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REVIEW

The Role of IL-37 in Non-Cancerous Diseases

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Abstract IL-37 is a newly discovered cytokine belonging to IL-1 family consisting of 11 members, which have similar β-barrel structures and associate with Ig-like receptors. Extensive studies have been done with IL-37 since its discovery. These studies suggest that IL-37 does not only play a role in tumorigenesis, but also has anti-inflammatory properties in immune responses through the down regulation of pro-inflammatory molecules. We have previously reviewed the role of IL-37 in cancer. Here, we will focus on the role of IL-37 in non-cancerous Diseases. Such a study might be helpful to design new strategies to treat IL-37 associated diseases.

Keywords IL-37 · Non-cancerous diseases

Introduction

IL-37, also called Interleukin 1 family member 7 (IL-1F7) was discovered in 2000 [1]. As a novel cytokine, IL-37 is part of the interleukin 1 family, whose members all have a critical function in non-specific innate response. The IL-1 cytokine family consists of 11 members. Seven of the members are pro-inflammatory agonists, which participate in the innate immune system and are produced after the stimulation of toll-like receptors (TLR), and the other four are receptor antagonists [2]. The production of pro-inflammatory cytokines can occur when the innate immune response is stimulated via TLRs; this event also stimulates the adaptive immune system, which is more specific and effective of the two immune responses [3]. Research has shown that IL-37 suppresses innate immune responses, but whether or not it is an immune system antagonist or agonist still needs to be determined [4]. The IL-1 family members are further categorized into subfamilies (IL-1, IL-18, and IL-36 subfamily) based on the length of the precursor and the length of the precursor's propiece, with the IL-1 subfamily having the longest propieces and the IL-18 subfamily having shorter ones. The underlying mechanism by which the propieces are removed is still not well defined. IL-37 is part of the IL-18 subfamily [5]. Most of the members of the IL-1 family have been mapped in chromosome 2, except for IL-18 and IL-33. The structure of IL-37 consists of 12 β-barrel strands that have IL-18-like structural pattern [6]. Five specific isoforms of IL-37, IL-37a-IL-37e, are encoded in five splice transcript variants [7–11]. IL-37a and d may be functional, but it is undetermined. IL-37 c and e are non-functional due to abnormal folding. IL-37b is the largest of the 5 isoforms, has the greatest amount exons (5 of 6 exons), and is biologically functional [3, 12]. IL-37 suppresses pro-inflammatory cytokine production, but interestingly, it does not inhibit the production of anti-inflammatory cytokines, such as IL-10 [6]. IL-1 A, IL-6, CCL-12, CSF-1, CSF-2, CXCL-13, IL-1β, IL-23 A and IL-1RA (IL-1 receptor antagonist) are some of the pro-inflammatory cytokines in which their production are suppressed by IL-37 [2]. It has also been discovered that it does not inhibit dendritic cell activation and has a potential role in adaptive immunity [13]. The main role of IL-37 is to decrease excessive inflammation through negative feedback mechanisms that function in the innate and

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adaptive immune responses [14]. The role of IL-37 in cancer and non-cancerous diseases has been extensively studied in recent years. Previously we extensively reviewed the critical role of IL-37 in tumorigenesis [15]. In this review, we will summarize the updated information about IL-37 in immunology field with a focus on its role in non-cancerous diseases.

IL-37 Expression and Receptors

IL-37 is found in multiple tissues, macrophages, epithelial cells, and peripheral blood mononuclear cells (PBMCs), where it was located in the nucleus or cytoplasm [3, 6]. There is an instability sequence expressed in exon 5 that limits the IL-37 mRNA half-life [3]. In monocytes, IL-37 transcript stability increases when stimulated with lipopolysaccharides (LPS), and as a result, mRNA and intracellular protein expression go up during inflammatory responses. Since both IL-18 and IL-37 have similar structures, IL-18 stability is also enhanced by LPS [16]. Similar to most of the other IL-1 family members, IL-37 protein processing starts with the production of initial precursors which have a signal sequence that lacks the pro-peptide domain. The IL-37 precursor has been observed to be abundant in the cytoplasm [3]. IL-37 maturation is dependent on caspase-1 as the intracellular processing enzyme, in order for the mature cytokine to be released into the extracellular space [17]. The cleavage site of caspase-1 can be found on the N-terminus of exon 1 [3]. Recently though, the potential of the involvement of another caspase-1 cleavage site or additional proteases in IL-37 protein maturation has been discovered. In a study, the incomplete inhibition of IL-37 maturation was observed after the cleavage site of caspase-1 was mutated in IL-37 cells [12, 17]. There is a possibility that the IL-37 found in the cytoplasm may be released through secretory vesicles, since it is observed near the Golgi apparatus, the endoplasmic reticulum, and the plasma membrane. After IL-37 has gone through proteolytic processing, it is translocated into the nucleus. In the nucleus, IL-37 downregulates pro-inflammatory cytokine expression [18]. Tumor necrosis factor (TNF), TLR agonists, and IL-1 are the primary cytokines that are reduced by IL-37 during inflammatory responses [2, 6].

To better understand how IL-37 functions as an anti-inflammatory cytokine, it is important to talk about the receptors of the IL-1 family. An intracellular Toll IL-1 Receptor Resistance (TIR) domain can be found on the receptors of the IL-1 family, which is involved in the initiation of the pro-inflammatory signaling cascade in the innate immune response. The IL-18α chain and the IL-18 binding protein (IL-18 BP) on the IL-18 receptor are non-competitively bound by IL-37, because both IL-37 and IL-18 both have some of the same critical amino acid residues [2, 9, 12, 19, 20]. Due to the high affinity of IL-18 BP to IL-18 and its role as a potent inhibitor of IL-18 through the association of the IL-18 receptor in target cells, IL-37 has been identified as an IL-18 inhibitor [2, 21]. IL-18 acts a major inducer of IFN-γ and as a promoter of T_{h1} lymphocyte and natural killer (NK) cell activation by associating with IL-18Rα and recruiting IL-18β and accessory proteins [3, 22]. The IFN-γ level increase is inhibited by an inactive complex that is formed by the binding of IL-37 to IL-18 BP, which later associated with IL-18Rβ. Whether or not IL-37 is a direct antagonist or agonist of the IL-18 receptor is still not well defined [11]. IL-18Rβ may not be the only accessory protein that is recruited by IL-37. TIR8/SIGIRR, TIGIRR-1, and TIFIRR2 may also be recruited by IL-37 in order to promote an anti-inflammatory cascade [23–25].

In recent studies, the co-receptor, IL-1R8 (TIR8/SIGIRR), is also necessary for various anti-inflammatory processes to occur after innate signal transduction [26]. On the surface of various cells, macrophages, DCs, and PBMCs, the IL-37 – IL-1R8 – IL-18Rα tripartite complex forms. This tripartite ligand complex suppresses inflammation by promoting pro-inflammatory cytokine production through the increase of STAT3 and PTEN activity and the inhibition of the transcription factor NF-κB. STAT3 activity increase promotes the transition of macrophages and DCs into an anti-inflammatory and tolerant state from a pro-inflammatory one. By inhibiting Akt and mTOR, PTEN inhibits the PI3K/Akt/mTOR pathway, which also causes NF-κB inhibition and pro-inflammatory mediator production, such as IL-6, TNF, and IL-1β. NF-κB is also directly inhibited by the tripartite complex via the inhibition of TAK1, an adaptor kinase [26]. The specific signaling pathway is still not completely understood, so further studies are needed to understand this multifaceted anti-inflammatory process.

IL-37 and the Immune System

The IL-37 precursor, Pro-IL-37, has been seen intracellularly in PBMCs. As mentioned previously, LPS and TLR agonists (IL-1β, IL-18, TNF-α, and TGF, and TGF-β) upregulate IL-37, but IL-4, IL-12, IL-32, and GM-CSF (granulocyte-macrophage colony-stimulating factor) downregulate its expression [16]. Clinical trials have been done that exhibited an increase in inflammatory cytokine production in PBMCs of healthy individuals who were treated with monoclonal anti-IL-37 [27]. Differentiation into M1 macrophages was also observed in PBMC adherent cells. IL-37 treated M1 macrophages were stimulated with LPS, and a down regulation of IL-1β, IL-6, and TNF-α expression was seen. The phosphorylation of p38, ERK, and JNK showed to also decrease [27]. IL-37 overexpression and its biological effects were studied using murine macrophage-like RAW 264.7 cells. LPS was used to stimulate cells over-expressing IL-37, and a reduction in TNF-α, IL-6, MIP-2 (macrophage inflammatory protein-2), and IL-1α

production was observed [28]. Nold et al. did further studies with RAW cells and IL-37 over-expression and found an abrogation of different inflammatory cytokines was present in these cells, but under similar conditions, anti-inflammatory cytokine expression did not change. An array of cytokines was studied in IL-37 over-expressing cells that were stimulated with LPS, and the study showed that inflammatory molecules, IL-1α, IL-1β, TNF-α, IL-6, GM-CSF, and MCSF (macrophage colony- stimulating factor), were significantly reduced, but the production of IL-13, a T_{h2} –related cytokine, increased. On the other hand, the production of IL-17 and MCP-1 increased, and IL-1Rα was inhibited, which suggest that IL-37 may have a more complex regulatory role than just anti-inflammatory activity [3]. IL-37 transfected THP-1 cells had a decrease in IL-1α, IL-1β, TNF-α, and IL-8 expression, and a suppression of cellular adhesion and migration regulators, FAK (focal adhesion kinase), Pyk2 (proline-rice tyrosine kinase- 2), and paxillin. Reduction in p53, TOR (target of rapamycin), and Hck (hematopoietic cell kinase) was also observed [6]. The data from the various studies suggest that IL-37 over-expression is correlated with a reduction in response to inflammatory stimulation [3, 6].

Another IL-37 functional study was done using RAW macrophage cells, in which secreted IL-37 was neutralized. Both the RAW macrophage cells and IL-37 transgenic mice were transfected with IL-37. Mock transfected cells and RAW-IL-37 cells were pre-incubated with either control IgG or goat anti-human IL-37 IgG for a 4-h time span, and then they went through an 18 h LPS stimulation. The RAW cells generated less IL-6 than the mock cells. The response of IL-6 was not affected in either the mock cells or RAW cells after pre-treatment of anti-IL-37 IgG. C57/B16 wild type (WT) mice and IL-37 transgenic mice both underwent treatment with the same antibodies used for the cells for 2 h, and then the mice received LPS injections. WT mice did not show any effects after anti-IL-17 IgG pre-treatment, but the IL-37 transgenic mice had a 2.5-fold increase of serum IL-6. This study presents the effect of neutralizing secreted IL-37 negating the anti-inflammatory response of IL-37 after stimulation with LPS [2, 29].

Pull-down assays that studied the proteins that interact with Smad3 showed that one of those proteins was IL-37, which is an important TGF-β (transforming growth factor-β) pathway transcriptional modulator [30]. TGF-β receptors phosphorylate Smad3, which causes its translocation into the nucleus. Once Smad3 is in the nucleus, it affects the transcription of genes [6]. In human monocyte cell lines, THP-1 cells, and A549 cells, IL-37 binds to non-phosphorylated and phosphorylated Smad3 [28]. In vitro and in vivo studies looking at the Smad3/IL-37 complex and its functional role in RAW 264.7 and THP-1 cells using a specific Smad3 inhibitor or a Smad3 siRNA were performed. The studies demonstrated a significant decrease in the anti-inflammatory properties of IL-37 after the endogenous Smad3 was silenced. After inhibition of Smad3 in the RAW and THP-1 cells, inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, and TNF-α) were enhanced in both the in vitro and in vivo experiments. The data from the studies reveals the abrogation of IL-37 function by Smad3 inhibition [2, 6]. IL-37 down regulated inflammation by selectively suppressing pro-inflammatory cytokine production via the Smad3-dependent mechanism [3]. Thus, making IL-37 a great target in immunological studies, even though the role of IL-37 had been studied in various autoimmune diseases and chronic inflammation since the discovery of its anti-inflammatory properties, there is still further studies that are needed for its effects to be completely elucidated.

The Role of IL-37 in Non-Cancerous Diseases

Autoimmune Diseases

The anti-inflammatory properties of IL-37 were studied in inflammatory bowel disease (IBD). IBD is characterized by chronic inflammation in the digestive tract that is triggered by environmental factors, which produce an abnormal immune response in genetically pre-disposed individuals [31]. McNamee et al. looked at IL-37 in human IL-37 transgenic (hIL-37tg) mice and WT mice that had dextran sulfate sodium (DSS) - induced colitis. hIL-37tg mice showed a reduction in the severity of DSS-induced colitis, and compared to the WT mice, hIL-37tg mice exhibited a higher decrease of histological indices of colitis. The transgenic mice also showed a decrease in leukocyte infiltrates, protection of epithelial cell integrity, and reduced edema and hyperplasia. There was also a reduction of leukocyte recruitment to the colonic lamina propria in hIL-37tg mice. It was also discovered that hematopoietic-derived hIL-37 is enough to protect mice against DSS colitis. Mice that were transduced with hematopoietic-derived hIL-37 were found to have a decrease in TNF-α and IL-1β. Interestingly, there was also an increase in IL-5 in these mice, but there was no correlation between the increase in IL-5 and the anti-inflammatory role of IL-37. IL-37 has protective properties against colitis, which suggests that it may be a key player in the protection against intestinal inflammation [32].

Imaeda et al. further studied IL-37 in the inflamed mucosa of IBD patients. Crohn's disease (CD) and ulcerative colitis (UC) are the two major phenotypic manifestations of IBD [33]. The expression of IL-37 was also studied in human colonic epithelial cells, the T84 cell line and the sub-epithelial myofibroblasts (SEMFs). It was found that normal colonic mucosa did not express IL-37, whereas, the inflamed mucosa of individuals with IBD showed a significant increase in epithelial IL-37. The inflamed mucosa of CD and UC individuals also showed enhanced expression of IL-37. The T84 cells

presented with an enhanced IL-37 mRNA expression by TNF-α. Further studies were done to find the underlying mechanism by which IL-37 is induced in T84 cells, and it was discovered that MAPK and PI3K activation are involved. The transcription factors NF-κB and AP-1 were also found to have a role in the TNF-α induced expression of IL-37. In SEMFs, the expression of TNF-α- induced IFN-γ-inducible protein (IP)-5 was considerably reduced by IL-37 at both mRNA and protein levels. IB patients, especially those with UC, exhibited an increased expression of epithelial IL-37. IL-37 mitigates inflammation in IBD patients via a negative feedback mechanism [34].

Systemic lupus erythematosus (SLE) is an inflammatory and autoimmune disease in which overactive T and polyclonal B cells are observed. The overactive B cells produce numerous auto-antibodies; also, type III hypersensitivity, which causes tissue and organ damage, was found to occur [35]. Cytokines also play an important role in the modulation of systemic inflammation, tissue damage, and immune response in SLE [36]. Some of the key SLE cytokines involved are TNF-α, IL-1β, IL-6, and IL-5 [37, 38]. Studies have shown an increased elevation in the levels of IL-37 in SLE patients [39]. There were higher levels of IL-37 in active SLE patients compared to both inactive SLE patients and healthy control groups. There is a positive correlation between IL-37 levels and SLE disease activity index (SLEDAI), but there is a negative correlation between serum IL-37 and complement 3 (C3) and complement 4 (C4) levels. There also seems to be higher levels of IL-37 in SLE patients with renal disease compared with patients without renal manifestations. IL-37 also seems to suppress pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, and their secretion in PBMCs in SLE patients. Thus, IL-37 is important in the regulation of SLE pathogenesis [40].

IL-37 levels were also found to be elevated in patients with Guillain-Barré syndrome (GBS) and rheumatoid arthritis (RA) [41–43]. In GBS, autoimmunity attacks peripheral nerves, which results in acute polyneuropathy [44]. RA is a systemic inflammatory disorder that primarily affects peripheral joints; this disorder is caused by autoimmunity and overproduction of various cytokines [45, 46]. The anti-inflammatory characteristics of IL-37 make it a potential therapeutic target in autoimmune disorders [47].

Obesity

IL-37 has been observed in morbid obesity studies. Morbid obesity is characterized by a state of chronic (low grade) inflammation, which is correlated with elevated generation of cytokines [48]. In the study by Moschen et al., an investigation on how excessive weight loss affects the expression of IL-1F cytokine members in subcutaneous adipose tissue and the liver was done. Tissue samples of severely obese patients were taken before and after their laparoscopic adjustable gastric banding surgery. IL-37 mRNA was found to be expressed at a higher level in subcutaneous/visceral adipose tissue compared to hepatic expression levels. Liver IL-37 mRNA expression continued to be stable before and after the surgery, whereas after surgery and extensive weight loss, IL-37 expression increased in subcutaneous adipose tissue. These findings show that a significant weight reduction alters the cytokine profile in adipose and liver tissue such that it is indicative of an anti-inflammatory state. IL-37 shows potential in contributing to the improvement of inflammation and insulin resistance in obese patients [48].

A recent study was done that showed the protective role IL-37 has against obesity-induced inflammation and insulin resistance. Mice transduced with human IL-37 (IL-37tg mice) were fed a high fat diet (HFD), and the mice were observed to have a reduction in adipose tissue macrophage numbers, an enhancement of circulating adiponectin levels, and maintained insulin sensitivity and glucose tolerance. In vitro studies showed a reduction in differentiation and direct activation of AMPK signaling in adipocytes treated with recombinant IL-37. IL-37tg mice also exhibited a significant decrease of adipose inflammation. In humans, insulin sensitivity and low inflammation in adipose tissue are positively correlates with IL-37 levels. The findings present a modulating role of IL-37 in obesity-induced inflammation and insulin resistance, and IL-37's potential as a treatment target in type 2 diabetes and obesity-induced insulin resistance [49].

Hepatic Disorders

The role of IL-37 was also investigated in hepatitis. Bulau et al. conducted a study that showed improvement of hepatitis and sepsis in mice that expressed IL-37. First, human IL-37 plasmid DNA injections were given to mice. Then, severe acute hepatitis was induced in the mice by concanavalin A (ConA) injections, and sepsis was induced in the mice using LPS. After ConA injection, the mice had a substantial reduction in IL-1α, IL-6, IL-5, and IL-9 levels. There was also a decrease in the level of these pro-inflammatory cytokines in LPS stimulated mice expressing IL-37. The data show that in in vivo IL-37 expression in mice causes a decrease in local and systemic inflammation in ConA-induced hepatitis and LPS-induced sepsis [50].

Another study was done that investigated the effects IL-37 has on hepatocytes and hepatic inflammation induced by ischemia/reperfusion (I/R). Hepatocytes, particularly Kupffer cells, are components of the inflammatory responses in hepatic I/R [51]. Pro-inflammatory chemokines and cytokines, like TNF-α, macrophage inflammatory protein (MIP-2), and KC are involved in reperfusion injury [52–57]. In this study, the production of these pro-inflammatory mediators was reduced in vivo with IL-37 treatment, and the successive neutrophil

recruitment was also weakened. The release of oxidants and proteases by neutrophils plays a critical role in hepatic I/R injury [51, 58, 59]. IL-37 was found to suppress activation of neutrophils and respiratory burst. The levels of hepatic reactive oxygen species (ROS) were significantly reduced after IL-37 treatment. There was also a reduction in levels of serum TNF-α, MIP-2, and alanine aminotransferase (ALT). In in vitro studies, MIP-2 and KC production was lowered by IL-37 after stimulation with LPS on hepatocytes and Kupffer cells. IL-37 was also observed to have a direct protective role against oxidative injury in liver cells. A decrease in hepatic cell death caused by oxidants after IL-37 treatment was exhibited. Bcl-2 was found to have a correlation with this cytoprotective property of IL-37. The data demonstrated an increased expression of Bcl-2 by IL-37 in hepatocytes, which results in the protective characteristics of IL-37. Thus, IL-37 may be a potential target treatment in inflammatory liver disease [51].

IL-37 was further studied in chronic hepatitis. Li et al. did a study to determine the serum IL-37 levels and HBeAg seroconversion in chronic hepatitis B virus (HBV) patients, chronic hepatitis C virus (HCV) patients, and healthy controls (HC). HBV infection was seen to have an increase in IL-37 concentrations that was dependent of viral load, but HCV did not show any difference. Chronic hepatitis B (CHB) patients with HBeAg clearance were the only individuals to show a reduction in the levels of IL-37, which suggests IL-37 may have a critical component in HBV infection with HBeAg seroconversion during telbivudine (LDT) treatment. HBV and HBC patients with high levels of ALT and AST were observed to have elevated levels of serum IL-37 compared to patients with normal ALT and AST levels. The increase of IL-37 seems to correlate with the increased serum ALT levels, which work together to suppress injury by excessive inflammation. IL-37 may be a crucial component in CHB patients with HBeAg seroconversion immune response [60].

Cardiovascular Diseases

Another disease class that has been investigated with IL-37 are the cardiovascular diseases. Atherosclerosis is an inflammatory disease caused by the major build-up of lipid deposition, and subsequently atherosclerotic foam cells, in arteries (coronary and carotid) [61]. In a study by Wu et al., IL-37 expression levels were rapidly up-regulated in PBMCs in the context of inflammation by inhibiting the production of inflammatory cytokines. IL-37 also suppressed macrophage and dendritic cell (DC) activation. Another study was done looking at IL-37 in acute coronary syndrome (ACS). ACS is an umbrella term for the clinical signs and symptoms of myocardial ischemia, such as unstable angina pectoris and acute myocardial infarction (MI). The plasma levels of IL-37 were significantly higher in patients with ACS than in healthy patients and stable angina pectoris patients. Levels of IL-18 and CRP, both inflammation biomarkers, have a positive correlation with IL-37 levels in individuals with ACS [62]. IL-37 has also been shown to ameliorate myocardial ischemia/reperfusion (I/R) in mice models. Mice treated with recombinant human IL-37 before reperfusion showed I/R injury amelioration, when compared to vehicle- treated mice. The size of the infarcted zone was decreased, cardiac troponin T levels were reduced, and cardiac function was improved in the IL-37 treated mice. The protective properties of IL-37 against I/R injury were attributed to pro-inflammatory cytokine, chemokine, and neutrophil infiltration suppression, which resulted in a reduction of ROS production and cardiomyocyte apoptosis. TLR-4 expression and NF-κB activation upregulation were inhibited by IL-37 after I/R, but IL-5 levels increased [63]. These findings present IL-37 as a promising therapeutic target for cardiovascular diseases.

HIV Infection

IL-37 affects the functional interaction between the innate and adaptive immune responses by inhibiting dendritic cell maturation, which in turn helps in the suppression of acquired immunity [6, 13]. Due to the anti-inflammatory and immunosuppressive characteristics IL-37 holds, it has been the subject of various therapeutic studies in illnesses caused by excessive inflammation. Excess immune activation is a property seen in HIV-1 infections. Therefore, the Højen lab investigated IL-37 potential role in HIV-1 infections [64]. The objective of this study was to investigate IL-37 expression in chronic human immunodeficiency virus-1 (HIV-1) infection and to determine the relationship between IL-37 with inflammation and reservoir size biomarkers. The levels of IL-37 mRNA in infected patients were compared to those of non-infected patients. Depending on the combinatorial antiretroviral therapy (cART) and $CD4^+$ T cell count of the HIV-1 infected patients, patients were divided into three subgroups (cART-naïve, IIRs, and responders). Non-infected healthy individuals made the fourth and final group, the control group. q RT-PCR was done on the PMBCs of patients to detect IL-37 mRNA and HIV-1 DNA. There was a higher level of IL-37 mRNA observed in HIV-1 infected patients compared to the control group, but no statistically relevant difference in IL-37 mRNA expression or monocyte proportion between the HIV-1 subgroups. The increase of IL-37 mRNA expression in the PMBCs was not due to increased numbers in monocytes, but to the increase of IL-37 mRNA per monocyte. Quantification of biomarkers in the plasma was done with ELISA, and flow cytometry was utilized to determine the activation of T-cells. Levels of sCD8, the monocyte inflammatory biomarker, were found to correlate with IL-37 mRNA levels, but T-cell activation was not observed to be associated with IL-37 levels. The difference in LPS stimulation between the PMBCs of each subgroup was

also studied. PBMCs of the HIV-1 infected groups and the non-infected control group were stimulated with LPS; after stimulation, there was an increase in IL-37 in the HIV-infected groups and not the non-infected group, with or without LPS stimulation. However, between the groups there was no noticeable difference of induction of IL-37. The IIRs group had a higher level of IL-37 mRNA compared with the other two HIV-1 infected groups when stimulated with LPS, and the responders had the lowest level of IL-37. The data show that chronic HIV-1 infection does have an effect on IL-37 mRNA levels, and the mechanism may be through the monocyte compartment activation. Also, there is a possibility of interaction between IL-37 and total viral HIV-1 reservoir size [64].

Spinal Cord Injury

While the anti-inflammatory role of IL-37 in the central nervous system still needs to be elucidated, a recent study by Coll-Miró et al. investigated what the effects of IL-37 are after spinal cord injury (SCI) in mice [65]. Mice, either transgenic for human IL-37 or wild-type, were subjected to SCI and then treated with recombinant human IL-37. In the uninjured spinal cords of IL-37tg mice, IL-37 was barely expressed, but 21 h and 72 h after SCI, the mice showed strong expression of IL-37. There was an increase in neuronal and myelin sparing and defense against locomotor loss in IL-37tg mice compared to WT mice. The injured spinal cords of the transgenic mice exhibited low numbers of neutrophils, macrophages, and activated microglia, and a decrease in cytokine levels, such IL-6. WT mice with SCI received treatment with an intra-spinal injection of full-length or processed recombinant IL-37, and it was observed that after treatment, the mice had increased locomotor skills (Basso Mouse Scale) and ran/walked at faster speeds on a treadmill. These results indicate that IL-37 has a suppressive role in inflammation on SCI, and it may be a potential treatment for acute SCI [65].

Conclusion

Since the discovery of IL-37 in 2000, because of its anti-inflammatory characteristics, IL-37 has been found to be a key modulator for both the innate and adaptive immunity. This finding also suggests that it might be a critical inflammatory regulator. In recent years, IL-37 has been proven to be a potential therapeutic target for various diseases, such as autoimmune diseases, obesity, cardiovascular diseases, chronic inflammatory disorders, and HIV infection. Even with all these research already done with IL-37, much still needs to be studied to get a complete understanding of the role of IL-37 and the mechanism by which it functions. Undoubtly, such studies will uncover the veil of mystery for IL-37 and might be beneficial to patients with IL-37 associated diseases.

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Compliance with Ethical Standards

Conflict of Interest The authors have no conflict of interest.

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