American Journal of BioMedicine
AJBM 2014;2(2): 99–105
Research Article doi: 10.18081/2333-5106/014-01/48-56

IL-37/IL-18Rα complex: receptors, signaling and pathogenesis of diseases

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Abstract

The interleukin 1 (IL-1) family, a subset of cytokines consisting of IL-1a and IL-1b, in addition, seven novel IL-1 family members have been identified based on their sequence homology, three-dimensional protein structure, gene location and receptor binding profile. These proteins are now termed IL-36Ra, IL-36a, IL-36b, IL-36g, IL-37, IL-38 and IL-33 (previously known as IL-1F5, IL-1F6, IL-1F8, IL-1F9, IL-1F7, IL-1F10 and IL-1F11, respectively). Its plays crucial roles in host defense mechanism and in the development of inflammatory diseases. Although IL-17A is the signature cytokine produced by T helper 17 (Th17) cells, IL-17A and other IL-17 family cytokines have multiple sources ranging from immune cells to non-immune cells. The IL-17 family signals via their correspondent receptors and activates downstream pathways that include NFκB, MAPKs and C/EBPs to induce the expression of anti-microbial peptides, cytokines and chemokines. The proximal adaptor Act1 is a common mediator during the signaling of all IL-17 cytokines so far and is thus involved in IL-17 mediated host defense and IL-17-driven autoimmune conditions. This review will give an overview and recent updates on the IL-37/IL-18Rα complex, the activation and regulation of IL-37 signaling as well as diseases associated with this cytokine family.

Key words: IL-37; MAPKs; C/EBPs; IL-17; IL-18Rα

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Received 03 January 2014; accepted 05, April 2014, Published May 30, 2014

Topic Review

The interleukin 1 (IL-1) family, a subset of cytokines consisting of IL-1a and IL-1b, in addition, seven novel IL-1 family members have been identified based on their sequence homology, three-dimensional protein structure, gene location and receptor binding profile. These proteins are now termed IL-36Ra, IL-36a, IL-36b, IL-36g, IL-37, IL-38 and IL-33 (previously known as IL-1F5, IL-1F6, IL-1F8, IL-1F9, IL-1F7, IL-1F10 and IL-1F11, respectively). The interleukin 1 (IL-1) family, a subset of cytokines consisting of IL-1a and IL-1b, in addition, seven novel IL-1 family members have been identified based on their sequence homology, three-dimensional protein structure, gene location and receptor binding profile. These proteins are now termed IL-36Ra, IL-36a, IL-36b, IL-36g, IL-37, IL-38 and IL-33 (previously known as IL-1F5, IL-1F6, IL-1F8, IL-1F9, IL-1F7, IL-1F10 and IL-1F11, respectively). Its plays crucial roles in host defense mechanism and in the development of inflammatory diseases. Although IL-17A is the signature

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In mouse macrophages stably transfected with human IL-37, ~20% of IL-37 translocate to the nucleus (7), which is associated with decreased cytokine production (2, 7). However, in the presence of a caspase-1 inhibitor, there is no translocation to the nucleus and no reduction in LPS-induced cytokines (7). Mutation of aspartic acid at the caspase-1 cleavage position 20 to alanine also results in failure to translocate to the nucleus and loss of the suppression of cytokine production (8). Thus, as with IL-1α and IL-33, IL-37 is the third member of the IL-1 family that translocate to the nucleus and affects cellular responses. Nevertheless, it remains unclear whether the reduction in cytokines in vitro or in vivo is due solely to nuclear translocation of IL-37.

Structure, Types, and Processing of IL-37

Human IL-37 gene is located on chromosome 2 with a length of 3.617 kb [4]. IL-37 has a molecular weight of about 17~25 kDa [8]. The structure of IL-37 is similar to that of IL-1 family (IL-1F) and consists of 12*β* tubular lines. The 6 exons encode five isoforms of IL-37 including IL-37a, IL-37b, IL-37c, IL-37d, and IL-37e [4, 8]. IL-37 molecule is an immature precursor peptide, and each isoform is converted from an inactive precursor peptide state to an active state by the cleavage of caspase-1 during expression, and all subtypes regulate each other to form relatively stable state [4]. It is currently believed that caspase-1 cleavage site is located between amino acid residues D20 and E21 expressed by exon 1 [4, 9, 10].

IL-37b (exons 1, 2, 4, 5, and 6) has an intact exon end with the largest molecular weight and has the most complex biological functions. IL-37b transits from an inactive propeptide to an active mature under the action of caspase-1 [4, 11]. Although IL-37a (exons 3, 4, 5, and 6) does not contain exons 1 and 2, its exon 3 encodes a unique N-terminus, and exons 4, 5, and 6 encode IL-1F homologous structure-*β* clover secondary structure. IL-37d (exons 1, 4, 5, and 6) also encodes the 12*β*-strand-containing protein structure, suggesting that these two subtypes also have biological functions [4, 11]. It has been confirmed that IL-37a has an anti-inflammatory effect similar to IL-37b [12].

IL-37c (exons 1, 2, 5, and 6) and IL-37e (exons 1, 5, and 6) do not encode *β*-clover secondary structure due to lack of exon 4, so they may do not have biological functions [4, 11].

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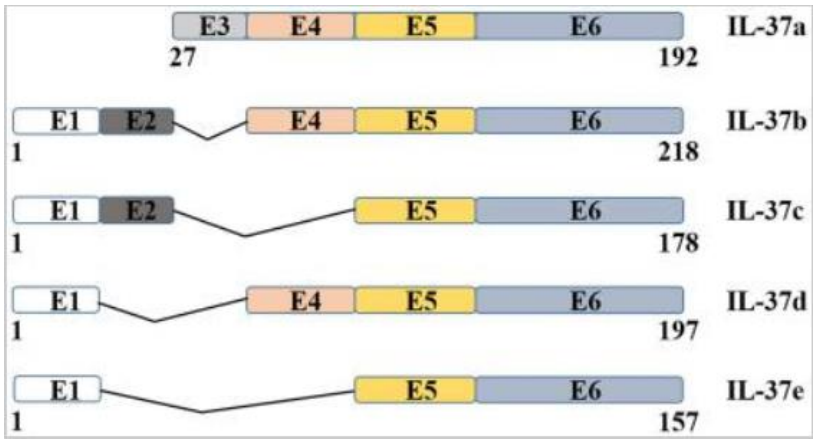

Figure 1.
Variants of IL-37. The five splice variants transcripts of the IL-37 gene are shown. Exons 5 and 6 are shared with all five isoforms. Exon 1 is absent in IL-37a only. IL-37c shares with IL-37b exons 1, 2, 5 and 6. IL-37d is similar to IL-37b, sharing exons 1, 4, 5 and 6. E, exon; IL, interleukin.

IL-37c shares a common N-terminal sequence with IL-37b and IL-37d and competes with IL-37b and IL-37d precursors for the same cleavage enzyme target; whereas IL-37c has no biological function, production of precursor IL-37c is recognized as a mechanism of downregulation of IL-37b and IL-37d [4]. In addition, IL-37e shares the same caspase-1 cleavage site with IL-37b in the region of exon 1, but IL-37e cannot compete with IL-37d due to deletion of exon 2 in the second cleavage site [4]. Therefore, the maturation of IL-37b can be effectively downregulated by IL-37c but only partially downregulated by IL-37e [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)

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(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).

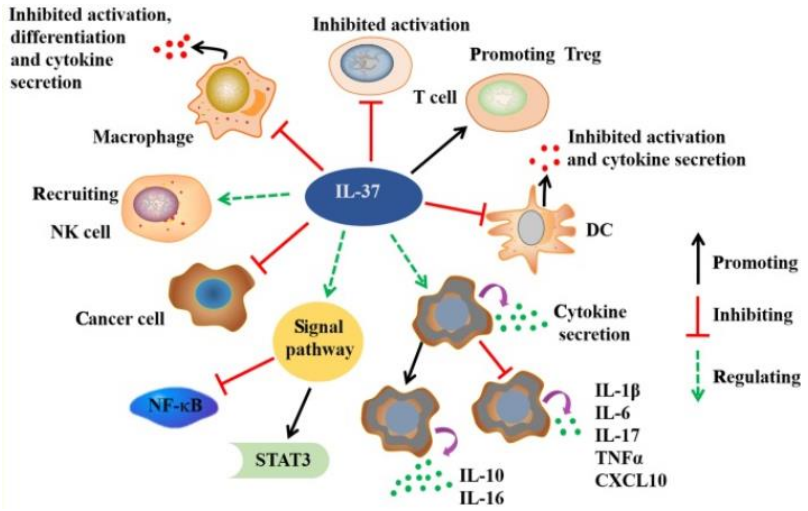

Figure 2.
Possible biological functions of IL-37. IL-37 exerts significant anti-inflammatory, anticancer, immune deviatory, immunosuppressive, and metaboregulatory effects. IL-37 dramatically reduces the cytokines secretion in macrophages and DCs. The activation and differentiation of macrophages, DCs 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.

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.

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Cardiac and cancer diseases

IL-37 expression is found to be increased in patients with acute coronary syndrome (61,75,76). Inflammation is 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). Furthermore, 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.

Competing interests

The authors declare that they have no competing interests.

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American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net