International Journal of Biomedicine 14(2) (2024) 209-216
http://dx.doi.org/10.21103/Article14(2)_RA1

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

Characteristics and Functions of IL-37

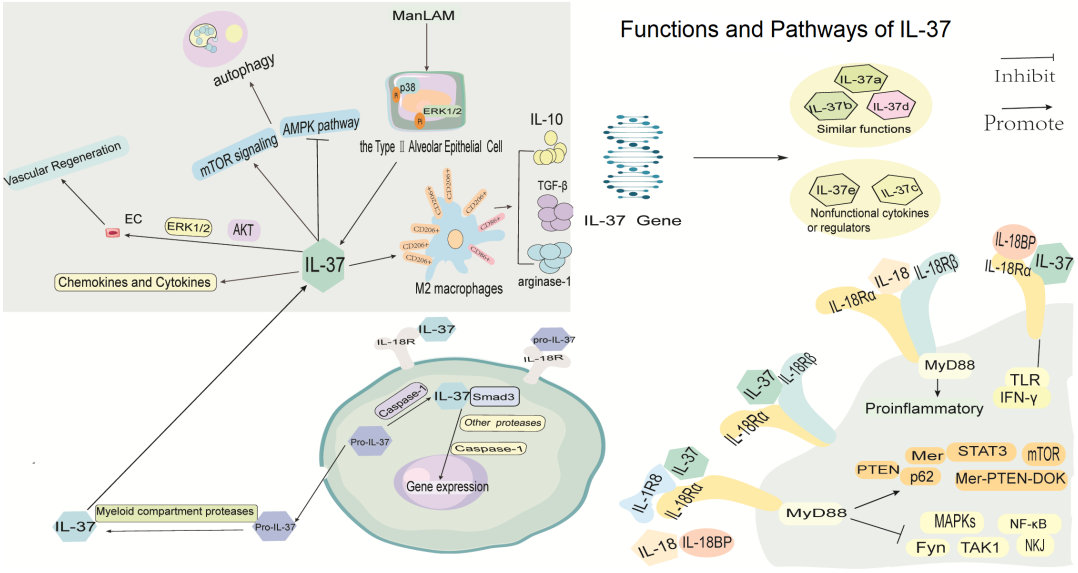
Fang Yang[1,2*], Li Gao[1*], Xinya Wu[1], Xuan Su[1], Weijie Ma[1], Lei Zhong[1], Aihua Liu[1,3**], Fukai Bao[1,3**]

[1]*The Institute for Tropical Medicine, Faculty of Basic Medical Sciences, Kunming Medical University, Kunming 650500, China*
[2]*The First Clinical College, The First Affiliated Hospital, Kunming Medical University, Kunming 650030, China*
[3]*Yunnan Province Key Laboratory of Children's Major Diseases Research, The Affiliated Children Hospital, Kunming Medical University, Kunming 650030, China*

Abstract

Interleukin-37 (IL-37), previously known as IL-1F7, is a member of the IL-1 family of cytokines. There are five basic subtypes of IL-37, including IL-37a, IL-37b, IL-37c, IL-37d, and IL-37e. Like other members of the IL-1 family, IL-37 is initially expressed as an immature precursor protein that needs to be processed enzymatically by caspase-1 to generate the bioactive protein. However, unlike most other members of the IL-1 family, IL-37 induces anti-inflammatory activities in IL-37 receptor-positive target cells. IL-37 functions as an extracellular protein by binding to the IL-18 receptor, IL-18R, and an intracellular protein via its interaction with SMAD family member 3 (SMAD3). This article reviews recent findings regarding the IL-37 protein maturation process and the biological functions mediated by this cytokine.**(International Journal of Biomedicine. 2024;14(2):209-216.)**

Keywords: IL-37 • IL-37 precursor • anti-inflammatory cytokine • IL-18 • Smad3 • IL-1R8 • IL-37 isoforms



Graphical Abstract

For citation: Yang F, Gao L, Wu X, Su X, Ma W, Zhong L, Liu A, Bao F. Characteristics and Functions of IL-37.. International Journal of Biomedicine. 2024;14(2):209-216. doi:10.21103/Article14(2)_RA1

* Fang Yang and Li Gao contributed equally to the review. ** Corresponding authors: Aihua Liu, Fukai Bao.

Abbreviations

AMPK, AMP-activated kinase; **DC**, dendritic cell; **Dok**, downstream of kinase; **ERK1/2**, extracellular signal-regulated kinase 1/2; **IL-18BP**, IL-18 binding protein; **IL-1F**, IL-1 family; **LPS,** lipopolysaccharide; **Mer**, a receptor tyrosine kinase expressed in **m**onocytes, **e**pithelial, and **r**eproductive tissues; **MAPK**, mitogen-activated protein kinase; **NLRP3**, NOD-, LRR-, and pyrin domain-containing protein 3; **NF-κB**, nuclear factor kappa B; **SIGIRR**, single immunoglobulin IL-1-related receptor; **Tregs**, regulatory T cells; **TGF-β**, transforming growth factor-beta; **TLR**, toll-like receptor; **USP**, ubiquitin specific protease; **VEGF**, vascular endothelial growth factor.

Biological Characteristics of IL-37

Interleukin (IL)-37, commonly known as IL-1F7, was discovered in 1999/2000 by searching human-expressed sequence tag databases and sequencing the IL-1 gene cluster located on human chromosome 2.[1-3] IL-37, a member of the IL-1 family, is a potent anti-inflammatory cytokine with immunomodulatory effects.[4]

The *IL-37* gene, located on chromosome band 2q12.2 between the *IL-1β* and *IL-36γ* genes, with a length of 3.617 kb, contains 6 exons.[5] The *IL-37* gene has a molecular weight of about 17~25 kDa.[6] Alternative splicing of *IL-37* pre-mRNA generates five cytokine isoforms, including IL-37a, IL-37b, IL-37c, IL-37d, and IL-37e.[7] Exons 1-3 encode unique N-terminal sequences of IL-37 that possess a caspase-1 cleavage site and can be processed to its mature form.[8,9] The action of IL-37 is mediated by a β-barrel structural unit in its secondary structure.[10] The 12-β-strand-containing proteins may be formed by amino acid sequences encoded by exons 4, 5, and 6.[11-13] The 12-hypothetical β-strand structural units that constitute the β-trefoil secondary structure of IL-37 are responsible for the protein's function. IL-37a (encoded by exons 3–6), IL-37b (encoded by exons 1, 2, 4–6), and IL-37d (encoded by exons 1, 4–6) contain the encoding sequences of 12 β-strands (exons 4–6) and are speculated to be functional cytokines. IL-37c (encoded by exons 1, 2, 5, and 6) and IL-37e (encoded by exons 1, 5, and 6) are predicted to be nonfunctional because of the lack of exon 4 encoding for *β*-trefoil secondary structure.

The expression of IL-37 isoforms is tissue-specific. For example, the brain, kidney, heart, bone marrow, and testis express IL-37a, IL-37b, IL-37c, IL-37d, and IL-37d, respectively.[11]

IL-37b, encoded by five of six IL-37 exons (exons 1, 2, 4–6), is the longest and the best characterized IL-37 isoform, and is known to possess the strongest anti-inflammatory effects.[11,14] IL-37b is detected in lymph nodes, placenta, colon, lung, kidney, testis, thymus, and uterus[15,16] and acts as an anti-inflammatory cytokine. IL-37b inhibits the expression of multiple pro-inflammatory cytokines, such as IL-1α, IL-1β, IL-6, and TNF-α. [6,17-20]

Isoform IL-37a, encoded by exons 3, 4, 5, and 6, does not contain exon 1, but it is the only variant that contains exon 3, which encodes a unique N-terminus.[10,11,21] Some studies indicate that IL-37a is protective against hepatic ischemia–reperfusion injury.[9] However, further investigations are needed to better understand IL-37a functions.

IL-37c and IL-37e probably could not represent a functional form of a cytokine. IL-37e, encoded by exons 1, 5, and 6, cannot bind to IL-18R because it lacks exon 4.[21,22]

IL-37d, encoded by exons 1, 4, 5, and 6, inhibits the activation of TNF-α-induced NF-κB in T cells. It is a positive feedback loop. The downregulation of the NF-κB pathway reduced the production of TNF-α, which lately abolished its stimulation to NF-κB activation.[23] Besides, IL-37d relies on the IL-1R8 receptor-mediated pathway to inhibit NLRP3[9,23] (Figure 1). The mature IL-37d could translocate into the nucleus, interacting with Smad3 and impacting its nuclear translocation to inhibit pro-inflammation, which is similar to IL-37b.[9]

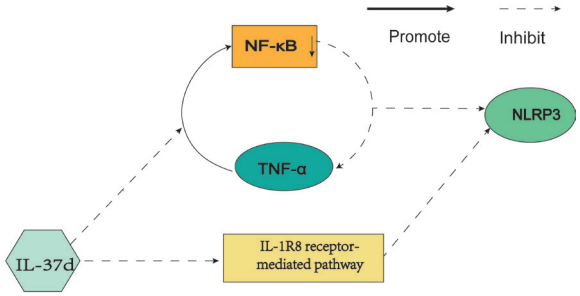


***Fig. 1**. IL-37d pathways for the inhibition of NLRP3 transcription.*

IL-37d inhibits NLRP3 transcription by suppressing the NF-κB signaling pathway. IL-37d inhibits the TNF-α-induced NF-κB activation via a positive feedback loop. The suppression of NF-κB signaling reduces TNF-α levels, thereby inhibiting its stimulation of NF-κB activation.[23] IL-37d inhibits NLRP3 via the IL-1R8 receptor-mediated pathway.[9,23]

Balanced selection keeps several human IL37 gene variations in the human evolution process. There have been 14 IL-37 protein variants found in various human populations. "Var1," "Var2," and "Ref" are three major variants occupying over 97% of those IL-37 protein variants.[24] Var2 induces a stronger, shorter-lived immune response due to preferential proteasome degradation compared to Var1 and Ref.[25]

Biological Activities of IL-37

IL-37 maturation process

Upon interaction with Smad3, IL-37 translocates into the nucleus, resulting in biological activity and the generation of its mature form via caspase-1 activity, although the mechanism requires further investigation.[26] Pan-caspase inhibition does not completely inhibit IL-37 processing, suggesting other proteases may be involved[26] (Figure 2).

The caspase-1 cleavage site maps between amino acid residues D20 and E21 on exon 1.[22,26] IL-37D20A-mutant cells have less mature IL-37 and lower rates of IL-37 nuclear translocation. However, the mutation does not completely inhibit IL-37 processing, indicating that other caspase-1 cleavage sites or other proteases may mediate IL-37 maturation.[27]

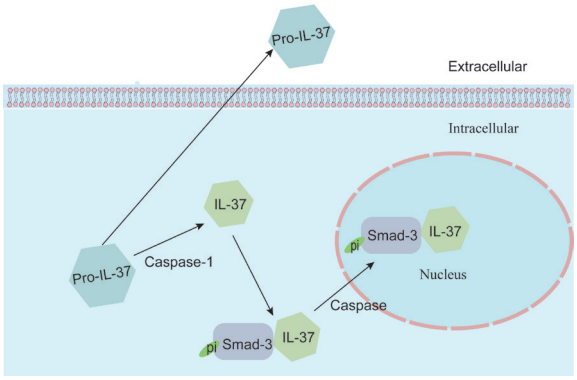


Fig. 2. *The maturation process of IL-37.*

The carboxyl domain of IL-37 binds to Smad3, leading to Smad3 phosphorylation and the translocation of the IL-37/Smad3 complex into the nucleus, where IL-37 matures and exerts biological activity.[1] Caspase-1 is required for this process.[22,27] The intracellular IL-37 precursor exits the cell through loss of membrane integrity or frank cell death.[8]

IL-37 precursor molecules localize in the cytoplasm. Some studies show that human blood monocytes stimulated with LPS and exogenous ATP mostly secrete precursor IL-37.[8] To mature, extracellular precursor IL-37 may need the activity of myeloid compartment proteases.[8] Moreover, the extracellular secretion of the IL-37 precursor does not require caspase-1 activity, and it can be secreted upon loss of membrane integrity or during cell death. However, the mature IL-37 is processed by caspase-1.[8,26] IL-37 is released via the classical ER-Golgi protein secretion pathway in response to LPS stimulation of TLR-4 on human monocytes.[28,29]

Both the IL-37 precursor and its mature form have biological activity, but the mature form binds more stably to receptors.[7,30] The caspase-1 cleavage site located on exon 1 between residues D20 and E21 generates an N terminus exactly nine amino acids upstream from the IL-1 family consensus sequence (A-X-D) to optimal folding of the beta-fold barrel structure for receptor binding of IL-1 family cytokines.[26] For example, IL-37b with the N-terminus at valine 46 is more active than the IL-37b precursor.[31,32]

Spontaneous dimerization and levels of IL-37 in normal serum

IL-37 mRNA has a ten-nucleotide A-rich homology box located at the 3'-end of exon 4 and may cause IL-37 instability.[28] However, IL-37b or IL-37c mutants that lack exon 5 exhibits significantly higher steady-state mRNA levels compared with the slight increase associated with exon 4-lacking IL-37c mutations. Thus, exon 5 may be more critical in limiting IL-37 mRNA stability. Exon instability causes IL-37 instability.[28]

IL-37 acts via a structural shift from dimeric to monomeric form.[33] Studies indicate that the symmetrical head-to-head IL-37b homodimer is created by subunits, including the β3–β4 loops and the β-trefoil sheet (β2-β3-β11).[10] IL-37 dimers can form the mature protein or from the precursor.[27] However, spontaneous IL-37 dimerization may cause a loss of biological function. When IL-37 levels are low, IL-37 dimers can dissociate into monomers. Thus, IL-37 homodimerization may be a mechanism for regulating IL-37 function.[27] Additionally, the function of IL-37 monomers increases with rising IL-37 levels.

The reference range for circulating IL-37 levels in healthy individuals has not been determined.[34] Its serum levels have not been found to vary significantly with gender and age.[35,36] However, the serum levels of IL-37 are higher in systemic lupus erythematosus patients of Asian ancestry when compared with patients of other ethnicities, and IL-37 levels (mean of weighted means) are also higher in the Chinese population than in non-Chinese populations.[36,37]

Functional and Regulatory Pathways of IL-37

IL-37 regulates inflammation by inhibiting IL-18 functions

IL-37 has two conserved amino acid residues (Glu-35 and Lys-124) that are structurally similar to the two conserved residues of IL-18 (Glu-35 and Lys-89),[38,39] indicating that IL-37 and IL-18 may have the same receptors (IL-18BP or IL-18Rα). IL-18 can play the proinflammatory activity by binding the complex IL-18Rα/IL-18Rβ, myeloid differentiation factor 88 (MyD88) combines with the TIR domain of the IL-18R chain to activate the proinflammatory signal.[8,38] The Tightness of binding between IL-37 and IL-18Rα is one-fiftieth as close as that of IL-18 and IL-18Rα.[27] Thus, IL-37 cannot affect IL-18 by combining with IL-18Rα. However, IL-37 can bind to IL-18Rα to form a complex with IL-18BP, a natural antagonist of IL-18. IL-37b can bind to IL-18BP to form a complex with IL-18Rβ, which can reduce the formation of IL-18Rα/β complex and thus inhibit the signal transduction pathway of IL-18.[14]

On the surface of peripheral blood mononuclear cells (PBMCs), the IL-37/IL-18Rα/IL-1R8 complex binds to MyD88 to block inflammation, which triggers multiple switches, including inhibiting the MAPKs, JNK, and NF-κB signaling pathways, activating the Mer-PTEN-DOK pathway and the pseudo-starvation effects of the mTOR pathway, inhibiting TAK1 and Fyn pathways, activating STAT3, Mer, and PTEN, and inducing p62 (dok) expression[8,40] (Figure 3). IL-1R8, also known as TIR8 or SIGIRR, acts as a negative regulator dampening ILR and TLR signaling and as a co-receptor for human IL-37. Inactivated IL-1R8 prevents MyD88 recruitment and then impacts the effect of IL-37, suggesting that IL-1R8 is the key for the IL-18Rα /IL-37 complex to play biological effects.[41] Being an orphan receptor, IL-1R8 also inhibits IL-1 and toll-like receptor (TLR)-dependent inflammation. IL-37 diminishes various inflammatory responses through ligation to its receptor IL-1R8/Sigirr. IL-37 induces Sigirr degradation in the ubiquitin-proteasome system through site-specific ubiquitination, which can be reversed by a deubiquitinase, USP13.[42] IL-37 activates glycogen synthesis kinase 3β (GSK3β), which plays a role in feedback control of IL-1R8/Sigirr abundance.[43] Besides, the activation of GSK3b promotes Sigirr phosphorylation, ubiquitination, internalization, and degradation by disrupting Sigirr association with USP13.[43] Thereby, IL-37 downregulates IL-1R8 expression by disturbing the internation USP13 with IL-1R8 and by promoting IL-1R8 phosphorylation (Figure 4).

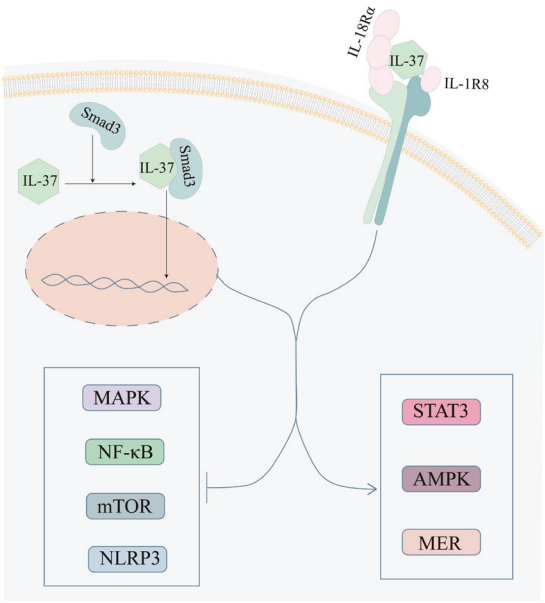


Fig. 3. *IL-37 pathways.*

Smad3 is a transcriptional regulator of the TGF-β pathway and plays an important role in IL-37 activity, which translocates into the nucleus. Upon caspase-1-mediated cleavage, IL-37 suppresses the expression of proinflammatory cytokines and the recruitment of neutrophils into the lungs by inhibiting the activity of the NLRP3 inflammasome.[5] IL-37 also inhibits kinases in the MAPK and NF-KB pathways and activates the anti-inflammatory factors, STAT3, and Mer. IL-37 also inhibits mTOR and activates AMPK.[41] On the surface of peripheral blood mononuclear cells (PBMCs), the IL-37/IL-18Rα/IL-1R8 complex binds to MyD88 to block inflammation, which triggers multiple switches, including inhibiting the MAPKs, JNK, and NF-κB signaling pathways, activating the Mer-PTEN-DOK pathway and the pseudo-starvation effects of the mTOR pathway, inhibiting TAK1 and Fyn pathways, activating STAT3, Mer, and PTEN, and inducing p62 (dok) expression.[8,40]

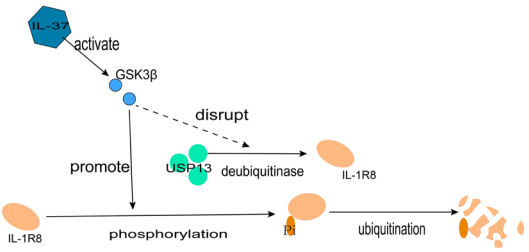


Fig. 4. *IL-37-mediated IL-1R8/Sigirr degradation.*

IL-37 induces IL-1R8/Sigirr degradation in the ubiquitin-proteasome system through site-specific ubiquitination, which can be reversed by a deubiquitinase, USP13.[42] IL-37 activates glycogen synthesis kinase 3β (GSK3β), which plays a role in feedback control of IL-1R8/Sigirr abundance.[43] The activation of GSK3b promotes Sigirr phosphorylation, ubiquitination, internalization, and degradation by disrupting Sigirr association with USP13.

Under physiological conditions, the concentration of plasma IL-18BP is ~20 times higher than that of IL-18, which prevents IL-18 from binding to its cellular receptor.[44,45] This effect also inhibits IL-18-induced IFNγ expression, indicating that IL-18BP has an anti-inflammatory function.[8] However, the anti-inflammatory properties of IL-18BP are lost at high IL-18BP concentrations, but the mechanism involved needs further investigation. The ternary complex, IL-37/IL-18Rβ/IL-18BP competes with IL-18 for IL-18Rβ, which inhibits IL-18 function. This complex also competes with IL-18 for IL-18BP.[21] It has been shown that IL-37 enhances the ability of IL-18BP to inhibit IL-18, but this requires further investigation.[28] Moreover, the IL-37/IL-18Rα/IL-18BP ternary complex inhibits immune responses and exerts anti-inflammatory effects by repressing the expression of IFN-γ and TLR signaling extracellularly.[21]

IL-18 mediates IFN-γ-induced Th1 responses and activates NK cell cytotoxic activity, the production of adhesion molecules, the synthesis of nitric oxide synthase, and the production of chemokines. IL-18 also drives Th2 responses and the expression of IL-13 and IL-4 [46,47] (Figures 5 and 6). IL-18 promotes the synthesis of pro-inflammatory Th1 cytokines, including IFN-γ and GM-CSF, and concurrently suppresses the production of the anti-inflammatory cytokine IL-10. Thus, IL-37 impacts IL-18 and then influences the above processes.

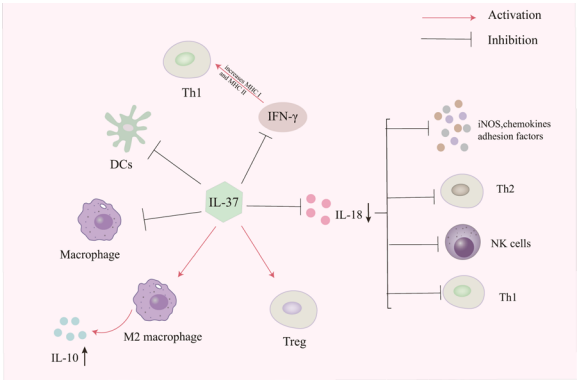


Fig. 5. *Functional and Regulatory Pathways of IL-37.*

IL-37 inhibits IL-18 activity and downregulates IL-18-mediated expression of pro-inflammatory factors, the development of IFN-γ-associated Th1 responses, the activation of NK cell cytotoxic activity, the production of adhesion molecules, the synthesis of nitric oxide synthase, chemokine production, as well as Th2 responses and the expression of IL-13 and IL-4.[47,48] Possible role of IL-37 in modulating the immune response of Tregs and function of DCs.[7] IL-37 promotes macrophage polarization toward the M2 subtype and inhibits macrophage transmigration, apoptosis, and proliferation.[56]

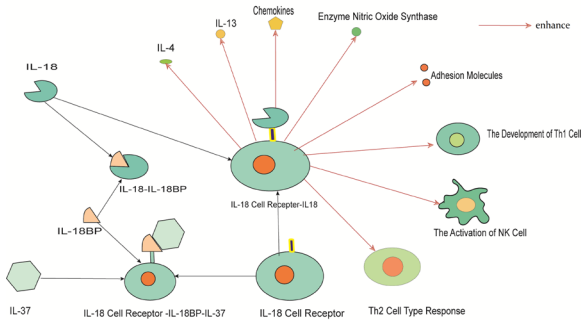


Fig. 6. IL-37 signaling via IL-18.

Excessive IL-18 levels are reduced by IL-18BP,[45] which blocks the binding of IL-18 to its cell receptor.[44,46] The IL-37/IL-18BP/IL-18Rβ complex may compete with IL-18Rβ, thereby inhibiting the function of IL-18. IL-18 triggers IFN-γ-associated Th1 response, the activation of NK cell cytotoxic activity, the production of adhesion molecules, the synthesis of nitric oxide synthase, chemokine production, as well as Th2 responses and the expression of IL-13 and IL-4.[47,48]

IL-37 interacts with Smad3 to influence gene expression

The binding of IL-37 to Smad3 is mediated by IL-37's carboxyl domain. The resulting complex then translocates to the nucleus upon Smad3 phosphorylation (Figure 2), where it regulates gene expression. IL-37 interacts with phosphorylated and non-phosphorylated Smads to regulate some key enzymes and signaling pathways, including focal adhesion kinase, proline-rich tyrosine kinase (Pyk2), MAP kinase p38α, signal transducer and activator of transcription (STAT), p53, and mTOR signaling[48] (Figure 3).

IL-37/Smad3 complexes also compete with Smad2/3/4 complexes. Smad2 and Smad4 may function in the nucleus by competing with IL-37 and reducing the phosphorylation of the IL-37/Smad3 complex, although the mechanism is unclear.[9]

Sources of IL-37 and ManLAM-induced IL-37 production

IL-37 is mainly secreted by macrophages. IL-37 can also be expressed in monocytes, activated B cells, plasma cells, CD4+Treg, dendritic cells, keratinocytes, renal tubular epithelial cells, synovial cells, tonsil B cells, gastrointestinal epithelial cells, carcinoma cells, testis, thymus, uterus, both in the nucleus and the cytoplasm.[7,49] Besides, some cells can secrete the IL-37 during the stimulation by LPS. Dendritic cells (DCs) can also secrete the IL-37 under no stimulated conditions.[8]

Mannose-capped lipoarabinomannan (ManLAM), the virulence factor of *Mycobacterium tuberculosis* (Mtb),[50] elevates IL-10 production by DCs while suppressing their production of IL-12. It also stimulates the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 in A549 cells and cell surface TLR2 expression. The phosphorylation of ERK1/2 and p38MAPK in the type II alveolar epithelial cell line, A549, induces IL-37 expression.[26] Several TLR2 and TLR4 ligands also induce IL-37 expression.[51] Impairing TLR2 expression markedly suppresses the phosphorylation of ERK1/2 and p38, and ManLAM-induced IL-37 expression. However, impairing TLR4 function did not affect IL-37 expression.[51] The interaction of LPS-activated TLR4 and its intracellular adaptor on the cell surface induces NF-κB-mediated transcriptional expression of proinflammatory genes. TLRs and proinflammatory factors also enhance IL-37 expression[22] (Figure 7).

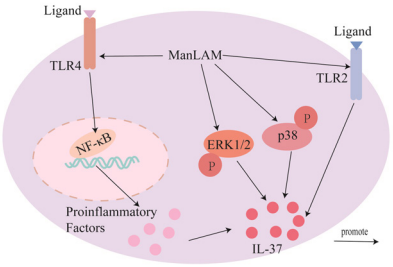


Fig. 7. *ManLAM and TLR4 enhance the expression of IL-37.*
Mannose-capped lipoarabinomannan (ManLAM) stimulates the phosphorylation of ERK1/2 and p38 (A549 cells) and induces TLR2 expression, which can induce IL-37 expression. Several toll-like receptor (TLR) ligands also induce IL-37 expression. The LPS-activated TLR4 stimulates NF-κB signaling, thereby driving the expression of pro-inflammatory genes. TLRs and proinflammatory factors enhance IL-37 production.[5]

Moreover, IL-37 levels are reported to rise upon treatment of relapsed TB, severe TB, and drug-resistant TB. In sputum smear (Mtb)+ patients, IL-37 levels fall after short-term anti-TB chemotherapy.[52] In vitro, TB-sensitive monocytes continuously produce IL-37b without antigen stimulation.[52]

IL-37 and Vascular Regeneration

Granuloma-associated angiogenesis may influence the occurrence, progression, and prognosis of diseases. IL-37 is a novel proangiogenic factor that promotes endothelial cell (EC) proliferation, migration, and capillary formation in vitro, as well as vessel sprouting from aortic rings ex vivo.[53] Hypoxia, which influences vascular regeneration, upregulates IL-37 expression; the IL-37 upregulation is suppressed by HIF-1α downregulation.[53] IL-37 also stimulates the activation of ERK1/2 and protein kinase B (AKT), which is critical for endothelial activation and viability.[54] Additionally, IL-37 promotes angiogenesis by modulating inflammatory responses[53] (Figure 8).

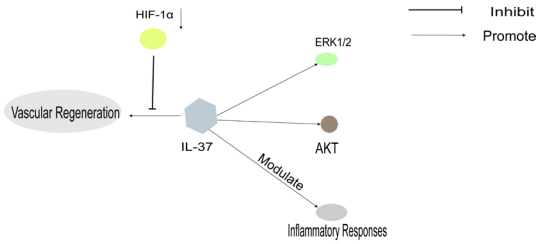


Fig. 8. *IL-37 and vascular regeneration.*
IL-37 upregulates vascular regeneration, but its effects can be inhibited by the downregulation of HIF-1α expression. IL-37 stimulates the activation of ERK1/2 and AKT, which are critical for endothelial activation and viability.[53] In addition, IL-37 promotes angiogenesis by modulating inflammatory responses.

However, other studies have suggested that the effect of IL-37 on blood vessels is dose-dependent. The dose-dependent proangiogenic effect of IL-37 might be because the impact of many angiogenic factors is biphasic. For example, at optimal concentration, PAI-1 has proangiogenic functions, but at high concentration, it has antiangiogenic activity. At low concentrations, IL-8 enhances the chemotaxis and proliferation of ECs, but its effects are diminished at high concentrations. IL-18Rα and IL-1R8 play a reserve role in angiogenesis in different concentrations.[53] IP-10 and thrombospondin suppress angiogenesis at low concentrations but at high concentrations, they induce EC chemotaxis.[53]

IL-37 and macrophage polarization

IL-37 is reported to inhibit macrophage transmigration, apoptosis, and proliferation. It enhances the expression of THP1-derived macrophages with a higher CD206+ and lower CD86+, which are markers of M2 macrophages. IL-37 also upregulates the mRNA levels of arginase-1, TGF-β, and IL-10. Besides, IL-37 suppresses the expression of CD 86, IL-1β, iNOs, and IL-12, which are markers of M1 macrophages. Because M2 macrophages enhance phagocytosis, IL-37-induced macrophage polarization drives phagocytosis.[55]

The inactive Mtb strain, H37Rv (iH37Rv), polarizes macrophages into the M1 subtype and increases the expression of CD86, iNOs, IL-12, and IL-1β, while reducing the levels of CD206, TGF-β, and IL-10. SiRNA-mediated IL-37 silencing enhanced this polarizing phenomenon. However, exogenous IL-37 has the opposite effect of polarizing macrophages toward the M2 subtype.[55] Although some studies have shown that endogenous lL-37 increases nitric oxide levels, exogenous IL-37 has the opposite effect.[55]

The role of IL-37 in the regulation of autophagy

IL-37 inhibits mTOR signaling and activates the AMPK pathway (Figure 3), triggering pseudo-starvation, the main autophagy regulation mechanism. Autophagy is thought to be critical for the delivery of bacteria to the lysosome for degradation, which limits the survival of intracellular bacteria. Other autophagy functions include promoting antigen presentation and reducing inflammation by sequestering and processing microbial components.[56,57] IL-37 influences antifibrotic activity associated with autophagy activation in fibrotic lungs.[58]

IL-37 modulates the expression of chemokines and cytokines

Some proinflammatory cytokines may promote the expression of IL 37, which may inhibit the overproduction of proinflammatory cytokines through negative feedback. In addition, IL-12, IL-32, and granulocyte-macrophage colony-stimulating factor (GM-CSF) suppress IL-37 production,[7] probably because GM-CSF and IL-4 stimulate the differentiation of monocytes to dendritic cells. In human immune cells, monocytes, DCs, and T cells may account for 81%–91%, 1%–2%, and 6%–8% of secreted IL-37.[8] So, GM-CSF and IL-4 suppresses monocyte-induced IL-37 levels.[22]

IL-37 inhibits the production of inflammatory factors, including IL-1α, IL-1β, IL-1Rα, IL-6, IL-17, IL-8, IL-23, TNF-α, IFN-γ, IL 4, IL-13, IL-3, IL-14, as well as cytokines IL-13, IL-10, and I-309, and the chemokines CXCL-2, CCL12, CXCL13, M-GSF, GM-CSF, IACM-1, NLRP3, MIP-2/CXCLE, MCP-5/CCL12, and BDCA-1/CXCL13, but elevates TNF-β and NO levels.[7,8,21,59,60]

IL-37 and various signal pathway

IL-37 suppresses immune responses by regulating the MertK-dependent pathway in monosodium urate crystals-stimulated THP-1 cells. IL-37 stimulates the AMPK pathway to counterbalance inflammation in THP-1 cells. Eosinophils, smooth muscle cells, and epithelial cells secrete VEGF, which is inhibited by IL-37.[61] IL-37 can also inhibit the Warburg effect by activating MAPK signaling and inhibiting the mTOR pathway.[8]

IL-37 exerts immunosuppressive effects by inhibiting the activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, which is a critical factor in various inflammatory signaling pathways.[62] By inhibiting the activity of the NLRP3 inflammasome, IL-37 suppresses the production of proinflammatory cytokines and the recruitment of neutrophils into the lungs.[63]

IL-37 affects T-cell balance. DCs from IL-37 transgenic mice exhibit a reduced ability to activate native T cells and antigen-specific T cells and an enhanced ability to cause Treg cell polarization. Thus, IL-37 affects T-cell balance and, therefore, attenuates T-cell-mediated inflammation.[7,64]

Conclusion

IL-37, through interaction with various receptors, inhibits the production of proinflammatory cytokines, promotes the proliferation and differentiation of macrophages, and regulates autophagy and vascular regeneration. A better understanding of the functions of IL-37 may uncover intervention strategies for various diseases.

Funding

National Natural Science Foundation of China (No. 81860644, 32060180, 82160304, 81860644) and Joint Foundation of Yunnan Province Department of Science, Technology-Kunming Medical University [No. 2019FE001 (-002) and 2017FE467 (-001)].

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China and Yunnan Province Department of Science and Technology-Kunming Medical University Joint Fund Projects. The funding institutions were not involved in the design of the study or the review of the manuscript.

Disclosure and Competing Interests

The authors declare that they have no competing interests. The views presented in this paper are the views of the authors and not the official position of the institution or funder.

References

1. Kumar S, McDonnell PC, Lehr R, Tierney L, Tzimas MN, Griswold DE, et al. Identification and initial characterization of four novel members of the interleukin-1 family. J Biol Chem. 2000 Apr 7;275(14):10308-14. doi: 10.1074/jbc.275.14.10308.
2. Mulero JJ, Pace AM, Nelken ST, Loeb DB, Correa TR, Drmanac R, Ford JE. IL1HY1: A novel interleukin-1 receptor antagonist gene. Biochem Biophys Res Commun. 1999 Oct 5;263(3):702-6. doi: 10.1006/bbrc.1999.1440.
3. Dunn E, Sims JE, Nicklin MJ, O'Neill LA. Annotating genes with potential roles in the immune system: six new members of the IL-1 family. Trends Immunol. 2001 Oct;22(10):533-6. doi: 10.1016/s1471-4906(01)02034-8.
4. Wang L, Quan Y, Yue Y, Heng X, Che F. Interleukin-37: A crucial cytokine with multiple roles in disease and potentially clinical therapy. Oncol Lett. 2018 Apr;15(4):4711-4719. doi: 10.3892/ol.2018.7982.
5. Liu H, Ge B. Interleukin-37: a new molecular target for host-directed therapy of tuberculosis. Future Microbiol. 2017 May;12:465-468. doi: 10.2217/fmb-2017-0030.
6. Tete S, Tripodi D, Rosati M, Conti F, Maccauro G, Saggini A, et al. IL-37 (IL-1F7) the newest anti-inflammatory cytokine which suppresses immune responses and inflammation. Int

J Immunopathol Pharmacol. 2012 Jan-Mar;25(1):31-8. doi: 10.1177/039463201202500105.
7. Nold MF, Nold-Petry CA, Zepp JA, Palmer BE, Bufler P, Dinarello CA. IL-37 is a fundamental inhibitor of innate immunity. Nat Immunol. 2010 Nov;11(11):1014-22. doi: 10.1038/ni.1944.
8. Cavalli G, Dinarello CA. Suppression of inflammation and acquired immunity by IL-37. Immunol Rev. 2018 Jan;281(1):179-190. doi: 10.1111/imr.12605.
9. Zhao M, Li Y, Guo C, Wang L, Chu H, Zhu F, et al. IL-37 isoform D downregulates pro-inflammatory cytokines expression in a Smad3-dependent manner. Cell Death Dis. 2018 May 22;9(6):582. doi: 10.1038/s41419-018-0664-0.
10. Zeng H, Zhou K, Ye Z. Biology of interleukin-37 and its role in autoimmune diseases (Review). Exp Ther Med. 2022 Jun 7;24(2):495. doi: 10.3892/etm.2022.11422.
11. Wang L, Quan Y, Yue Y, Heng X, Che F. Interleukin-37: A crucial cytokine with multiple roles in disease and potentially clinical therapy. Oncol Lett. 2018 Apr;15(4):4711-4719. doi: 10.3892/ol.2018.7982.
12. Quirk S, Agrawal DK. Immunobiology of IL-37: mechanism of action and clinical perspectives. Expert Rev Clin Immunol. 2014 Dec;10(12):1703-9. doi: 10.1586/1744666X.2014.971014.
13. Cavalli G, Dinarello CA. Suppression of inflammation and acquired immunity by IL-37. Immunol Rev. 2018 Jan;281(1):179-190. doi: 10.1111/imr.12605.
14. Sakai N, Van Sweringen HL, Belizaire RM, Quillin RC, Schuster R, Blanchard J, et al. Interleukin-37 reduces liver inflammatory injury via effects on hepatocytes and non-parenchymal cells. J Gastroenterol Hepatol. 2012 Oct;27(10):1609-16. doi: 10.1111/j.1440-1746.2012.07187.x.
15. Taylor SL, Renshaw BR, Garka KE, Smith DE, Sims JE. Genomic organization of the interleukin-1 locus. Genomics. 2002 May;79(5):726-33. doi: 10.1006/geno.2002.6752.
16. Dinarello CA, Bufler P. Interleukin-37. Semin Immunol. 2013 Dec 15;25(6):466-8. doi: 10.1016/j.smim.2013.10.004.
17. Banchereau J, Pascual V, O'Garra A. From IL-2 to IL-37: the expanding spectrum of anti-inflammatory cytokines. Nat Immunol. 2012 Oct;13(10):925-31. doi: 10.1038/ni.2406.
18. Chen HM, Fujita M. IL-37: a new player in immune tolerance. Cytokine. 2015 Mar;72(1):113-4. doi: 10.1016/j.cyto.2014.11.025.
19. Xie Y, Li Y, Cai X, Wang X, Li J. Interleukin-37 suppresses ICAM-1 expression in parallel with NF-κB down-regulation following TLR2 activation of human coronary artery endothelial cells. Int Immunopharmacol. 2016 Sep;38:26-30. doi: 10.1016/j.intimp.2016.05.003.
20. Zeng M, Dang W, Chen B, Qing Y, Xie W, Zhao M, Zhou J. IL-37 inhibits the production of pro-inflammatory cytokines in MSU crystal-induced inflammatory response. Clin Rheumatol. 2016 Sep;35(9):2251-8. doi: 10.1007/s10067-015-3109-5.
21. Jia H, Liu J, Han B. Reviews of Interleukin-37: Functions, Receptors, and Roles in Diseases. Biomed Res Int. 2018 Apr 1;2018:3058640. doi: 10.1155/2018/3058640.
22. Boraschi D, Lucchesi D, Hainzl S, Leitner M, Maier E, Mangelberger D, et al. IL-37: a new anti-inflammatory cytokine of the IL-1 family. Eur Cytokine Netw. 2011 Sep;22(3):127-47. doi: 10.1684/ecn.2011.0288.
23. Li Y, Chu H, Zhao M, Li C, Guan Y, Guo C, et al. IL-37d Negatively Regulates NLRP3 Transcription via Receptor-mediated Pathway and Alleviates DSS-induced Colitis. Inflamm Bowel Dis. 2021 Jan 1;27(1):84-93. doi: 10.1093/ibd/izaa124.
24. Kang B, Cheng S, Peng J, Yan J, Zhang S. Interleukin-37 gene variants segregated anciently coexist during hominid evolution. Eur J Hum Genet. 2015 Oct;23(10):1392-8. doi: 10.1038/ejhg.2014.302.
25. Yan J, Zhang Y, Cheng S, Kang B, Peng J, Zhang X, et al. Common genetic heterogeneity of human interleukin-37 leads to functional variance. Cell Mol Immunol. 2017 Sep;14(9):783-791. doi: 10.1038/cmi.2016.48.
26. Bulau AM, Nold MF, Li S, Nold-Petry CA, Fink M, Mansell A, et al. Role of caspase-1 in nuclear translocation of IL-37, release of the cytokine, and IL-37 inhibition of innate immune responses. Proc Natl Acad Sci U S A. 2014 Feb 18;111(7):2650-5. doi: 10.1073/pnas.1324140111.
27. Ellisdon AM, Nold-Petry CA, D'Andrea L, Cho SX, Lao JC, Rudloff I, et al. Homodimerization attenuates the anti-inflammatory activity of interleukin-37. Sci Immunol. 2017 Feb 10;2(8):eaaj1548. doi: 10.1126/sciimmunol.aaj1548.
28. Bufler P, Gamboni-Robertson F, Azam T, Kim SH, Dinarello CA. Interleukin-1 homologues IL-1F7b and IL-18 contain functional mRNA instability elements within the coding region responsive to lipopolysaccharide. Biochem J. 2004 Jul 15;381(Pt 2):503-10. doi: 10.1042/BJ20040217.
29. Rudloff I, Cho SX, Lao JC, Ngo D, McKenzie M, Nold-Petry CA, Nold MF. Monocytes and dendritic cells are the primary sources of interleukin 37 in human immune cells. J Leukoc Biol. 2017 Apr;101(4):901-911. doi: 10.1189/jlb.3MA0616-287R.
30. Shi Y, Massagué J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell. 2003 Jun 13;113(6):685-700. doi: 10.1016/s0092-8674(03)00432-x.
31. Pan G, Risser P, Mao W, Baldwin DT, Zhong AW, Filvaroff E, et al. IL-1H, an interleukin 1-related protein that binds IL-18 receptor/IL-1Rrp. Cytokine. 2001 Jan 7;13(1):1-7. doi: 10.1006/cyto.2000.0799.
32. Li S, Neff CP, Barber K, Hong J, Luo Y, Azam T, et al. Extracellular forms of IL-37 inhibit innate inflammation in vitro and in vivo but require the IL-1 family decoy receptor IL-1R8. Proc Natl Acad Sci U S A. 2015 Feb 24;112(8):2497-502. doi: 10.1073/pnas.1424626112.
33. Bello RO, Chin VK, Abd Rachman Isnadi MF, Abd Majid R, Atmadini Abdullah M, Lee TY, et al. The Role, Involvement and Function(s) of Interleukin-35 and Interleukin-37 in Disease Pathogenesis. Int J Mol Sci. 2018 Apr 11;19(4):1149. doi: 10.3390/ijms19041149.
34. Jiang J, Jiang Z, Xue M. Serum and peritoneal fluid levels of interleukin-6 and interleukin-37 as biomarkers for endometriosis. Gynecol Endocrinol. 2019 Jul;35(7):571-575. doi: 10.1080/09513590.2018.1554034.
35. Farrokhi M, Rezaei A, Amani-Beni A, Etemadifar M, Kouchaki E, Zahedi A. Increased serum level of IL-37 in patients with multiple sclerosis and neuromyelitis optica. Acta Neurol Belg. 2015 Dec;115(4):609-14. doi: 10.1007/s13760-015-0491-3.
36. Santarelli DM, Vincent FB, Rudloff I, Nold-Petry CA, Nold MF, Russo MA. Circulating Interleukin-37 Levels in Healthy Adult Humans - Establishing a Reference Range. Front Immunol. 2021 Jul 23;12:708425. doi: 10.3389/fimmu.2021.708425.
37. Godsell J, Rudloff I, Kandane-Rathnayake R, Hoi A, Nold MF, Morand EF, Harris J. Clinical associations of IL-10 and IL-37 in systemic lupus erythematosus. Sci Rep. 2016 Oct 6;6:34604. doi: 10.1038/srep34604.
38. Bufler P, Azam T, Gamboni-Robertson F, Reznikov LL,

Kumar S, Dinarello CA, Kim SH. A complex of the IL-1 homologue IL-1F7b and IL-18-binding protein reduces IL-18 activity. Proc Natl Acad Sci U S A. 2002 Oct 15;99(21):13723-8. doi: 10.1073/pnas.212519099.
39. Kim SH, Azam T, Novick D, Yoon DY, Reznikov LL, Bufler P, et al. Identification of amino acid residues critical for biological activity in human interleukin-18. J Biol Chem. 2002 Mar 29;277(13):10998-1003. doi: 10.1074/jbc.M108311200.
40. Nold-Petry CA, Lo CY, Rudloff I, Elgass KD, Li S, Gantier MP, et al. IL-37 requires the receptors IL-18Rα and IL-1R8 (SIGIRR) to carry out its multifaceted anti-inflammatory program upon innate signal transduction. Nat Immunol. 2015 Apr;16(4):354-65. doi: 10.1038/ni.3103.
41. Garlanda C, Anders HJ, Mantovani A. TIR8/SIGIRR: an IL-1R/TLR family member with regulatory functions in inflammation and T cell polarization. Trends Immunol. 2009 Sep;30(9):439-46. doi: 10.1016/j.it.2009.06.001.
42. Li L, Wei J, Li S, Jacko AM, Weathington NM, Mallampalli RK, et al. The deubiquitinase USP13 stabilizes the anti-inflammatory receptor IL-1R8/Sigirr to suppress lung inflammation. EBioMedicine. 2019 Jul;45:553-562. doi: 10.1016/j.ebiom.2019.06.011.
43. Li L, Wei J, Suber TL, Ye Q, Miao J, Li S, et al. IL-37-induced activation of glycogen synthase kinase 3β promotes IL-1R8/Sigirr phosphorylation, internalization, and degradation in lung epithelial cells. J Cell Physiol. 2021 Aug;236(8):5676-5685. doi: 10.1002/jcp.30253.
44. Dinarello CA, Novick D, Kim S, Kaplanski G. Interleukin-18 and IL-18 binding protein. Front Immunol. 2013 Oct 8;4:289. doi: 10.3389/fimmu.2013.00289.
45. Novick D, Kim S, Kaplanski G, Dinarello CA. Interleukin-18, more than a Th1 cytokine. Semin Immunol. 2013 Dec 15;25(6):439-48. doi: 10.1016/j.smim.2013.10.014.
46. Wawrocki S, Druszczynska M, Kowalewicz-Kulbat M, Rudnicka W. Interleukin 18 (IL-18) as a target for immune intervention. Acta Biochim Pol. 2016;63(1):59-63. doi: 10.18388/abp.2015_1153.
47. Wawrocki S, Kielnierowski G, Rudnicka W, Seweryn M, Druszczynska M. Interleukin-18, Functional IL-18 Receptor and IL-18 Binding Protein Expression in Active and Latent Tuberculosis. Pathogens. 2020 Jun 8;9(6):451. doi: 10.3390/pathogens9060451.
48. Chen YH, Zhou BY, Wu XJ, Xu JF, Zhang JA, Chen YH, Liang SS. CCL22 and IL-37 inhibit the proliferation and epithelial-mesenchymal transition process of NSCLC A549 cells. Oncol Rep. 2016 Oct;36(4):2017-24. doi: 10.3892/or.2016.4995. Epub 2016 Aug 2. Erratum in: Oncol Rep. 2021 Feb;45(2):786.
49. Dinarello CA, Nold-Petry C, Nold M, Fujita M, Li S, Kim S, Bufler P. Suppression of innate inflammation and immunity by interleukin-37. Eur J Immunol. 2016 May;46(5):1067-81. doi: 10.1002/eji.201545828.
50. Józefowski S, Sobota A, Pawłowski A, Kwiatkowska K. Mycobacterium tuberculosis lipoarabinomannan enhances LPS-induced TNF-α production and inhibits NO secretion by engaging scavenger receptors. Microb Pathog. 2011 Jun;50(6):350-9. doi: 10.1016/j.micpath.2011.03.001.
51. Huang Z, Zhao GW, Gao CH, Chi XW, Zeng T, Hu YW, Zheng L, Wang Q. Mannose-capped Lipoarabinomannan from Mycobacterium tuberculosis induces IL-37 production via upregulating ERK1/2 and p38 in human type II alveolar epithelial cells. Int J Clin Exp Med. 2015 May 15;8(5):7279-87. Erratum in: Int J Clin Exp Med. 2015;8(10):19791.
52. Zhang JA, Liu GB, Zheng BY, Lu YB, Gao YC, Cai XZ, et al. Tuberculosis-sensitized monocytes sustain immune response of interleukin-37. Mol Immunol. 2016 Nov;79:14-21. doi: 10.1016/j.molimm.2016.09.018.
53. Yang T, Lin Q, Zhao M, Hu Y, Yu Y, Jin J, et al. IL-37 Is a Novel Proangiogenic Factor of Developmental and Pathological Angiogenesis. Arterioscler Thromb Vasc Biol. 2015 Dec;35(12):2638-46. doi: 10.1161/ATVBAHA.115.306543.
54. Shiojima I, Walsh K. Role of Akt signaling in vascular homeostasis and angiogenesis. Circ Res. 2002 Jun 28;90(12):1243-50. doi: 10.1161/01.res.0000022200.71892.9f.
55. Huang Z, Gao C, Chi X, Hu YW, Zheng L, Zeng T, Wang Q. IL-37 Expression is Upregulated in Patients with Tuberculosis and Induces Macrophages Towards an M2-like Phenotype. Scand J Immunol. 2015 Oct;82(4):370-9. doi: 10.1111/sji.12326.
56. Liang M, Habib Z, Sakamoto K, Chen X, Cao G. Mycobacteria and Autophagy: Many Questions and Few Answers. Curr Issues Mol Biol. 2017;21:63-72.
57. Pan Y, Wen X, Hao D, Wang Y, Wang L, He G, Jiang X. The role of IL-37 in skin and connective tissue diseases. Biomed Pharmacother. 2020 Feb;122:109705. doi: 10.1016/j.biopha.2019.109705.
58. Kim MS, Baek AR, Lee JH, Jang AS, Kim DJ, Chin SS, Park SW. IL-37 Attenuates Lung Fibrosis by Inducing Autophagy and Regulating TGF-β1 Production in Mice. J Immunol. 2019 Oct 15;203(8):2265-2275. doi: 10.4049/jimmunol.1801515.
59. Lei H, Sun Y, Quan S. IL-37 relieves allergic inflammation by inhibiting the CCL11 signaling pathway in a mouse model of allergic rhinitis. Exp Ther Med. 2020 Oct;20(4):3114-3121. doi: 10.3892/etm.2020.9078.
60. Shen Y, Ke X, Yun L, Hu GH, Kang HY, Hong SL. Decreased expression of interleukin37 and its antiinflammatory effect in allergic rhinitis. Mol Med Rep. 2018 Jan;17(1):1333-1339. doi: 10.3892/mmr.2017.7988.
61. Meyer N, Akdis CA. Vascular endothelial growth factor as a key inducer of angiogenesis in the asthmatic airways. Curr Allergy Asthma Rep. 2013 Feb;13(1):1-9. doi: 10.1007/s11882-012-0317-9.
62. Moretti S, Bozza S, Oikonomou V, Renga G, Casagrande A, Iannitti RG, et al. IL-37 inhibits inflammasome activation and disease severity in murine aspergillosis. PLoS Pathog. 2014 Nov 6;10(11):e1004462. doi: 10.1371/journal.ppat.1004462.
63. Cavalli G, Justice JN, Boyle KE, D'Alessandro A, Eisenmesser EZ, Herrera JJ, et al. Interleukin 37 reverses the metabolic cost of inflammation, increases oxidative respiration, and improves exercise tolerance. Proc Natl Acad Sci U S A. 2017 Feb 28;114(9):2313-2318. doi: 10.1073/pnas.1619011114.
64. Liu H, Zheng R, Wang P, Yang H, He X, Ji Q, et al. IL-37 Confers Protection against Mycobacterial Infection Involving Suppressing Inflammation and Modulating T Cell Activation. PLoS One. 2017 Jan 11;12(1):e0169922. doi: 10.1371/journal.pone.0169922.

Corresponding authors:

Prof. Aihua Liu, PhD, The Institute for Tropical Medicine, Faculty of Basic Medical Sciences, Kunming Medical University, Kunming 650500, China, E-mail: liuaihua@kmmu.edu.cn

Prof. Fukai Bao, MD, The Institute for Tropical Medicine, Faculty of Basic Medical Sciences, Kunming Medical University, Kunming 650500, China, E-mail: baofukai@kmmu.edu.cn