



Review paper

Interleukin 35: An overview

Natalia Zdanowska¹ , **Agnieszka Barbara Owczarczyk-Saczonek¹**,
Wojciech Zdanowski², **Waldemar Juliusz Placek¹**

¹ Department of Dermatology, Sexually Transmitted Diseases and Clinical Immunology, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland

² Department of Obstetrics, Perinatology and Gynecology, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland

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ABSTRACT

Introduction: Interleukin 35 (IL-35) has recently been characterized as a cytokine connected with the IL-12 group. The secretion of IL-35 was described in forkhead box protein 3 (Foxp3) + regulatory T cells (T_{regs}), peripheral $\gamma\delta$ T cells, CD8+ T cells, placental trophoblasts, antigen-presenting cells (APCs) and regulatory B cells (B_{reg}).

Aim: The aim of this paper is to systematize current knowledge about IL-35 production and discuss its impact on the pathophysiology and outcome of various diseases.

Material and methods: Literature review was conducted.

Results and discussion: IL-35 plays a pivotal role in the immune dysregulation in the pathogenesis of cardiovascular diseases including atherosclerosis, psychiatric and neurologic disorders, cancer, allergic and autoimmune diseases and psoriasis, inducing the expression of T_{reg}-related cytokines and inhibiting the expression of Th1- and Th17-related cytokines.

Conclusions: Due to the numerous signaling pathways of IL-35, it may be described as an innovative biomarker in the prognosis and treatment of various diseases.

1. INTRODUCTION

Interleukin (IL)-35 has recently been characterized as a cytokine connected with the group of IL-12, which consists of the IL-27 β chain Epstein-Barr virus-induced gene 3 (Ebi3) and the IL-12 α chain p35 connected by a disulfide bond. Ebi3 resembles IL-12 p40, whose expression may be induced, while IL-12 p35 expression is pervasive.¹

IL-35 secretion had formerly been characterized in regulatory T (T_{reg}) cells, forkhead box protein 3 (Foxp3)⁺, which was subsequently verified by confirming the co-expression of p35 and Ebi3 in peripheral $\gamma\delta$ T cells, CD8⁺ T cells, and placental trophoblasts. Other cells that might also produce IL-35 are antigen-presenting cells and regulatory B (B_{reg}) cells.^{2,3}

IL-35 has four groups of receptors with IL-12R β 2/gp130, gp130/gp130, IL12R β 2/IL27R α , and IL-12 β 2/IL12R β 2 subunits, which finally trigger signal transducer and activator of transcription (STAT) – STAT1 and STAT4 – signaling pathways.^{1,4}

STAT1 mediates the IL-12R β 2/IL-27R α receptor that is expressed on B_{reg} cells, and STAT1/STAT4 mediate IL-35

production by relating to their proper regions on Ebi3 and IL-12A gene promoters. STAT4 mediates the IL-12R β 2/IL-12R β 2 and gp130/gp130 receptors. STAT1/STAT3 obtain the expression of IL-10 and IL-35 by penetrating the nucleus. Moreover, the STAT3 pathway may facilitate B_{reg} lymphocytes to increase the production of IL-10.⁴

IL-12p35 may induce the expression of itself, Ebi3 and IL-10, while IL-35 may inhibit the proliferation of proinflammatory Th17 lymphocytes by IL-10 development (promoted by B_{reg} cells) [5].

Li et al. suggested that IL-35 should be described as a responsive cytokine that stops inflammation development in contrast to transforming growth factor beta (TGF- β), the house-keeping cytokine, that inhibits the start of the inflammatory process.⁶

IL-35 dominantly suppresses Th1 and Th17 lymphocytes (effector CD4⁺ T cells) as a consequence of T_{reg} population and inhibitory activity increase. Furthermore, it stimulates the expression of interferon α , β , and λ 1.^{7,8}

IL-35 signaling pathways and functions are shown in Figure 1.^{1,3,8}

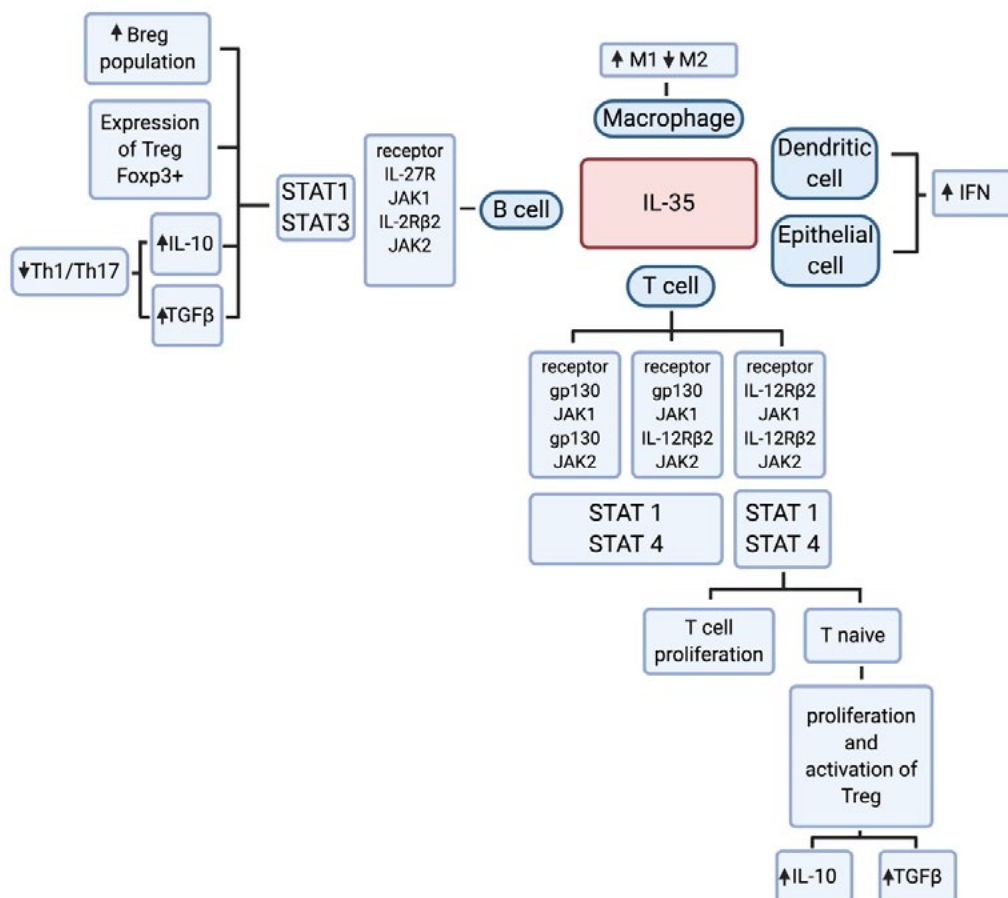


Figure 1. Signaling pathways and functions of IL-35. Abbreviations: IL-35 – interleukin 35; IFN – interferon; M1 – M1 macrophage; M2 – M2 macrophage; B cell – B lymphocyte; T cell – T lymphocyte; STAT1,3,4 – signal transducer and activator of transcription 1,3,4; JAK1 – Janus kinase 1; JAK2 – Janus kinase 2; gp130 – glycoprotein 130; IL-27R – interleukin 27 receptor; IL-2R β 2 – interleukin 2 receptor, beta 2 subunit; IL-12R β 2 – interleukin 12 receptor, beta 2 subunit; Th1 – T helper cell 1; Th17 – T helper cell 17; T_{reg} – regulatory T cell; B_{reg} – regulatory B cell; Foxp3 – forkhead box protein 3; IL-10 – interleukin 10; TGF β – transforming growth factor beta. Figure made using BioRender (<http://biorender.com>).

2. AIM

The aim of this paper was to systematize the current knowledge of IL-35, with special regard to the possible clinical significance.

3. MATERIAL AND METHODS

A review of the literature was conducted using the PubMed database.

4. RESULTS AND DISCUSSION

4.1. IL-35 in cardiovascular diseases and atherosclerosis

It is known that the development of cardiovascular diseases, and the progress of atherosclerosis, may be consequences of an inflammatory process. Immunosuppression as a part of the action of T_{reg} and B_{reg} lymphocytes seems to present protective properties.⁹

IL-12A and Ebi3 were described in atherosclerotic aortic lesions, and their polymorphisms correlated with altered ischemic heart disease risk. In patients with coronary artery disease, B lymphocytes demonstrated the reduced production of IL-35, and IL-10 and T lymphocytes showed the reduced expression of interferon γ (IFN γ) and tumor necrosis factor α (TNF α).⁹

4.2. IL-35 and cancer, allergic and autoimmune diseases other than psoriasis

IL-35 plays a key role in the immune system and in the pathogenesis of related diseases such as autoimmune diseases, allergies or cancers, mainly through its immunomodulating and immunosuppressive properties. Therefore, its expression and serum concentration may be different in various diseases and at different stages of the same disease. Recent reports supported it as a new target of immunotherapy, when it may be blocked in case of the overexpression, and also as a recombinant protein (in diseases with the decreased expression).¹⁰

The serum levels and expression of IL-35 in cancer, allergic and autoimmune diseases other than psoriasis are listed in Table 1.

The elevated expression and high serum concentration of IL-35 are associated with the unfavorable prognosis in pancreatic ductal adenocarcinoma, acute myeloid leukemia and non-small-cell lung cancer.⁴ IL-35 plasma levels were negatively correlated with the severity of systemic lupus erythematosus¹⁴ and rheumatoid arthritis.¹⁵ The treatment of mice with allergic rhinitis with the intranasal application of IL-35 resulted in the inhibition of allergic response by the reduction in IgE, eosinophils, IL-4 and IL-5, and the upregulation of T_{reg} lymphocytes and IL-10.^{9,27}

Despite numerous studies conducted on the role of IL-35 in the pathogenesis of psoriasis, it still remains unclear. Therefore, it was decided to systematize the reports on the relationship between IL-35 and psoriasis in a separate section below. The role of IL-35 in Behcet disease is described in the section concerning neurological and psychiatric conditions.

4.3. IL-35 in psoriasis

As regards the pathogenesis of psoriasis, IL-35 contributes to the imbalance of the immune system. It is probably due to inducing the expression of TGF- β and IL-10 (T_{reg} -related cytokines) and suppressing the expression of Th1- and Th17-related cytokines.²⁸

Beside antigen presentation and antibody secretion, B lymphocytes may influence immune regulation as B_{reg} cells, in which immunosuppressive function is mainly related to IL-10 secretion under the stimulation of CD40L, which is a toll-like receptor agonist. Moreover, B_{reg} lymphocytes are also capable of producing IL-35 and rIL-35 may induce B_{reg} to secrete IL-10 and IL-35.⁸

B_{reg} might also act as inflammation regulators in psoriasis. According to a study of Mavropoulos et al., B_{reg} generating IL-10 were decreased in patients with psoriasis and psoriatic arthritis and demonstrated a negative correlation with T lymphocytes producing IL-17A and IFN γ .²⁹

Aberrancy in T_{reg} cells was associated with inflammation in the course of psoriasis. By producing IL-10, they may decrease inflammation by downregulating the expression of proinflammatory cytokines, chemokines, and adhesion molecules.

Foxp3 positive T_{reg} cells have a possible role in the pathogenesis of psoriasis. High levels of those lymphocytes in peripheral blood and skin lesions positively correlated with disease severity in a study of Georgescu et al.³⁰

Table 1. The serum levels and expression of IL-35 in cancer, allergic and autoimmune diseases other than psoriasis.

Plasma concentration/expression of IL-35 decreased	Plasma concentration/expression of IL-35 increased
Immuno-related hemocytopenia ¹¹	Dermatomyositis/polymyositis ¹⁸
Primary Sjogren syndrome ¹²	Pancreatic ductal adenocarcinoma ¹⁹
Diabetes mellitus type 1 ¹³	Hepatocellular carcinoma ²⁰
Systemic lupus erythematosus ¹⁴	Non-small-cell lung cancer ²¹
Inflammatory bowel disease ⁷	Breast cancer ²²
Rheumatoid arthritis ¹⁵	Gastric cancer ²³
Asthma ¹⁶	Acute myeloid leukemia ²⁴
Chronic obstructive pulmonary disease ¹⁶	Multiple sclerosis ²⁵
Colorectal cancer ¹⁷	Systemic sclerosis ²⁶

IL-35 plasma level was lower in patients with psoriasis than in the control group according to the results by Li et al. it was negatively correlated with disease severity (psoriasis area and severity index – PASI score), IFN γ , TNF α , IL-17 and positively correlated with the serum concentrations of IL-10 and TGF β .²⁸

IL-35 may be an additional therapeutic strategy for psoriasis. Zhang et al. demonstrated that IL-35 reduced the quantity of macrophages and revealed a prolonged period of therapeutic efficacy.³¹

4.4. IL-35 in psychiatric and neurological conditions

Rose et al. demonstrated significantly decreased plasma IL-35 levels in children with autism spectrum disorders compared to typically developing children. It was also associated with worse behaviors (similarly to the decreased levels of TGF β and IL-10).³²

The pathogenesis of relapsing-remitting multiple sclerosis may be associated with IL-35. Badihan et al. showed the decreased serum concentration of IL-35 in those patients compared to healthy controls.³³

Prior to the treatment the plasma levels of IL-35 in patients with multiple sclerosis had been higher. Subsequently, they significantly decreased after treatment.³⁴

In patients suffering from acute motor axonal neuropathy, serum IL-35 concentration was decreased and negatively correlated with the outcomes, which may be related to the anti-inflammatory role of IL-35 in those patients.³⁵

Decreased serum levels of IL-35 in patients with the active stage of Behcet disease compared to inactive Behcet patients and healthy controls might be a sign of the flexibility of T_{reg} lymphocytes depending on the stage of the disease.³⁶

4.5. IL-35 and infections

IL-35 suppresses the differentiation of Th1 and Th17 lymphocytes and may be related to the chronicity of tuberculosis. IL-35 positive cells were identified in the pleural tissue of those patients. Furthermore, IL-35 level was higher in tuberculous pleural effusion.³⁷

Shen et al. demonstrated an improved resistance to infection with *Salmonella enterica* serovar Typhimurium in mice in which no expression of IL-35 was observed in B cells compared to control mice.³⁸

Chronic hepatitis B virus infection was associated with the suppression of virus replication which activated a reduction in the responsiveness of T_{reg} secreting IL-17 under IL-35 stimulation. It may constitute the evidence of the immunosuppressive activity of IL-35 in this disease.³⁹

5. CONCLUSIONS

IL-35 is an important cytokine in the inflammatory process, especially linked to the regulation of immune responses, neutralizing Th1, Th2, and Th17 expansion.^{8,38}

The pathogenesis of autoimmune diseases, including psoriasis, is complex, and further research should illustrate

its immunosuppressive properties and therapeutic advantages, especially in humans.¹

The clarification of doubts concerning the receptors and signaling pathways of IL-35 will allow the use of IL-35 as an innovative biomarker in the prognosis and treatment of various diseases.⁴

Conflict of interest

None declared.

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None declared.

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