Review

Role of IL-37 in Cardiovascular Disease Inflammation

Ziyi Yang, BS,[a] Lin Kang, PhD,[b,c] Yan Wang, MS,[a] Jiaqing Xiang, MS,[a] Qianying Wu, BS,[a] Cong Xu, BS,[a] Yanqing Zhou, BS,[a] Shaoyuan Chen, MS,[d] Hongcheng Fang, MS,[e] Jie Liu, PhD,[a] and Ming Dong, PhD[a]

[a] Department of Pathophysiology, Guangdong Key Laboratory of Genome Stability and Human Disease Prevention, Shenzhen University Health Science Center, Shenzhen, Guangdong, China

[b] Department of Endocrinology, The Second Clinical Medical College of Jinan University, Shenzhen People's Hospital, Shenzhen, Guangdong, China

[c] Clinical Medical Research Center, The First Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong, China

[d] Department of Cardiology, Nanshan Hospital, Guangdong Medical College, Shenzhen, Guangdong, China

[e] Department of Cardiology, Shenzhen Shajing Hospital, affiliated with Guangzhou Medical University, Shenzhen, Guangdong, China

ABSTRACT

Inflammation is closely related to the pathogenesis and prognosis of cardiovascular disease (CVD). Interleukin-37 (IL-37), an anti-inflammatory IL-1 family cytokine, shifts cytokine expression from pro- to anti-inflammation via regulation of macrophage polarization and lipid metabolism. In macrophages, IL-37 functions through both intracellular and extracellular pathways to regulate the activity of NF-kB and PTEN as well as the expression of cytokines, including IL-1β, IL-6, and IL-10. Moreover, IL-37 levels are increased in the serum of patients with heart failure, atherosclerosis, and acute coronary syndrome with no evidence of anti-inflammatory effects. However, transgenic overexpression of IL-37 improves cardiac infarct and attenuates atherosclerosis plaque expansion. Hence, it is worthwhile to investigate the precise mechanism and role of IL-37 in the pathogenesis of CVD, which may provide deeper understanding of the inflammatory response in this context. This review summarizes the regulatory role of IL-37 in systematic inflammation induced by CVD and highlights recent advancements in the clinical application of IL-37 as a therapeutic agent or biomarker for diagnosis of CVD.

RÉSUMÉ

L'inflammation est étroitement liée à la pathogenèse et au pronostic des maladies cardiovasculaires (MCV). L'interleukine-37 (IL-37), une cytokine anti-inflammatoire de la famille IL-1, change l'expression des cytokines pro-inflammatoires à des cytokines anti-inflammatoires par la régulation de la polarisation des macrophages et du métabolisme des lipides. Dans les macrophages, l'IL-37 agit par l'intermédiaire des voies intracellulaires et extracellulaires pour réguler l'activité de NF-kB et de PTEN ainsi que l'expression des cytokines, à savoir l'IL-1β, l'IL-6 et l'IL-10. De plus, les concentrations de l'IL-37 sont accrues dans le sérum des patients atteints d'insuffisance cardiaque, d'athérosclérose et d'un syndrome coronarien aigu, mais n'ont pas d'effets anti-inflammatoires. Toutefois, la surexpression transgénique de l'IL-37 réduit le risque d'infarctus cardiaque et atténue l'expansion des plaques d'athérome. Par conséquent, il conviendrait d'examiner le mécanisme et le rôle précis de l'IL-37 dans la pathogenèse des MCV pour avoir une meilleure compréhension de la réponse inflammatoire dans ce contexte. La présente revue résume le rôle de l'IL-37 dans la régulation de l'inflammation systématique induite par les MCV et met en évidence les avancées récentes dans l'application clinique de l'IL-37 comme agent thérapeutique ou biomarqueur dans le diagnostic des MCV.

The pathogenesis and prognosis of cardiovascular diseases (CVDs)—severe diseases with high morbidity—have been the focus of research for many years. A series of complicated interactions involving lipoproteins (LPs), vascular wall components, blood cells, and the immune system are crucial to the pathogenetic process of CVD. Inflammation, one of the most important mediators of these interactions, is considered a core risk factor for some cardiovascular diseases.[1] Inflammation leads to increased proinflammatory cytokine levels, disrupting the systematic balance between pro- and anti-inflammatory cytokines. Indeed, adverse cardiovascular events—for instance, acute heart infarction and heart failure (HF)—are associated with proinflammatory cytokine production, characterized by elevated IL-1β, TNF-α, and IL-6 levels.[2] Therefore, restoring the anti-inflammatory balance might have protective effects against CVD.

Interleukin-37 (IL-37) is an anti-inflammatory cytokine that was initially described in 2000.[3] It belongs to the IL-18

subfamily and has a similar structure, allowing IL-37 to bind with IL-18Rα, but the binding affinity of IL-37 to IL-18Rα is only 1/50th of that with IL-18.[4] Of note, IL-18 is a proinflammatory cytokine that, once bound to IL-18R, induces activation of NF-κB.[5] IL-37 is unable to trigger the proinflammatory pathway when binding with IL-18Rα, as it fails to recruit IL-18Rβ.[6] Instead, it recruits IL-18-binding protein (IL-18BP) to form a triplex with IL-18Rα, which inhibits the interaction between IL-18 and IL-18R[4] and the subsequent activation of the inflammatory pathway. The natural function of IL-18BP, an antagonist of IL-18, is enhanced by binding with IL-37.[6]

There are 5 variants of IL-37 that are denoted a to e.[7,8] IL-37b is considered the dominant functional IL-37 subtype and has been widely studied.[9] IL-37b and c are the only 2 members of the IL-37 group that have a caspase-1 cleavage site, but the cleavage site of IL-37c is nonfunctional because of abnormal folding.[10] Caspase-1 cleaves the precursor IL-37 (pre-IL-37) to form mature IL-37 that is capable of binding with Smad3 and translocating into the nucleus where it acts as a transcriptional regulator.[11] IL-1β and IL-6 expression is also regulated by this pathway.[11] IL-37d, expressed in the bone marrow and testis, was recently shown to have a similar function to IL-37b via the Smad3 pathway in tumour cells.[12,13] As research on IL-37 subtypes progresses, additional immune- and inflammatory-related functions for IL-37 may be identified.

IL-37 in Inflammation

IL-37 is categorized as an anti-inflammatory cytokine that downregulates production of proinflammatory cytokines, including TNF-α, IL-1α, IL-6, and IL-8.[10,14-16] Decreased expression of IL-37 is a crucial event in the pathogenesis of many diseases, especially chronic diseases that are accompanied by severe inflammation. Ye et al. reported that reduced IL-37 might enhance expression of reactive oxygen species (ROS) and proinflammatory cytokines by activating Th1 and Th17 in the pathogenesis of Behçet disease (BD).[17] Unlike in BD, IL-37 accumulates significantly in atherosclerotic plaques.[18] In addition, expression levels of IL-37 are increased in the plasma of patients with heart failure and acute coronary syndrome (ACS), with no obvious suppression of inflammation.[19,20] Ahmad et al.[17] described similar findings in patients with Crohn disease. In addition, Toll-IL-1 receptor-8 (TIR-8, IL-1R8 or SIGIRR), a second subunit of the IL-37 receptor, accumulates in serum caused by shedding from the cell surface.[17] The addition of soluble TIR-8 into THP-1 cell cultures resulted in significant repression of the anti-inflammatory function of IL-37, thus demonstrating that TIR-8 neutralizes IL-37 function.[17] Although no further experiments were conducted involving patients with CVD, this finding provides a possible explanation for excessive IL-37 accumulation, with no evident anti-inflammatory effects. The function of IL-37 may be attenuated by other components, such as TIR-8, indicating that the anti-inflammatory effects of IL-37 are not solely dependent on dose. Accordingly, IL-37 inhibitors may be potential therapeutic agents for inflammatory diseases. Further investigation of IL-37 inhibitors may lead to a deeper understanding of inflammation and the function of IL-37 in various other diseases.

IL-37 regulates multiple cell types during inflammation. More precisely, monocytes and dendritic cells (DCs) are major producers of IL-37 in inflammatory states after LPS stimulation, but only DCs release IL-37 at a baseline physiological state. Meanwhile, IL-37 derived from epithelial cells controls activation of T cells and DCs.[21] In addition, IL-37 expression by macrophages leads to a significant reduction in the expression of proinflammatory cytokines at both the transcriptional and translational levels.[22]

Mechanisms by Which IL-37 Regulates Macrophages

IL-37 strongly regulates macrophages, which are the primary sources of proinflammatory cytokines and the primary participants in inflammation, to restrain the autoimmune response, although monocytes and DCs, not macrophages, are the main sources of IL-37.[23,24] IL-37 promotes macrophage polarization from the pro-inflammatory subtype (M1) to the anti-inflammatory subtype (M2) in atherosclerosis.[22,25] Several studies have also demonstrated that mRNA expression and activation of NF-κB attenuates elevated IL-37 levels in macrophages.[22,26] NF-κB expression and activity are closely connected to inflammatory cytokine synthesis and macrophage M1 polarization.[27] In an IL-37-treated macrophage cell line, NF-κB downstream genes (IL-1b and TNF-α) were inhibited;[28] however, the upstream regulatory pathway remains ill defined.

Macrophages can activate the IL-37-related signalling pathway, both intracellularly and extracellularly. Intracellular IL-37 attenuates transcription of proinflammatory cytokines and chemokines, such as IL-6 and TNF-α, by interacting with mothers against decapentaplegic homolog 3 (Smad3).[13,29] IL-37 binding to Smad3 initiates Smad3 translocation. Within this pathway, caspase-1 cleaves pre-IL-37 to promote the interaction between IL-37 and Smad3.[11] NLRP3 inflammasomes, the activator of caspase-1, and ATP are also required for this Smad3-dependent pathway. In caspase-1-suppressed macrophages and NLRP3 inflammasome-deficient macrophages, IL-37 anti-inflammatory function is impaired.[11] Both premature and mature IL-37 release from macrophages after LPS stimulation occurs following prolonged exposure to ATP for 15 to 20 minutes in vitro.[11] Therefore, caspase-1, NLRP3, and ATP are all necessary for IL-37 cleavage and externalization. Precursor and mature forms of IL-37 can then be secreted into the extracellular space.[13,29]

IL-37, acting as a cytokine, largely depends upon TIR-8 and IL-18Ra to trigger the anti-inflammatory pathway extracellularly.[30] The anti-inflammatory function of IL-37 is impaired by knockout of TIR-8 and IL-18Ra.[26] IL-37 binds with IL-18Ra and recruits TIR-8, upregulating the activity of Mer, PTEN, and STAT3 pathways in macrophages,[31] while reducing phosphorylation of TAK1, Fyn, and NF-κB pathway mediators (IκBε, p65, and p105).[32] The NF-κB pathway stimulates macrophage polarization toward M1 rather than M2.[27] In contrast, the STAT3 pathway is the key pathway for inducing M2 differentiation.[33] Given these findings, STAT3 may be a potential target of IL-37 in M2 macrophage polarization regulatory pathways[34] (Fig. 1). Meanwhile, another group of researchers demonstrated that IL-37 regulates macrophage polarization via the Notch 1/NF-kB pathway.[25]

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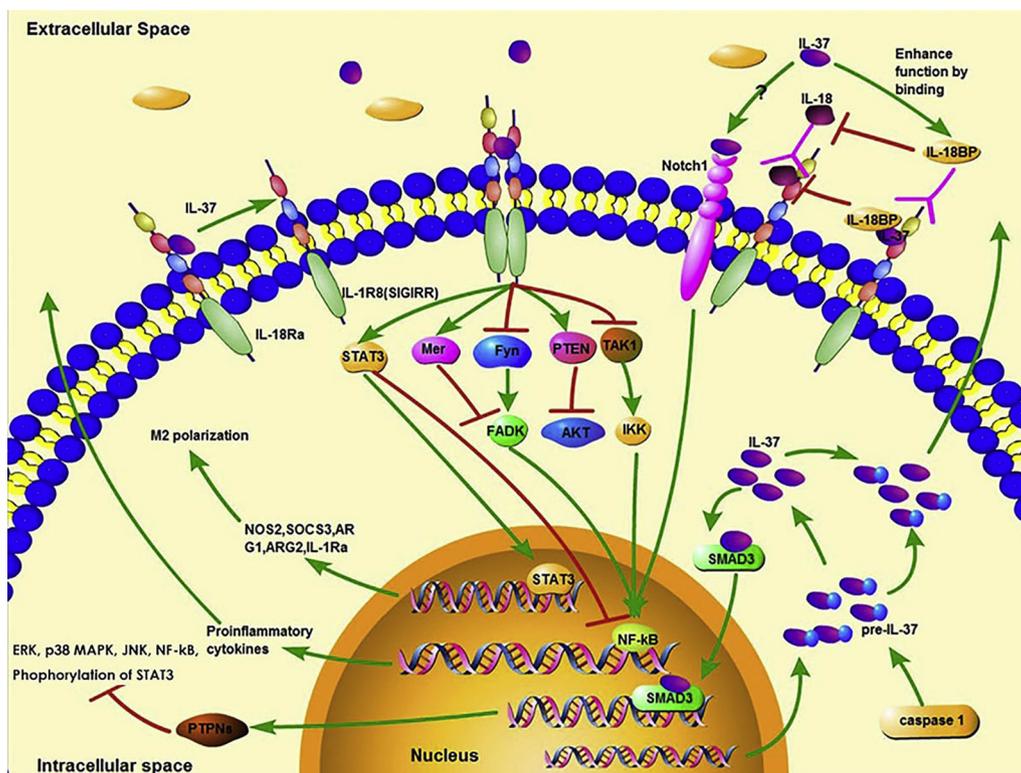IL-37 in Cardiovascular Disease Inflammation

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Figure 1. The IL-37 pathway as described in this review. Extracellular IL-37 binding to IL-18Ra and IL-1R8 triggers the STAT3, Mer, Fyn, PTEN, and TAK1 pathways. Meanwhile, extracellular IL-37 interacts with Notch 1 to regulate NF-kB activity, but the details of this interaction require further investigation. IL-37 enhances the inhibitory function of IL-18BP on IL-18. Furthermore, IL-37 binding with IL-18Ra recruits IL-18BP to form a complex that inhibits the binding between IL-18 and IL-18Ra. Intracellular pre-IL-37 is cleaved by caspase 1 to form mature IL-37. Both mature and pre-IL-37 are secreted into the extracellular space. Mature IL-37 initiates nuclear translocation of SMAD3 upon binding to it.

However, there is, at present, no further information to affirm the direct binding of IL-37 to Notch 1. The polarization of M2 macrophages may be the result of a combination of these 2 pathways. In addition, the subtype of IL-37 that interacts with Notch 1 has not been verified. Most studies have not separately verified the cytokine functions of the IL-37 subtypes. Thus, it remains unclear whether distinct extracellular functions exist in those IL-37 subtypes, including pre-IL-37.

Understanding of the underlying mechanisms of IL-37 expression in macrophages is limited. Studies have confirmed that LPs stimulate expression of IL-37 in the RAW cell line.[12] In human peripheral blood mononuclear cells (PBMCs), IL-37 expression is markedly increased by activating TLRs: specifically, TLR7 and TLR8.[24,35] He et al.[36] demonstrated that triptolide/triptonide induces ERK1/2 and p38 mitogen-activated protein kinase (MAPK) activation, enhancing expression of IL-37 mRNA in THP-1 cell macrophages. This study further revealed that IL-37 expression may be related to MAPK signalling, which is the primary pathway involved in immune response.[36]

In addition to macrophages, mast cells (MCs) also participate in both inflammatory and immune responses. MCs secrete numerous vasoactive, chemoattractant, and inflammatory compounds through degranulation.[37] Previously, MAPK-related pathways were shown to be inhibited by IL-37 in activated MCs.[38] IL-37 also restricts activation of MCs by downregulating IL-1.[39] Activation of MCs leads to robust atherogenic plaque expansion, whereas an MC

stabilizer suppresses this enhanced expansion in apolipoprotein E-/- (APOE-/-) mice.[40] Conti et al. hypothesized that IL-37 may confer protection against inflammation and innate immune-related diseases, such as atherosclerosis and asthma, by regulating MC activation and degranulation.[37,41] Sun et al. further confirmed that MC-derived IL-6 and IFN-γ directly ameliorated atherosclerotic lesions,[42] illustrating that MCs are another potential therapeutic target for atherosclerosis. However, there remains a lack of direct evidence for the beneficial effects of IL-37 in regulating MCs. Which regulatory target of IL-37, macrophages, or MCs is dominant in the pathogenesis and prognosis of diseases *in vivo* remains to be elucidated.

Therapeutic Effect of IL-37 in CVD

Atherosclerosis

The inflammatory response is essential for the formation and development of coronary atherosclerotic plaques.[43] The initial phase of the inflammatory response includes activation of danger-associated molecular patterns (DAMPs) following by triggering of the TLR pathway.[44] The activation of DAMPs continuously stimulates chemokine expression to recruit inflammatory-related cells, accelerating adhesion of molecules to promote formation of plaque.[45] Vascular smooth muscle cells (VSMCs), endothelial cells, T lymphocytes, and macrophages secrete IL-37 in atherosclerosis plaques. It is interesting that

VSMCs and CD4+ T lymphocytes are the primary sources of IL-37 throughout plaque formation, but during calcification, macrophages become the primary contributor.[46] IL-37 may then function in a Smad-3-dependent manner to directly control the abundance of macrophages around the plaque while limiting lipid accumulation and formation of foam cell within the plaque.[47] Furthermore, IL-37 treatment efficiently subdues the expansion of calcified lesions and plaques in ApoE-/- mice with atherosclerosis and calcifications. Thus, the IL-37-dependent function of macrophages in atherosclerosis plaque calcification requires further clarification, and mechanisms of IL-37 regulation of plaque calcification are worthy of further exploration.

Accumulating evidence illustrates that IL-37 significantly alters expression of proinflammatory cytokines to attenuate formation of atherosclerotic plaque. Atherosclerotic plaque size was significantly reduced, from 2.90 ± 0.24 mm^2 to 0.20 ± 0.17 mm^2, in APOE-/- mice after IL-37 treatment.[18] Following IL-37 treatment, inflammation was restrained, which was reflected by the suppression of IL-1β, IL-6, IL-12, IL-17, IFN-γ, TBX21, and RORγt levels and the elevation of IL-10, TGF-β1, and FOXP3 levels.[38] Total plaque area in mice decreased after injecting macrophage-derived IL-37 in this study. Name et al. also observed reduced proliferation of macrophages around plaques with no alterations in plaque composition.[22] IL-37b transgenic mice present with smaller atherosclerotic lesions than wild-type ApoE-/- mice, while smooth-muscle cell apoptosis is suppressed to stabilize plaques *in vivo*.[46] Although the therapeutic potential of IL-37 in atherosclerosis is evidently pronounced in preclinical mouse models, these findings have yet to be confirmed in clinical trials.

IL-37 in acute coronary syndrome

Acute coronary syndrome (ACS), a clinical form of acute onset coronary heart disease that includes unstable angina pectoris (UAP) and acute myocardial infarction (AMI), is associated with acute plaque rupture. Plaque rupture usually occurs at the fibrous cap with concomitant inflammation.[48] Studies revealed a positive correlation between IL-6 and TNF-α levels with ACS severity and in-hospital mortality.[49] Levels of C-reactive protein (CRP), an inflammatory biomarker, are elevated in all UAP and patients with MI. Moreover, observed mortality is higher in patients with ACS and higher CRP levels than in patients with lower CRP levels.[2] Notably, plasma IL-37 levels were substantially increased without obvious anti-inflammatory effects in patients with ACS.[10,20] Several groups have indicated that plasma IL-37 levels are positively correlated with the severity of stable angina pectoris (SAP) and in patients with ACS and coronary stenosis,[2] while being negatively correlated with left ventricle ejection faction (LVEF) in patients with ACS.[50] There is no significant difference between IL-37 levels in coronary arteries and peripheral blood in patients with ACS, indicating that IL-37 elevation is systemic rather than local in nature[50] (Table 1). To our knowledge, inflammatory cytokines, such as IL-1 and inflammatory signals triggered by LPS, continuously stimulate expression of IL-37,[14] which may account for the positive correlation between IL-37 and inflammatory biomarkers. Furthermore, our previous study indicated that patients with extremely low IL-37 levels

presented poor prognoses.[51] Therefore, elevated IL-37 levels may not be sufficient to re-establish the balance between pro- and anti-inflammatory cytokine levels, so excess IL-37 may be unable to attenuate inflammation in patients. Surprisingly, IL-37 was recently shown to cause excessive inflammation and tissue damage in response to infection with *Streptococcus pneumoniae* by potentiating recruitment of alveolar macrophages and neutrophils.[52] This observation provides another, quite different possible perspective on the potential consequences of the upregulated IL-37 levels that accompany cardiac contraction deficiency in ACS. The apparent contradictions concerning the precise role of IL-37 in AMI warrant further investigation.

Rho-associated protein kinases (ROCKs)/NF-kB pathways. IL-37 reverses enhanced ROCK activity in peripheral blood mononuclear cells after ischemia/reperfusion injury and onset of ACS.[51,53] The Rho/ROCK pathway regulates NF-kB and MAPK pathways, affecting infarct size in AMI.[54] NF-κB signalling is activated in the myocardium of MI mice, and blocking the NF-kB pathway after MI has reportedly improved cardiac function and survival in a mouse model.[55] The NF-kB signalling pathway is also involved in myocardial remodelling after AMI, specifically with respect to collagen deposition and apoptosis.[56] After intraperitoneal injection with recombinant IL-37 in a C57BL/6 mouse MI model, inflammatory NF-κB signalling was effectively inhibited.[57] In addition, recombinant IL-37 significantly ameliorates ventricular remodelling after MI in mice, as demonstrated by reduced infarct size and myocardial fibrosis.[58] Importantly, Zhu et al.[58] reported that tolerogenic DCs (tDCs) and regulatory T cells may respond to this effect, as shown by treatment of tDCs with IL-37 plus TnI.

The AMP-activated protein kinase (AMPK) pathway. AMPK is another potential target of IL-37 for cardioprotection in response to severe ischemia—reperfusion injury. AMPK has protective effects on cardiac ischemia—reperfusion (I/R) injury, as myocardial recovery is attenuated after ischemia and during I/R in AMPK deficient mice.[59] IL-37 improves skeletal muscle exercise performance by upregulating AMPK and AMP/ATP ratios in muscle tissue while reducing nucleotides, nucleotide derivatives, and oxidative stress-related metabolites such as kynurenine and oxidized glutathione.[60] Although the mechanism for these actions by AMPK has not been directly observed in cardiac muscle, IL-37 has been shown to regulate AMPK levels in skeletal muscle cells. Consequently, IL-37 may directly affect cardiomyocytes during I/R injury.

Regulation of IL-18 and IL-10. IL-37 also binds to IL-18R and blocks the proinflammatory interaction between IL-18 and IL-18R to improve AMI.[61] Blockade of IL-18 resulted in improved left ventricular developed pressure and LVEF.[61,62] However, the affinity of IL-18BP for IL-18 is much higher than that of IL-37,[63] so the efficiency of inhibition by IL-37 might be limited. Of note, amplified inhibition of IL-18BP through binding with IL-37 restricts the effect of IL-18.[26] A delayed increase in IL-18BP was also observed following increased IL-18 levels.[61] Hence, the

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Table 1. Summary of IL-37 alternation in CVDs and result of IL-37 treatment

Diseases	IL-37 level in patients	Effect of IL-37		Pathway	Reference
Atherosclerosis	↑	Attenuate atherosclerosis plaque formation	↓IL-1β, IL-6, IL-12, IL-17, IFN-γ, TBX21, and RORγt ↑IL-10, TGF-β1, and FOXP3	Unclear	[18]
		Reducing the proliferation of macrophages		Smad3-related pathway (assumption)	[22]
		Decrease in calcified lesions and the size		Unclear	[48]
		Increase plaque stability and limit smooth muscle cell apoptosis		Unclear	[46]
Acute coronary syndrome (ACS)	↑	Suppress inflammation		Inhibit ROCK/NF-kB pathway	[55,56,57]
				Binding IL-18BP to inhibit IL-18	[26]
				Enhance expression of IL-10	[65, 66]
		Decreased infarction size and myocardial fibrosis		tolerogenic DCs/T cells, ROCK/NF-kB pathway is potentially response to this regulatory function	[59]
		Improve I/R injury		AMPK pathway in cardiomyocyte	[60, 61]
	↓	Poor prognosis		unclear	[67–69]
Heart failure	↑	IL-37 is a biomarker of heart failure		/	[70]
		Retard progression of heart failure		Enhance Treg cells via Foxp3 pathway and inhibit CD4+ T cells	[71,72]
Atrial fibrillation (AF)	↑	IL-37 is a biomarker of AF; therapeutic effect remains Unknown		/	[75]

inhibitory function of IL-37 on IL-18 is not solely dependent upon the immediate presence of IL-37. IL-10, another IL-1 family proinflammatory cytokine, improves scar formation after AMI, as shown through continuous administration with a mini pump in mice. Expression of IL-10 is not significantly elevated after MI but is upregulated after administration of IL-37.[57,64,65] Thus, IL-37 exerts protective effects via multiple pathways, highlighting its therapeutic potential in ACS.

Heart failure

Heart failure (HF), one of the most lethal types of CVD worldwide, is considered an end-consequence of acute cardiac events. The poor prognosis of HF has been correlated with high levels of proinflammatory cytokines in multiple studies.[66-68] However, the role of inflammation in the pathogenesis of HF remains elusive. Current reports involving IL-37 in HF are inadequate to define the mechanisms involved and associated consequences. Shou et al.[69] demonstrated that IL-37 was abundant in patients with HF, similar to traditional widely used HF biomarkers, such as hs-TnT, hs-CRP, and NT-proBNP. Furthermore, the IL-37 level is an independent predictor of major adverse cardiac events within 12 months.[19] In one study, patients with high IL-37 levels exhibited low rehospitalization rates and reduced mortality rates caused by HF.[19] However, the direct causal relationship between IL-37 and HF pathogenesis remains elusive. IL-37 is negatively correlated with LVEF,[69] suggesting that it may represent a biomarker or predictor for EF-preserved HF. However, the ability of IL-37 to predict HF with preserved LVEF is unknown.

Recently, Bansals et al.[70] confirmed that CD4+ T cells (Th1, Th17 cells) and Treg cells are increased in mouse myocardium, spleen, and mediastinal lymph nodes with ischemic HF. CD4+ T cells induce long-term left ventricular dysfunction, fibrosis, and hypertrophy.[70] Cardiac and splenic CD4+ T cells are primed to induce cardiac injury and remodelling, and they retain this memory on adoptive transfer in HF.[70] When cocultured with bone marrow-derived dendritic cell (BMDCs) from IL-37 transgenic (IL-37tg) mice, T regulatory (Treg) cells accumulated, whereas polarization of naive T cells to Th1 and Th17 was repressed.[15,18,58] Subsequently, the inflammatory response in the infarcted heart was inhibited, and cardiac function was improved.[58] Osborne et al.[71] further revealed that the suppressive function of Treg cells is facilitated by endogenous IL-37 from T cells via the Foxp3 pathway followed by modulating activation and proliferation of CD4+ cells.[71] These findings demonstrate that T-cell-induced IL-37 may also be self-regulated. IL-37 could potentially slow the progression of HF though T cells.

Age-related CVD

Aging is accompanied by chronic low-grade inflammatory processes,[72] and proinflammatory cytokine production is stimulated during the aging process. This proinflammatory shift that occurs in aging increases the risk of multiple cardiac events such as hypertension, atherosclerosis, and ACS.[73] IL-37 was recently shown to be related to age and age-related diseases. Atrial fibrillation (AF) is directly related to inflammation and commonly emerges with advancing age. IL-37 is elevated in patients with AF. Furthermore, the serum level of IL-37 in patients with paroxysmal AF is higher than in patients with permanent AF. Potential therapeutic effects of IL-37 in AF have been suggested based on *in vitro* experiments, but direct experimental testing has not been performed *in vivo*.[74] Administration of recombinant IL-37 for 2 weeks improved carotid artery dilation, as well as metabolic and motor function, in old mice.[75] Moreover, IL-37 attenuated inflammatory responses in old mice with endotoxemia, which exhibited 46.8% cardiac output recovery and significantly reduced NF-kB pathway activity in response to IL-37

treatment.[76] Although evidence indicating that IL-37 suppresses the aging process or directly acts as a therapeutic target of age-associated CVD is still lacking, IL-37 has been shown to restore the inflammatory environment during aging. Given these findings, the function of IL-37 in aging and age-related CVD warrants further investigation.

Summary and Conclusions

IL-37 has been recognized as an anti-inflammatory cytokine for more than a decade. IL-37 can regulate macrophages and MCs to suppress production of proinflammatory cytokines. It is interesting that the IL-37 level increases in patients with CVD, but inflammation is still intense. We assume that enhanced IL-37 is insufficient to recover the homeostasis of cytokines in pathological states. Moreover, IL-37 subtypes have distinct underlying mechanisms. IL-37b is demonstrated to increase tissue damage in lung infection. Therefore, it is essential to clarify the role of IL-37 subtypes in CVDs. Notably, miRNAs also regulate inflammatory response via IL-37 in gestational diabetes and lung injury.[77,78] There is still a research gap in understanding post-transcriptional regulation of IL-37 in CVD. Although the regulatory mechanisms of IL-37 in CVD are still unclear, administration of IL-37 has demonstrated positive effects in mouse models. Hence, the role and mechanisms of IL-37 warrant further investigation, which will lead to a better understanding of the pathogenesis of CVD and potentially provide new clinical therapeutic targets to combat systematic inflammation and its consequences.

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Disclosures

The authors have no conflicts of interest to disclose.

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