituitary-adrenal axis and decreased by the parasympathetic system) [7]
Coronary artery disease [1]
Asthma [31-33]
Allergic rhinitis [9, 34]
Atopic dermatitis [3, 13, 18, 34-37]

dermatitis, despite the significant level of IgE [16]. Furthermore, it was proved that IL-18 regulates the production of IgE *in vivo* in the absence of allergens and, in the absence of specific allergens, it is responsible for the induction of atopic phenotype [14, 16].

In summary, IL-18 is a pleiotropic cytokine, which, depending on the environment of cytokines and genetic background, activates a Th1 or Th2 response [3-5, 12-15, 19]. Moreover, Sugama and Conti [7] suggest its neuro-immuno-modulating role and, additionally, its contribution in the control of appetite and obesity development.

Up till now, the contribution of IL-18 in the development of cancer, autoimmune, infectious, inflammatory and allergic diseases has been documented. An elevated level of this cytokine was described in examined patients' blood serum in the majority of those entities [7, 20-34]. Diseases and conditions proceeding with an increase of IL-18 are presented in Table 2.

The gene of human IL-18 is localized on chromosome 11q22.2-22.3 [5, 9]. Its molecular weight is 20.8 kb [1]. It consists of 6 exons and its expression is controlled by 2 promoters: promoter 1 (exon 1) and promoter 2 (exon 2); the starting codon is localized on exon 2. Of note, chromosome 11q22 has been identified as a gene candidate for atopy [5, 9]. Numerous studies have been performed concerning the relation between the IL-18 gene and diabetes type I, multiple sclerosis, Crohn's disease, idiopathic arthritis, graft versus host disease (GVHD), and coronary artery disease [1]. In the domain of allergic diseases, a relation between polymorphism of IL-18 gene [1, 38] and polymorphism of IL-18 receptor [39, 40] and pathogenesis of asthma has been confirmed. In a German population of atopic patients, a relation between IL-18 polymorphism and rhinitis has been revealed [9], and in the Czech population, it was suggested that genetic variants of IL-18 may contribute to pathogenesis of allergic rhinitis [34]. German researchers [5] have demonstrated a connection of IL-18 gene polymorphism with high level of IgE and specific hypersensitivity in patients with atopic dermatitis, whereas Korean scientists [3] have described a relation between IL-18 gene polymorphism and allergic type of atopic dermatitis. A relation between the gene's polymorphism and atopic dermatitis development has also been demonstrated in the Polish population [41].

Conclusions

New genetic and immunological data theoretically indicate the key role of IL-18 in pathogenesis and development of atopic dermatitis. However, that requires further, more extensive clinical studies. Considering the function and mechanisms of action of IL-18 and remembering that this cytokine is tested as a new agent in cancer immunotherapy [42], and its receptor-inhibitor is used in treatment of psoriasis [2, 11] and rheumatoid arthritis [2], we can presume that this cytokine could be a new target in therapy of those diseases and possibly, atopic dermatitis [11].

Despite the knowledge of many functions of IL-18, this cytokine still remains an interesting subject of scientific studies.

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