Interleukin-37: A crucial cytokine with multiple roles in disease and potentially clinical therapy (Review)

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Abstract. Interleukin (IL)-37, a new IL-1 family member, has received increasing attention in recent years. In the past decade, it has been determined that IL-37 is expressed in various normal cells and tissues and is regulated by inflammatory stimuli and pro-cytokines via different signal transduction pathways. Recently, it has been found that IL-37 is expressed in a variety of cancers, chronic inflammatory and autoimmune disorders, and exerts anti-inflammatory effects. Moreover, a growing body of literature demonstrates that IL-37 plays a vital role in inhibiting both innate and adaptive immune responses as well as inflammatory reactions. In addition, IL-37 may prove to be a new and potentially useful target for effective cytokine therapy. Further evidence is needed to clarify in more detail the effects of IL-37 in experimental and clinical studies. Based on an extensive summary of published data, the aim of this review is to outline the current knowledge of IL-37, including the location, structure, expression, regulation and function, as well as the potential clinical applications of this cytokine.

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Abbreviations: IL-1, interleukin-1; IL-37, interleukin-37; IL-1F7, IL-1 family member 7; IL-18R, IL-18 receptor; NK, natural killer; TLR, toll-like receptor; IFN, interferon; TGF-β1, transforming growth factor β1; TNF, tumor necrosis factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; YFP, yellow fluorescence protein; CFP, cyan fluorescence protein; MAPK, mitogen activated protein kinases; JNK, the Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; PI3Ks, Phosphatidylinositol 3-kinases; TwHF, *Tripterygium wilfordii* Hook F; hBD-3, human β-defensin-3; DCs, dendritic cells; HCAECs, human coronary artery endothelial cells; MHC, major histocompatibility complex; Tregs, regulatory T cells; DSS, dextransulfate sodium; UC, ulcerative colitis; CD, Crohn's disease; MC, microscopic colitis; AS, Ankylosing spondylitis; GD, Graves' disease; FT3, free triiodothyronine; FT4, FT4, freethyroxine; TSH, thyrotropin; TRAB, thyrotropin receptor antibody; Lm, *Liseria monocytogenes*; SLE, systemic lupuserythematosus; IBD, inflammatory bowel disease; AR, allergic rhinitis; AMI, acute myocardial infarction; ASTEMI, acute ST-segment elevation myocardial infarction; HCC, hepatocellular carcinoma; DFS, disease-free survival; OS, overall survival; CC, cervical cancer; STAT3, signal transducer and activator of transcription 3; NSCLC, non-small cell lung cancer; CAD, coronary artery disease

Key words: IL-37, inflammation, expression, regulation, function, clinical application

Contents

1. Introduction

The immune system is a complex, balanced and organic entity. Under normal conditions, cells of the immune system recognize foreign antigens and destroy them, while playing a continuous role in immune regulation, it is vital to maintain a balanced immune response. Cytokines are small secreted proteins which function as the mediators of cell differentiation, specificity, inflammation, immunopathology and immune responses (1-3). The interleukin-1 (IL-1) family cytokines play a central role in mediating the activation of innate and adaptive immune responses (4). So far, eleven IL-1 family members have been identified, including seven receptor agonists (IL-1α,

IL-1β, IL-18, IL-33, IL-36α, IL-36β and IL-36γ), three ligands with antagonist activity (IL-1Ra, IL-36Ra and IL-38) and a newly renamed anti-inflammatory cytokine, IL-37 (4-6). IL-37, originally known as IL-1 family member 7 (IL-1F7), is the seventh member of the IL-1 family discovered by computational cloning in 2000 and was renamed in 2010 (7-9). IL-37 has been investigated as a natural inhibitor of immune responses in chronic inflammatory and autoimmune disorders and cancer. In this review, we will summarize the current knowledge of the location, structure, expression and regulation of IL-37. Furthermore, we will discuss the function and potential clinical application of IL-37 for identifying novel therapeutic targets and developing new IL-37-based therapies for the treatment of human diseases.

2. Location and structure of IL-37

The human IL-37 gene cluster is located on chromosome 2 (9,10). The IL-37 gene seems to be absent in mice as no cDNA or genomic sequence related to human IL-37 has been reported (9,11). The IL-37 gene size is 3.617 kb and includes six exons which encode a 17-26 KDa protein (9,12). The IL-37 gene undergoes alternative splicing; five different splice variants of IL-37 have been identified and termed IL-37a-e, of which IL-37b is the largest (218 amino acids) and best characterized isoform (Fig. 1) (8,9,13,14). The transcript variant encoded by IL-37b contains exons 1 and 2 and has an N-terminal prodomain, which includes a potential caspase-1 cleavage site, leading to the IL-37b precursor being spliced into mature IL-37b (9,11). In addition, IL-37b also encodes exons 4-6 which contain the 12 putative β-strands necessary for forming the IL-1-like β-trefoil secondary structure (9,15). IL-37b shares a β-barrel structure which is commonly present in other members of the IL-1 family, and binds to the IL-18 receptor (IL-18R) α chain (16,17). IL-37a has a distinctive start codon in exon 3 which encodes a unique N-terminus and is absent in IL-37c, IL-37d and IL-37e, which is then spliced in exons 4 to 6 (9,16). The sequence encoded by exon 3 results in a prodomain which is processed into the mature form of IL-37a protein (10). IL-37c, first reported by Busfield *et al*, is similar to IL-37b (18). The IL-37c transcript variant comprises exons 1 and 2 followed by exons 5 and 6 (9). It seems that IL-37c could not represent a functional form a cytokine (9). Exon 2 of IL-37d is missing, instead it contains only exon 1 followed by exons 4-6 and may function as a cytokine (9). IL-37e comprises only exons 1, 5 and 6 and can not bind to IL-18R as a result of lacking exon 4 (9). Interestingly, a chimeric transcript including exons 1, 4 and 5 of IL-37 has been found to be cleaved into the 5'UTR of the full length IL-36γ message (9,10).

3. Expression and regulation of IL-37

Expression. IL-37a, IL-37b, and IL-37c are found to be expressed in a variety of normal cells and tissues including natural killer (NK) cells, stimulated B cells, monocytes, skin keratinocytes, epithelial cells, lymphnode, thymus, lung, colon, uterus and bone marrow (9,18-25). However, some IL-37 isoforms are expressed in a tissue specific manner. Brain only expresses IL-37a, kidney only IL-37b, heart only IL-37c, and bone marrow and testis only IL-37d (9,10,26,27). IL-37b was first discovered in bone marrow, and was synthesized by neutrophils (28). Following this, IL-37b has been found mainly in blood cells, skin keratinocytes, and the respiratory and gastrointestinal tracts (28). The chimeric transcript including exons 1, 4 and 5 of IL-37 is also found in testis and placenta, but its function remains unclear (9).

It is estimated that IL-37 protein translocates to the nucleus, redistributes between intracellular and extracellular sites and affects cellular responses, which may explain why the IL-37 level is reduced in serum (28,29). What is noteworthy is that IL-37 expression is seemingly dependent on the inflammatory milieu and inflammatory cells (11). Emerging evidence demonstrates that IL-37 is expressed at low levels in human cells and tissues but upregulated by inflammatory stimuli and pro-cytokines including several toll-like receptor (TLR) agonists, IL-18, interferon (IFN)γ, IL-1b, transforming growth factor β1 and tumor necrosis factor (TNF) (Table I) (17,30,31). Other factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) plus IL-4, suppress IL-37 expression (17). Li *et al* proved that IL-37 is increased after stimulation by TLR agonists in monocytes (28). Interestingly, Nold *et al* clarified that IL-37b protein expression increased dose-dependently after stimulation with LPS in a mouse macrophage RAW cell line that stably expresses human IL-37b (17).

To further investigate the intracellular expression pattern of IL-37b, Sharma *et al* generated fusion proteins of IL-37b, with either yellow fluorescence protein (YFP) at the C terminus (IL-37b-YFP) or cyan fluorescence protein (CFP) at the N terminus (IL-37b-CFP) by using protein fusing techniques (29). They then transfected mouse RAW cells with these two different IL-37b fusion proteins, intracellular expression of which were found to be at low levels. However, after LPS stimulation, only IL-37b-YFP translocated into the nucleus, which suggests that the N terminus of IL-37b is processed before nuclear translocation (29). Therefore, only the post-cleavage mature form of the IL-37b precursor, but not the N terminal fragment, specifically translocates to the nucleus after LPS exposure (29). Thus, after stimulation, IL-37 is processed from pro-protein to its mature form (9).

Regulation. The mitogen activated protein kinases (MAPK) signal pathway is one of the main signaling pathways involved in immune responses, with vital roles in the regulation of cytokine and chemokine responses (32). There are three main components in the MAPK signaling pathway: The Jun N-terminal kinase (JNK 1/2/3), extracellular signal-regulated kinase (ERK1/2, ERK 3/4, ERK5, ERK 7/8,) and p38 MAPKs (p38α/β/γ/δ) (33-36). Once stimulated, the MAPKs, which are expressed in all cell types, are activated and participate in various physiological and biologic processes including inflammation, growth, differentiation, survival and apoptosis of cells (35-37). Phosphatidylinositol 3-kinases (PI3Ks) are a family of lipid kinases that play important roles in intracellular signal transduction and regulation of inflammatory and immune processes (38,39). Based on protein structure and substrate specificity, PI3Ks are classified into three classes, PI3K I-III (39).

Recent studies have identified MAPK and PI3K signaling pathways as mediators of regulating various agents in IL-37 expression. Triptolide and triptonide, two

Table I. Factors and signal pathways involved in IL-37 expression.

Cell type	Triggering factor	Regulation	Signal pathway involved	(Refs.)
Monocytes	TLR agonists	Increased	Unclear	(28)
RAW cell line	LPS	Increased	Unclear	(17)
THP cells	Triptolide, triptonide	Increased	ERK1/2, p38	(30)
Human cells	TNF-a	Increased	MAPK, PI3K, NF-kB, AP-1	(28)
Epithelial cells	Mannose-capped lipoarabinomannan	Increased	ERK1/2, p38	(40)
Keratinocytes	Human β-defensin-3	Increased	CCR6	(43)
Human cells	IL-18, IFN-γ, IL-1b, TGF-β1	Increased	Unclear	(17,30,31)
Human cells	GM-CSF, IL-4	Iecreased	Unclear	(17)
Endothelial cells	ICAM-1, NF-κB	Iecreased	TLR2 activation	(45)
BMDMs	M-CSF, GM-CSF, IL-6	Iecreased	Unclear	(49)
HUVECs	VEGF	Iecreased	Unclear	(75)

BMDM, bone marrow-derived macrophages; HUVECs, human umbilical vein epithelial cells; IL, interleukin; TLR, toll-like receptors; LPS, lipopolysaccharide; TNF-a, tumor necrosis factor α; IFN, interferon; TGF-β1, transforming growth factor β1; GM-CSF, granulocyte macrophage-colony stimulating factor; NF-κB, nuclear factor κB; ICAM-1, intercellular adhesion molecule 1; M-CSF, macrophage colony stimulating factor; VEGF, vascular endothelial growth factor; ERK1/2, extracellular signal-related kinase; MAPK, mitogen activated protein kinase; PI3K, phosphoinositide 3-kinase; AP-1; activator protein 1; p38, tumor protein 38.

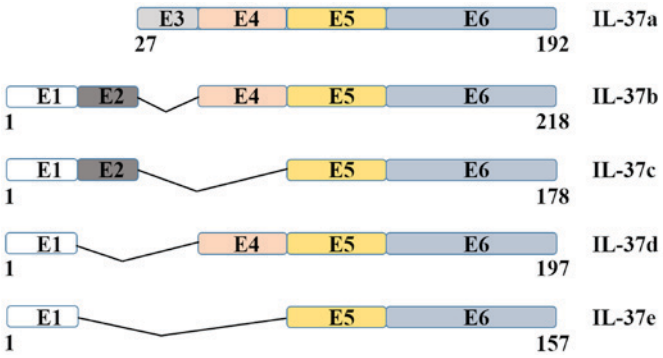

Figure 1. Variants of IL-37. The five splice variants transcripts of the IL-37 gene are shown. Exons 5 and 6 are shared with all five isoforms. Exon 1 is absent in IL-37a only. IL-37c shares with IL-37b exons 1, 2, 5 and 6. IL-37d is similar to IL-37b, sharing exons 1, 4, 5 and 6. E, exon; IL, interleukin.

active components extracted from the herb *Tripterygium wilfordii* Hook F (TwHF), upregulate IL-37 expression and this expression is suppressed by inhibitors of the ERK1/2 and p38 signal pathways in THP cells (30). TNF-α induces IL-37b mRNA expression by activating MAPK and PI3K signaling pathways and the transcription factors NF-κB and AP-1 (28). Mannose-capped lipoarabinomannan purified from *Mycobacterium tuberculosis* induces IL-37 production in a time- and dose-dependent manner via upregulating TLR2 expression and enhancing p38 and ERK1/2 phosphorylation in human type II alveolar epithelial cells (40).

A study in human PBMCs has shown that *IL-1F7* expression is markedly increased by activation of each TLR, except TLR7 and TLR8 (41). Optimization of the TLR5 response causes a significant increase in IL-37 mRNA and protein expression in intestinal epithelial cells (42). In a recent study, it has been demonstrated that human β-defensin-3 (hBD-3) upregulates IL-37 expression via CCR6 in human keratinocytes (43). In addition, hBD-3 also induces the release of IL-37 into the culture supernatants. However, the signaling pathways participating in IL-37 expression remain to be defined, and the mechanisms of IL-37 regulation will continue to attract further attention.

4. The function of IL-37

The biological function of IL-37 is just beginning to be explored (Fig. 2) (26). There is still a long way to go before the specific role of IL-37 is completely elucidated, but so far, the anti-inflammatory effect of IL-37 has been comprehensively reported. As an inhibitor of both innate and adaptive immunity and inflammatory responses, IL-37 plays a pivotal role in the antimicrobial response, including antiviral, antibacterial, neutralization of endotoxins and anti-immune and tumor regulation, mainly by changing the permeability of bacterial cells (28).

IL-37 significantly decreases proinflammatory cytokines secreted by macrophages and dendritic cells (DCs), inhibits their activation and macrophages differentiation (11). SiRNA knockdown of IL-37 in PBMCs and human renal tubular epithelial cells increases the production of IL-6, TNF-α and IL-1β induced by inflammatory stimuli and cytokines (44). In human coronary artery endothelial cells (HCAECs), IL-37 suppresses both NF-κB and ICAM-1 expression upon TLR2 activation (45). Moreover, Li *et al* demonstrated that epithelial cell-derived IL-37 inhibits T cell and DCs activation in the inflammatory mucosa of inflammatory bowel disease (IBD), possibly by reducing CD86 and major histocompatibility complex (MHC) II surface expression in DCs (28). IL-37 induction of tolerogenic DCs may help to induce regulatory T cells (Tregs) (11). Nold *et al* found that IL-37 functions partly via the IL-37-smad3 complex in the nucleus and smad3 knockdown reduces the activity of IL-37 (17). McNamee *et al* proved that transgenic expression of human IL-37 (IL-37tg) remarkably protects against LPS-induced shock in a mouse model (31).

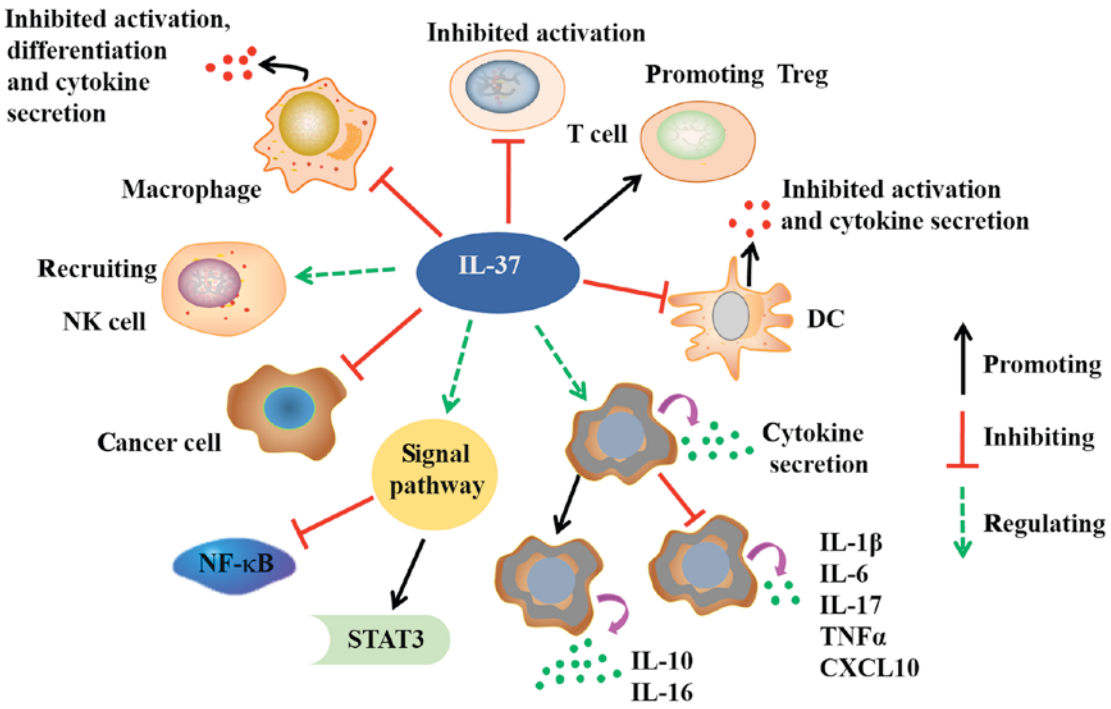

Figure 2. Possible biological functions of IL-37. IL-37 exerts significant anti-inflammatory, anticancer, immune deviatory, immunosuppressive, and metabo-regulatory effects. IL-37 dramatically reduces the cytokines secretion in macrophages and DCs. The activation and differentiation of macrophages, DCs and T cells are also inhibited by IL-37. In addition to healthy tissues, IL-37 is variably expressed in many cancer cells. IL-37 exerts antitumor immune responses through recruiting NK cells into tumors tissues. The binding of IL-37 to its receptor activates STAT-3, and inhibits NF-kB signals. IL, interleukin; STAT-3, signal tranducer and activator of transcription 3; NF-kB, nuclear factor kB; DC, dendritic cell; Treg, T regulatory cell; TNFα, tumor necrosis factor α; CXCL10, C-X-C motif chemokine 10.

In addition, IL-37tg mice subjected to dextransulfate sodium-induced colitis show a lower level of colonic inflammation, decreased IL-1β and TNF-α secretion, but increased IL-10 production (31). Furthermore, IL-10 is not necessary for IL-37 function as an IL-10 receptor blocking antibody has no effect on IL-37-mediated anti-inflammatory effects (31). rIL-37tg mice also exhibit inhibition of cytokine and chemokine (IL-6, IL-1a, IL-13, GM-CSF, etc) expression after spinal cord injury (46). Therefore, IL-37 plays a vital role in modulation of intestinal and spinal cord inflammation. Besides, IL-37 strongly inhibit TNF-α-induced IP-10 expression (47). Except for its anti-inflammatory effects, Zhao *et al* indicated that IL-37 is also a negative regulator of immune responses in *Liseria monocytogenes* (Lm) infection due to reduced production of colony-stimulating factors and increased macrophage apoptosis (48).

Similar to IL-33 and IL-1α, IL-37 also translocates into the nucleus in a caspase-1-dependent manner, decreases cytokine production and affects innate and adaptive immune responses (29,49). Li *et al* reported an extracellular function of the IL-37 precusor, which suppresses LPS-induced IL-6 production in human M1 differentiated macrophages (49). IL-37 acts as an extracellular cytokine by binding to the IL-18 receptor and requires the IL-1 family decoy receptor IL-1R8 for its anti-inflammatory function (49) It has been shown that these pro-inflammatory cytokines (TNF-α, IL-1α, IL-1β, IFN-γ) could play pivotal roles in experimental autoimmune thyroiditis, multiple sclerosis, insulin-dependent diabetes mellitus or experimental autoimmune diabetogenesis, which may indirect suggest the biological and potentially therapeutic relevance of IL-37 to these diseases (50-55). However, it remains unknown whether nuclear translocation of IL-37 is the only mechanism that leads to reduction in cytokine expressions. The specific mechanism of IL-37-mediated suppression of the adaptive immunity also remains unclear. Therefore, further studies on IL-37 function are needed.

5. IL-37 expression in human diseases

A growing body of literature has demonstrated that IL-37 is expressed and exerts anti-inflammatory effects in a variety of diseases including melanoma, rheumatoid arthritis, morbid obesity, contact hypersensitivity, atopic dermatitis, liver inflammatory injury, systemic lupus erythematosus (SLE) and IBD, among others (Table II) (13,14,28,56-65). In addition, as IL-37 has a strong effect on inhibiting inflammatory responses, many studies have focused on proving an association between IL-37 expression levels and the severity of inflammatory and autoimmune disease (66,67).

Chronic inflammatory and autoimmune disorders. In recent years, it has been reported that IL-37 expression is apparently related to IBDs. The IL-37 expression level is significantly upregulated in macrophages of Crohn's disease (CD) lesions and in the skin lesions of psoriasis patients (9). Increased epithelial IL-37b protein expression has also been identified in the inflamed mucosa of IBD patients (22). Serum IL-37 levels are significantly reduced in ulcerative colitis (UC) and CD patients compared with healthy subjects (28). IL-37 is expressed in intestinal epithelial and inflammatory

Table II. Expression and clinical significance of IL-37 in human disorders.

Author	Year	Disease	No. of samples	Methods	Expression level	Association	(Refs.)
Liu *et al*	2014	Children with allergic rhinitis	40	ELISA	Decreased	The efficacy of intranasal steroid therapy	(14)
Li *et al*	2014	Graves' disease	40	RT-PCR and ELISA	Increased	TNF-a, IL-6, IL-17 and disease activity	(13)
Li *et al*	2014	Inflammatory bowel disease	27	ELISA	Decreased	UC activity	(28)
Højen *et al*	2015	Chronic HIV-1-infected individuals	60	Quantitative RT-PCR	Increased	The size of the total viral HIV-1 reservoir	(56)
Wan *et al*	2014	Intervertebral disc degeneration	14	RT-PCR and western blotting	Decreased	Disease aggravation	(57)
Günaltay *et al*	2014	Microscopic and ulcerative colitis	31	Quantitative RT-PCR	Decreased	Possible UC remission	(58)
Chen *et al*	2015	Ankylosing spondylitis	46	RT-PCR and ELISA	Increased	Disease activity	(59)
Ye *et al*	2014	Systemic lupus erythematosus	66	RT-PCR and ELISA	Increased	Disease activity	(60)
Ji *et al*	2014	Acute coronary syndrome	257	ELISA	Increased	The onset of ACS	(61)
Wang *et al*	2015	Myocardial infarction	56	Immunoblotting	Decreased	Possible leukocytic inflammation	(62)
Yu *et al*	2016	Arterial calcification	125	Immunohistochemistry and ELISA	Increased	The onset of arterial calcification	(63)
Zhao *et al*	2014	Hepatocellular carcinoma	163	Immunohistochemical staining	Decreased	Tumor size, OS, DFS, the density of tumor-infiltrating NK cells	(64)
Ge *et al*	2016	Non-small cell lung cancer	182	Immunohistochemical staining and RT-PCR	Decreased	Tumor angiogenesis	(65)

RT-PCR, reverse transcription polymerase chain reaction; OS, overall survival; DFS, disease-free survival; NK cells, natural killer cells; TNFα, tumor necrosis factor α; IL, interleukin; HIV, human immunodeficiency virus; ACS, acute coronary syndrome; UC, ulcerative colitis.

cells and serum IL-37 levels show an inverse correlation with UC activity (28). Immunohistochemistry and western blot analyses prove that IL-37 protein expression levels are higher in UC and CD patients than in healthy people, and are highest in samples from UC patients compared with that of CD patients (28). Nevertheless, the function of IL-37 is still not completely understood in different inflammatory diseases and the inflammation in microscopic colitis (MC) is more subtle than in UC and CD (58). Günaltay *et al* further found that UC remission patients demonstrated increased expression levels of IL-37 mRNA, suggesting that IL-37 may be involved in inflammation and therefore contributing to UC remission (56). On the contrary, low IL-37 expression may contribute to the chronicity of colonic inflammation in MC and UC patients (56).

IL-37 protein is higher in synovial cells of rheumatoid arthritis patients compared with those of healthy donors (17,28). Luo *et al* proved that IL-37 expression in DCs impairs the activation of effector T-cell responses, induces Tregs and regulates adaptive immunity in contact hypersensitivity (68). Ankylosing spondylitis (AS) is a common chronic, progressive, immune-mediated inflammatory disorder characterized by sacroileitis and axial inflammation (69). Chen *et al* showed that IL-37 secretion and mRNA levels are significantly higher in PBMCs isolated from AS patients compared with healthy controls (59). IL-37 level is also correlated with the activity of AS, particularly with the primary pro-inflammatory cytokines involved in AS (59). Furthermore, human recombinant IL-37 dramatically impairs LPS-stimulated IL-6, IL-17, IL-23 and TNF-α production in PBMCs from AS patients (59).

A recent study showed that over-expressed IL-37 mRNA levels in adipose tissue may lead to better insulin sensitivity and protect against insulin resistance in obesity-related inflammation (70). Additionally, a remarkable positive correlation between IL-37 mRNA level and the size of the HIV-1 reservoir has been elucidated (56). LPS exposure increases IL-37 mRNA expression to higher levels in HIV-1-infected patients compared with non-infected individuals (56). Previously it has been reported that the monocyte inflammatory marker sCD14 is associated with increased mortality in HIV-1 infection, and high levels of sCD163 were observed among HIV-1-infected patients (71,72). However, recently a positive correlation between sCD14 and IL-37 mRNA, rather than sCD163, has been observed in a cross-sectional cohort study, which implies a functional link between IL-37 and monocyte activation (65).

Li *et al* verified that the levels of IL-37 in PBMCs and serum are remarkably increased in patients with Graves' disease (GD) (13). Higher IL-37 mRNA and serum protein levels are positively correlated with the activity of GD (13). Moreover, serum IL-37 is positively associated with free triiodothyronine (FT3) and free thyroxine (FT4) but negatively correlated with thyrotropin (TSH) (13). Serum IL-37 is also significantly associated with TSH receptor antibody (TRAB), IL-6, IL-17 and TNF-α (13). Surprisingly, IL-37 inhibits the production of TNF-α, IL-6 and IL-17 in PBMCs of GD patients during GD pathogenesis (13). Wan *et al* reported that decreased IL-37 expression leads to the increased secretion of pro-inflammatory cytokines including IL-16 and IL-1β in degenerative intervertebraldisc, which suggests a function for IL-37 in delaying the progression of intervertebral disc degeneration (57). It has also been shown that IL-37 expression is significantly higher in the plasma of patients with SLE and that IL-37 suppresses the secretion of pro-inflammatory cytokines in PBMCs of SLE patients (60,73,74). IL-37b expression levels in serum and nasal lavage are significantly increased in children with allergic rhinitis (AR) (14). Furthermore, IL-37b decreased Th2 cytokine secreted by PBMCs via MAPK and PI3K signal pathways (14). Conversely, Imaeda *et al* found that IL-37b suppresses the Th1-chemokine, CXCL10, which implies a possible function of IL-37b in inhibiting Th1 inflammation (22).

In conclusion, these results suggest complicated biological functions of IL-37 in different diseases. IL-37 expression in autoimmune diseases seems to decrease excessive inflammatory immune responses. However, further detailed study remains necessary to explore the specific mechanisms and potential immunosuppressive functions of IL-37 in inflammatory and autoimmune diseases.

Cardiac diseases. IL-37 expression is found to be increased in patients with acute coronary syndrome (61,75,76). Inflammationis an important step and the NF-κB signaling pathway is activated after acute myocardial infarction (AMI). Moreover, inhibition of the NF-κB signaling pathway improves cardiac function after AMI through decreasing the left ventricular shortening fraction (77-79). IL-37 expression level is normally low in PBMCs, being mainly expressed in DCs and monocytes, but rapidly increases in the context of inflammation following AMI (61). Plasma IL-37 expression is decreased in patients with acute ST-segment elevation myocardial infarction (ASTEMI) (62). In patients with arterial calcification, high concentrations of IL-37 have been detected and IL-37 is positively correlated with age, fasting glucose, alkaline phosphatase, IL-6, TNF-α, C-reactive protein and Agatston scores (63).

Excessive myocardial inflammatory responses to endotoxemia frequently leads to cardiac dysfunction. Expression of IL-37 suppresses LPS-induced MCP-1 and ICAM-1 production and NF-κB activation in cardiac microvascular endothelial cells (80). In addition, Xu *et al* found that IL-37 suppresses MPO expression and recombinant IL-37 effectively suppresses activation of the NF-κB signaling pathway, and finally results in an anti-inflammatory effect in AMI mice (77).

Cancer. Transcripts of IL-37 have been detected in human cancers and human cancer cell lines including THP-1, U937 and A431 (30,64). However, the biological role of IL-37 in cancers and the relationship between this cytokine and cancer is largely unknown.

To explore IL-37 expression, Zhao *et al* examined a relatively large series of hepatocellular carcinoma (HCC) clinical specimens by immunohistochemistry (64). IL-37 is decreased in tumor tissues compared with adjacent non-tumor tissues and normal liver samples (64). The expression level of IL-37 is negatively correlated with tumor size and high IL-37 expression is linked to disease-free survival (DFS) and better overall survival (OS) in HCC patients, which suggests that IL-37 may be a potentially valuable prognostic marker for HCC patients (64). Wang *et al* offered evidence that IL-37 inhibits the proliferation and invasion of cervical cancer (CC) cells via the signal transducer and activator of transcription 3 (STAT3) signaling pathway (12). IL-37 upregulated STAT3 expression at the gene and protein levels and reduced STAT3 phosphorylation (12). After transfection with siSTAT3, CC cell proliferation and invasion inhibited by IL-37 was significantly reversed. STAT3 overexpression restored the CC cell growth and invasion, and increased the transcription of TNF-α and IL-1β (12).

IL-37 expression is upregulated in breast carcinoma tissues, which indicates that this cytokine may have a role in tumor progression (9,81). However, IL-37 expression is downregulated in lung cancer tissues and, it suppresses tumorigenesis in non-small cell lung cancer (NSCLC) *in vivo*. IL-37 may thus have an inhibitory function in NSCLC development (65,82). However, the specific mechanism and signaling pathways involved in the IL-37-induced immune responses in cancer remain unclear and need further exploration. Infiltration of NK cells into the tumor area is necessary for the activation of potent antitumor immunity (83). IL-37 expression in HCC is positively linked to the density of CD57-positive NK cells, and consequently IL-37-overexpressing HCC cells significantly inhibit tumor growth and recruit more NK cells into tumor tissues *in vivo* mice experiments (64). Thus, IL-37 may be involved in antitumor immune responses via regulating NK cells in the tumor microenvironment.

6. Potential roles of IL-37 in clinical therapy

A comprehensive knowledge of the function of cytokines in the pathogenesis of human disorders has led to the exploration of new therapies targeted at neutralizing specific cytokines or

inhibiting their signaling pathways (3,84-87). IL-37 plays a vital role in innate and adaptive immunity and may be a useful molecule for effective cytokine therapy.

It has been shown that IL-37 suppresses the innate immunity to infection-mediated inflammation, which may be of therapeutic value in reducing pulmonary damage in bacterial diseases (8). Zhao *et al* and Gao *et al*found that intra-tumoral injection of IL-37 leads to strong inhibition of tumor growth and this effect is dependent on T cells and B cells as it is reversed in IL-12-, IFN-γ- or Fas ligand-deficient mice and in nude and SCID mice (64,88). Yin *et al* showed that a single nucleotide polymorphism in the *IL-37* gene (rs3811047) is significantly associated with coronary artery disease (CAD), which suggests that IL37 represents a new susceptibility gene for CAD (89). However, there have been no clinical trials to date to prove the effect of IL-37 on disease treatment. Therefore, it is of great significance to evaluate whether IL-37 can be implicated in cytokine therapy for curing diseases in the future.

7. Conclusion

In summary, as a new anti-inflammatory inhibitor, IL-37 plays important roles in immune responses, protects from inflammatory and autoimmune diseases, and holds great potential for clinical applications. As such, IL-37 research continues to receive increasing attention. However, several IL-37 mysteries remain unclear, and further detailed study remains necessary to fully determine the possible functions of IL-37. While challenges and opportunities still coexist for IL-37, this cytokine may emerge as a new target for diagnosis and therapy of cancer, inflammatory and autoimmune diseases in the near future.

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