REVIEW ARTICLE

Role of Interleukin-37 in Inflammatory and Autoimmune Diseases

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ABSTRACT

Interleukin-1 family 7 (IL-1F7) is a novel member of IL-1F cytokines. IL-1F7 is more commonly known as IL-37. IL-37 can join the α-subunit of the IL-18 receptor, or IL-18 binding protein (IL-18BP), and binding of these proteins can enhance the IL-18 suppression. IL-37 also translocates to the cell nucleus and affects gene transcription. IL-37 inhibits the phosphorylation of p38 mitogen-activated protein kinases. Almost all reports showed that IL-37 has remarkable anti-inflammatory activity. IL-37 plays an important role in a variety of inflammatory and autoimmune diseases. Recently, studies demonstrated that the expression of IL-37 is abnormal in many diseases such as inflammatory bowel diseases, inflammatory respiratory diseases, atherosclerosis, hepatitis, obesity, contact hypersensitivity, Graves' disease, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, multiple sclerosis, psoriasis, and Behcet's disease. Here, we will review the biological characteristics of IL-37 and its key roles in various inflammatory and autoimmune diseases.

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Keywords: Anti-Inflammatory, Autoimmune Diseases, Interleukin-37, Inflammation-Related Diseases

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INTRODUCTION

The interleukin-1 family (IL-1F) is comprised of eleven members that have similar secondary structures and cell surface receptors. The classical IL-1F members, IL-1α, IL-1β, and IL-18 have been studied extensively. IL-1F7 was discovered by computational cloning and originally identified through *in silico* research in 2000 (1). It has since been assigned the name IL-37. Recent reports have found that IL-37 has a pivotal role in many diseases (2). Here, we summarize the biological activity of IL-37 and the potential role of IL-37 in a variety of inflammation-related and autoimmune diseases.

1. Biological Characteristics of IL-37.

1.1 IL-37 Expression.

IL-37 is expressed in many normal tissues and tumors, such as colon tumors, thymus, lymph node, bone marrow, lung, placenta, testis, and uterus (3). Further discovered in many human cell lines, are transcripts of IL-37 (4). Rudloff *et al.*(5) reported that IL-37 was mainly produced by human monocytes and dendritic cells. Tonsil plasma cells and breast carcinoma cells can also secrete IL-37 protein (6).

1.2 IL-37 Structure.

Located on chromosome 2, human IL-37 gene undergoes alternative splicing, and there exist five splice variants from IL-37a to IL-37e. IL-37a uses an initiation codonin the third exon, which is spliced in exons 4 to 6. IL-37b encodes the longest transcriptional variant, consisting of exons 1, 2, 4, and 6. IL-37c is a transcriptional variant containing exons 1 and 2, followed by exons 5 and 6. IL-37d has a prodomain limited to exon 1followed by exons 4 to 6. IL-37e is only comprised of exons1, 5, and 6 (3).Containing 218 amino acids, IL-37b is the longest sequence in the five isoforms of IL-37. The N-terminal of IL-37b represents the prodomain, which is cleaved off upon cytokine maturation and has a caspase-1 cleavage site (3).

1.3 IL-37 Receptor and Signaling Pathway.

Although IL-37 is able to bind to the IL-18 receptor α subunit (IL-18Rα), it has low affinity, which is not competitive for IL-18. Accordingly, IL-37 has no significant effect on the physiological function of IL-18. IL-37 is also able to bind to the IL-18 binding protein (IL-18BP) and form a complex. The binding of IL-37 and IL-18BP can enhance the IL-18 suppression by IL-18BP. IL-37 is further translocated to the cell nucleus, influencing gene transcription. Against decapentaplegic homolog 3 (Smad3), IL-37 and mothers form a functional complex that affects gene transcription, preventing Toll-like receptor (TLR) from inducing inflammatory cytokine expression and dendritic cell (DC) activation. The signal transducers and activators of transcription1–4 phosphorylation are associated with multiple pro-inflammatory cytokine signaling. The p38 mitogen-activated protein kinases (MAPK) phosphorylation plays a key role, particularly in inflammatory signaling cascades. IL-37 inhibits the phosphorylation of the kinase, and promotes the phosphorylation of glycogen synthase kinase (GSK)-3α/β, thereby inactivating the kinases, which indicates the direct anti-inflammatory mechanism of IL-37 (7). A study on the stable transfection of murine RAW264.7 macrophages reported that these cells lacked IL-37 protein expression. Moreover, IL-37 mRNA rapidly degraded through a 3′-UTR of IL-37 transcript stabilityin transfected cells. Following lipopolysaccharide (LPS) stimulation, both IL-37 mRNA and protein levels are increased in human monocytes, suggesting that LPS can stabilize IL-37 mRNA. Deletion of downstream exon 5 from the full-length IL-37 cDNA can significantly

augment the IL-37 mRNA expression, indicating that the IL-37 mRNA coding region contains functional instability determinants (8).

2. IL-37 Function.

A variety of TLR ligands, transforming growth factor-β (TGF-β), and interferon-γ (IFN-γ) can induce IL-37 expression in peripheral blood mononuclear cells (PBMCs). Inhibition of IL-37 expression in PBMCs significantly increased the production of IL-1β, IL-6, tumor necrosis factor-α (TNF-α), and other inflammatory cytokines after small interfering RNA (siRNA) against IL-37 interference (9). Unlike T cells, both monocytes and mDC secrete IL-37 under LPS stimulation, with the latter able to release IL-37 even at a steady state (5). Nold *et al.* (7) found that IL-37b expression through immunohistochemical staining was high in the synovial lining tissue of Rheumatoid Arthritis (RA) patients. The same study was able to stably express human IL-37 intransfected RAW cells. IL-37 reduced the expression of TLR-induced IL-1β, TNF-α, and chemokine (C-X-C motif) ligand 2 (CXCL2) in the RAW-IL-37 cells. Similar to IL-6 and IL-1, the expression of certain cytokines in the IL-37 transgenic (IL-37tg) mice was significantly decreased, *in vivo*. Moreover, the reduction of IL-37 protein in RAW cells via a specific antibody increased the production of TNF-α, IL-1, and macrophage inflammatory protein (MIP)-2. Similarly, IL-37 was also able to inhibit the production of these pro-inflammatory cytokines in monocyte and epithelial cells. These results indicate that IL-37 is a negative feedback inhibitor of inflammatory responses (7). Intravenous LPS can induce high inflammatory cytokine expressions in mice, which entailed inflammatory shock. However, compared with wild-type mice, IL-37tg mice had lower levels of LPS-induced inflammation , and IL-37tg mice correspondingly had lower plasma IL-1β, IL-17, IL-6, and IFN-γ levels, hence the fact that IL-37 was capable of inhibiting inflammatory shock (3). Additionally, IL-37 inhibited LPS-induced inflammation both *in vivo* and *in vitro* through directly inhibiting the expression of pro-inflammatory cytokines (2). Furthermore, IL-37b-Smad3 complex formation has been demonstrated by immunofluorescence, and Smad3 may be involved in the signal transduction of IL-37b. Using specific inhibitor SIS3 to block Smad3 activation, IL-37 inhibited the expression of pro-inflammatory cytokines in the RAW cells (7). IL-37 and IL-1R8 (SIGIRR or TIR8) belong to the IL-1 ligand family and IL-1 receptor family, respectively. IL-37 activated multifaceted intracellular anti-inflammatory procedures through binding to IL-18Rα and utilizing IL-1R8. IL-37tg mice with intact IL-1R8 were protected from endotoxemia (10). It was shown that the up-regulation of IL-37 expression was most likely by activating ERK1/2 and p38 MAPK pathways (11). Regulatory T cells (Tregs) suppress autoimmunity and can prevent the immune-mediated pathology in the early phase of sepsis. Wang *et al.*(12) revealed that IL-37 silence in human Tregs observably lowered the suppressive activity of Tregs; moreover, recombinant IL-37 treatment obviously increased the suppressive activity of Tregs isolated from naive mice.

3. IL-37 and Inflammatory Diseases.

3.1 IL-37 and Inflammatory Bowel Disease.

The role of IL-37 in digestive system is well characterized. Günaltay *et al.*(13) showed that the reduction of IL-37 promoted the expression of chemokine ligand 3 (CCL3), CXCL8, CXCL10, and CXCL11 mRNA and protein, in a colon epithelial cell line T84. Following the stimulation of T84 with TLR5, the CCL2 mRNA, CCL3, CCL20, and chemokine (C-X-X-X-C motif) ligand 1 (CX3CL1) mRNA expression and protein expression were elevated, while the CCL44 and CCL22 mRNA expression was

significantly decreased. McNamee *et al.* (14) found that IL-37 plays a crucial role in intestinal inflammation. The clinical and histological scores of IL-37tg mice were significantly reduced during the development of colitis. Furthermore, Li *et al.* (15) verified that inflammatory bowel disease (IBD) patients had significantly higher IL-37b gene expressions than healthy controls. In one study, IL-37 was significantly synthesized in intestinal circulating B cells, active NK cells and monocytes, indicating that the reduction of inflammation in active IBD patients might be associated with the up-regulation of IL-37(16). IL-37 levels, which were higher in patients with Crohn's disease (CD) and ulcerative colitis (UC), were correlated with the histological severity of inflammation (17). These studies show that IL-37 might be a potentially novel biomarker for IBD. In yet another report, IL-37 was involved in the pathophysiology of UC, and the therapeutic effect of mesenchumal stromal cells (MSC) was enhanced by IL-37b gene transfer in dextran sulfate sodium (DSS)-induced colitis mice through inducing Tregs and myeloid-derived suppressor cells (MDSCs) and regulating cytokine production (18). The expression of IL-37 was reduced in both collagenous colitis (CC) and lymphocytic colitis (LC) patients with a trend similar to that observed in UC patients; on the contrary, IL-37 was increased in UC remission patients compared with controls and active UC patients (19).

3.2 IL-37 and Inflammatory Respiratory Diseases.

IL-37 has been identified as an anti-inflammatory cytokine and is able to suppress allergic asthma inflammation by reducing the production of inflammatory cytokines. Charrad *et al.*(20) showed that IL-37 levels, correlated with disease severity, were decreased in induced sputum. Moreover, recombinant IL-37 prevented the increase in inflammatory cytokines in induced sputum cells of asthmatic patients. Lunding *et al.* (21,22) demonstrated that IL-37 inhibited allergic airway inflammation and hyperresponsiveness in asthmatic mice, suggesting that IL-37 may be involved in the pathogenesis of asthma. However, the anti-inflammatory roles of IL-37 were completely suspended in mice deficient for IL-18Rα or SIGIRR/IL-1R8.Therefore, IL-37 or its receptors could be potential targets for asthma therapy. Additionally, Di *et al.*(23) showed that the expression of IL-37in the bronchial mucosa may be involved in the progression of stable chronic obstructive pulmonary disease (COPD).

3.3 IL-37 and Atherosclerosis.

The development of atherosclerosis is related to monocyte infiltration and inflammation. McCurdy *et al.* (24) showed that macrophage-expressed IL-37 reduced the production and effects of pro-inflammatory cytokines, prevented foam cell formation, and decreased the development of atherosclerosis. Ji *et al.*(25) found IL-37 to be involved in the formation of atherosclerosis. Furthermore, a histopathological detection indicated that IL-37 was highly expressed in human atherosclerotic plaques. Exogenous IL-37 mitigates atherosclerosis by inducing Treg cell response. These results indicate that IL-37 may be a novel therapeutic approach to prevent and treat atherosclerotic diseases.

3.4 IL-37 and Other Inflammation-Related Diseases.

In vivo, the inflammation in LPS challenge and concanavalin A (ConA)-induced hepatitis were reduced when human IL-37 was expressed in mice (26). IL-37 can inhibit the expression of pro-inflammatory cytokines in LPS-stimulated mice, and decrease the serum levels of IL-1α, IL-5, IL-6, and IL-9 in ConA-induced mice.

Moschen *et al.* (27) found that the expression of IL-37 was significantly higher in subcutaneous/visceral adipose tissue compared with the liver in obese mice. Following high fat diet (HFD), IL-37tg mice exhibit decreased the number of adipose tissue

macrophages, enhanced adiponectin circulating levels, and increased insulin sensitivity and glucose tolerance. *In vitro* recombinant IL-37 inhibits the adipogenesis of adipocytes and activates AMP-activated protein kinase signaling. There was a positive correlation in humans between elevated steady state mRNA levels of IL-37 in adipose tissue and insulin sensitivity and lower inflammatory states of adipose tissue. These results indicate that IL-37 is a key anti-inflammatory cytokine in mice and human obesity-induced inflammation and insulin resistance (28). Luo *et al.*(29) proved that DCs expressing IL-37 were tolerogenic, impairing the activation of effector T-cell responses and inducing Treg cells. Contact hypersensitivity challenge to dinitrofluorobenzene was significantly decreased in IL-37tg mice compared with wild-type mice.

4. IL-37 and Autoimmune Diseases.

4.1 IL-37 and Graves' Disease.

Graves' disease (GD) is an autoimmune disease characterized by the production of autoantibodies against the thyroid-stimulating hormone receptor, which mimics the stimulatory effects of thyroid stimulating hormone (TSH), resulting in hyperthyroidism and diffuse thyroid gland hyperplasia. Although the pathogenesis of the disease is not clear, evidence suggests that the destruction of pro- and anti-inflammatory cytokines balance leads to B cell activation, producing autoimmune antibodies against thyroid antigens. Li *et al.* (30) revealed that IL-37 plays an important role against inflammatory effect in GD by inhibiting the production of pro-inflammatory cytokines. They further found that IL-37 levels were significantly augmented in patients with GD compared with healthy controls. Moreover, IL-37 suppressed the production of IL-6, IL-17, and TNF-α in patients with GD.

4.2 IL-37 and Rheumatic Disease.

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by the infiltration of activated immune cells and the production of inflammatory cytokines, eventuating in the formation of synovial hyperplasia and pannus, and the destruction of cartilage and joints. Although the etiology and pathogenesis of RA are yet to be fully known, it has been shown that IL-37 has anti-arthritic effects in RA patients and in collagen-induced arthritis (CIA) mice (31). IL-37 levels were higher in active RA patients compared with those in inactive RA and healthy controls. Cavalli *et al.* (32) demonstrated that low doses of IL-37 inhibited joint inflammation and significantly decreased synovial IL-1β, TNF-α, IL-6, CCL3, CXCL1 or MIP-1α in mice. These reductions were associated with the recruitment of fewer neutrophils into the joint. These studies demonstrate that IL-37 is a crucial anti-inflammatory cytokine as regards controlling RA pathogenesis. In addition, Zeng *et al.* (33) indicated that IL-37 is an important anti-inflammatory cytokine in acute gouty arthritis. IL-37 was able to partly limit the monosodium urate crystal-induced inflammation in a Mer receptor tyrosine kinase (Mertk)-dependent fashion (34).

4.3 IL-37 and Ankylosing Spondylitis.

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by chronic inflammation in the shaft and peripheral joints and bone erosion. One study showed that IL-37 plays a key role in the pathogenesis of AS. The serum IL-37 level in AS patients is upregulated, and is closely related to AS disease activity and associated proinflammatory cytokines secretion.IL-37 reduced the expression of pro-inflammatory cytokines in AS patients, suggesting that IL-37 has potential anti-inflammatory effects on AS patients (35).

Table 1. Roles of IL-37 in inflammation and autoimmune diseases.

Disease	Role of IL-37	Ref.
Colitis	Leukocyte recruitment ↓ IL-1β, TNF-α ↓ IL-10 ↑	(14)
Allergic asthma	Eosinophils in BAL, airway inflammation ↓ Number of mucus producing goblet cells ↓ Level of inflammatory cytokines in BAL ↓ AHR ↓	(21)
Atherosclerosis	Pro-inflammatory cytokines ↓ foam cell formation ↓ Development of atherosclerosis ↓ Treg cells ↑	(24, 25)
Hepatitis	IL-1α, IL-6, IL-5, IL-9 ↓	(26)
Obesity-induced inflammation and insulin resistance	Number of adipose tissue macrophages ↓ Adiponectin circulating levels ↑ Insulin sensitivity, glucose tolerance ↑ Adipogenesis of adipocytes ↓	(28)
Contact hypersensitivity	Effector T-cell responses ↓ Treg cells ↑ Antigen challenge ↓	(29)
Graves' disease	IL-1β, IL-6, IL-12 ↓ IL-10 ↑ Pro-inflammatory cytokines IL-6, IL-17, TNF-α ↓ IL-17, IL-17-triggering cytokine ↓	(30)
Arthritis	TNF-α, IL-17, IL-6 in RA patient PBMCs ↓ Synovial IL-1β, TNF-α, IL-6, CCL3, CXCL1, MIP-1α in mice ↓ Joint inflammation ↓ Neutrophils recruitment ↓	(31, 32,33)
Ankylosing spondylitis	Pro-inflammatory cytokines from PBMCs ↓	(35)
Systemic lupus erythematosus	Inflammatory cytokines ↓	(39)
Psoriasis	Pro-inflammatory cytokines ↓	(41)
Behcet's disease	IL-6, IL-1β, TNF-α, ROS ↓ IL-27 ↑ Th17, Th1 cell responses ↓	(44)

AHR: airway hyperresponsiveness; BAL: broncho-alveolar lavage; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; MIP-1α: macrophage inflammatory protein-1α; PBMCs: peripheral blood mononuclear cells; RA: rheumatoid arthritis; ROS: reactive oxygen species; Treg: regulatory T cells.

4.4 IL-37 and Systemic Lupus Erythematosus.

The plasma IL-37 levels in systemic lupus erythematosus (SLE) patients were significantly higher than those in the control group (36). Wu *et al.* (37) demonstrated that IL-37 might be implicated in SLE; they also found that plasma IL-37 level was up-regulated and associated with anti-Sm, anti-RNP and C3 in SLE patients. Tawfik *et al.*(38) showed that the increase in IL-37 levels in SLE patients was correlated with high disease activity, and mucocutaneous and renal involvement. Song *et al.*(36) showed that the increase in IL-37 in active SLE patients was related to inflammatory cytokines and systemic lupus erythematosus disease activity index (SLEDAI). Another finding indicated that IL-37 has an important part in controlling the pathogenesis of SLE by inhibiting the production of inflammatory cytokines (39). Thus, IL-37 may provide a new target for studying the pathogenesis and treatment of SLE.

4.5 IL-37 and Multiple Sclerosis.

Multiple sclerosis (MS) is a common autoimmune disease in the central nervous system in which neurodegenerative and inflammatory mechanisms lead to neurological damages. Farrokhi *et al.* (40) showed that IL-37 may be a part of the feedback loop to control inflammation in MS pathogenesis. In their study, the serum IL-37 level was markedly increased in MS patients compared with the healthy controls and correlated with the disease severity.

4.6 IL-37 and Psoriasis.

Psoriasis is a chronic inflammatory skin disorder associated with the metabolic syndrome and its components. IL-37 played an effective immunosuppressive role in experimental psoriasis by down-regulating pro-inflammatory cytokines (41). In mouse model, the level of systemic IL-10 was reduced, local IFN-γ gene was transcribed, and there was a mild mast cell infiltration into the psoriatic lesions of the mice. Moreover, based on immunohistochemical analysis, IL-37 was expressed by effector memory T cells and macrophages in human psoriatic plaques. Several studies have demonstrated that IL-37 is highly expressed in psoriatic skin, and human beta-defensin-3 increases the expression of IL-37 through CCR6 in human keratinocytes (42,43).

4.7 IL-37 and Behcet's Disease.

Behcet's disease (BD) is a chronic systemic inflammatory disease. Bouali *et al.*(44) showed that the expression of IL-37 was decreased in BD and the low IL-37 expression in BD patients was associated with a high inflammatory response. Moreover, the treatment of active BD patients with corticosteroids augmented the level of IL-37 mRNA expression, suggesting that the treatment can be partly mediated by the regulation of IL-37 production and reduction of inflammatory cytokines. Moreover, the lower IL-37 expression in patients with active BD induced the production of pro-inflammatory cytokines and reactive oxygen species in correlation with activation of Th1 and Th17 cells via DCs (45).

DISCUSSION

Although the role of IL-37 remains to be explored in many diseases, the accumulated evidence now corroborates the remarkable performance of IL-37 in various inflammation and autoimmune diseases (roles summarized in Table 1). It is to be noted that the change in IL-37 expression is different in patients. On the other hand, IL-37tg mice are immune to disease progression; however, the expression of IL-37 in such diseases is significantly increased, which is positively correlated with the disease activity. Accordingly, the mechanisms of IL-37 in different diseases needs to be further studied, and understanding the function and regulation of IL-37 is certainly beneficial to the treatment of diseases (46).

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