The Role of Interleukin-27 in Atherosclerosis: A Contemporary Review

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The Role of Interleukin-27 in Atherosclerosis: A Contemporary Review

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Abstract
Atherosclerosis is a chronic inflammation characterized by an imbalance between inhibitors and stimulators of the inflammatory system that leads to the formation of atherosclerotic plaques in the vessel walls. Interleukin (IL)-27 is one of the recently discovered cytokines that have an immunomodulatory role in autoimmune and inflammatory diseases. However, the definite role of IL-27 in the pathogenesis of atherosclerosis remains unclear. Recent studies on cardiomyocytes and vascular endothelium have demonstrated mechanisms through which IL-27 could potentially modulate atherosclerosis. Upregulation of the IL-27 receptor was also observed in the atherosclerotic plaques. In addition, circulatory IL-27 levels were increased in patients with acute coronary syndrome and myocardial infarction. A regenerative, neovascularization, and cardioprotective role of IL-27 has also been implicated. Future studies are warranted to elucidate the biologic function and clinical significance of IL-27 in atherosclerosis.

Introduction

Atherosclerosis has been considered as a chronic inflammatory condition, in which the formation of atherosclerotic plaque occurs as a result of an imbalance between pro-inflammatory and anti-inflammatory mediators [1, 2]. The role of inflammation in the pathogenesis of atherosclerosis has been investigated in several studies that identify T cells, macrophages, neutrophils, and related cytokines as key players [2]. Clonal expansion of CD4+ T cells in atherosclerotic lesions was reported in earlier studies; since then, the effect of several T cell subsets including type 1 T helper cells (Th1), type 2 T helper cells (Th2), and interleukin (IL)-17-secreting T helper cells (Th17) has been investigated [3].

As a part of cellular immunity, Th1 cells exert pro-inflammatory effects by secreting cytokines such as interferon gamma (IFN-γ) and IL-2. On the other hand, as a part of the humoral immunity, Th2 cells are able to mediate anti-inflammatory response via secretion of IL-4, IL-5, IL-10, and IL-13. Th17 cells, as a part of host defense against extracellular pathogens, were discovered approximately 20 years after the development of Th1/Th2 paradigm, and studies have shown that dysregulation of Th17 cells may be involved in the inflammatory process and

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autoimmunity disease [4, 5]. Moreover, regulatory T (Treg) cells are another subtype of CD4+ T cells that have regulatory effects on Th1, Th2, and Th17.

Conventionally, the pathogenesis of inflammation in atherosclerosis has been attributed to the imbalance between pro-inflammatory Th1 and anti-inflammatory Th2 cytokines as well as the impaired Treg responses. Recent studies revealed that IL-27, a new member of the IL-12-related cytokines, plays an important role in all subsets of CD4+ T cells [5–8]. Studies have shown that hyperlipidemia elevates the secretion of IL-27 in a TLR4-dependent manner from $CD11b^+$ dendritic cells (DCs), accelerating the development of autoantibodies. Our article aims to summarize the current knowledge regarding the effects of IL-27 signaling pathways and review the studies regarding the IL-27-driven inflammation in the setting of atherosclerosis.

IL-27 Structure and Function

IL-27 was introduced as a new heterodimeric cytokine and a member of the IL-12 family and is structurally similar to IL-12, IL-23, and IL-35 [9–11]. It is composed of 2 subunits:

1. Epstein-Barr virus-induced gene 3 (EBI3) which is an IL-12p40-related protein.
2. p28, which is an IL-12p35-related polypeptide [10, 12].

This cytokine can be secreted by antigen-presenting cells, monocytes, endothelial cells (ECs), and DCs. During the inflammation process, IL-27 shows suppressive effects on both naive and effector T cells and induces expression of pro-inflammatory cytokines and chemokines such as tumor necrosis factor (TNF)-α, macrophage inflammatory protein (MIP)-1 alpha, and MIP-1 beta, IL-6, and IFN-γ-inducible protein (IP)-10 [10, 13–15]. The EBI3 subunit, also known as IL-27 subunit beta, was found to be expressed in human ECs and atherosclerotic lesions in the setting of symptomatic stenosis of the carotid artery [16].

IL-27 Receptor

IL-27 receptors can be expressed on various cells such as T cells, macrophages, eosinophils, DCs, and ECs [16–19]. IL-27 receptor is a heteromeric signaling receptor complex that consists of signal-transducing chain glycoprotein 130 (gp130) and the orphan cytokine receptor WSX-1 (also known as IL-27Rα). The subunit gp130 is shared with IL-6 and IL-35 receptors, whereas WSX-1 is found exclusively in the IL-27 receptor [9, 17].

IL-27 Signaling and T Cell Differentiation

One of the pro-inflammatory effects of IL-27 resides in promoting the differentiation of naive CD4+ T cells to Th1 cells [10, 20]. Specifically, IL-27 signaling is mediated via signal transducer and activator of transcription (STAT) 1 and STAT3 pathways (Fig. 1, 2) [21]. Phosphorylation of the STAT1 and STAT3 molecules via Janus kinase-signal transducer and activator of transcription (JAK-STAT) system and activation of p38 mitogen-activated protein kinase (P38-MAPK) system induce a series of actions [13, 17, 22]. Consequently, IL-27 exerts different effects on T cell differentiation. In general, IL-27 stimulates Th1 cell differentiation. However, excessive induction of Th1 cells leads to the secretion of IL-10 by Th2 cells, reflecting the regulatory effect of IL-27 through the STAT3 pathway [9].

STAT1 Signaling Pathway

STAT1 activation triggers the activation of T-bet, a downstream transcription factor of Th1 cells, which subsequently induces the secretion of IFN-γ and further differentiation of naive T cells into Th1 cells. T-bet also inhibits Th17 differentiation via interaction with the transcription factor ROR-gamma t [23–26]. During the differentiation of Th1 cells, IL-27 has a paracrine effect on IL-12 through the expression of IL-12Rb2 and activation of T-bet [27]. In addition, there is a T-bet-independent pathway in the STAT1 system that works via intercellular adhesion molecule-1 (ICAM-1) activation and helps the differentiation of Th1 cells and secretion of IFN-γ.

Another effect of STAT1 activation is the anti-inflammatory response secondary to GATA3 inhibition. GATA3 is a transcription factor that promotes the differentiation of Th2 cells [28] via downregulating IL-12 subunit receptor. IL-27 was found to be an essential cytokine required for IL-12 receptor. The net effect of IL-27 is the inhibition of Th2 cell differentiation [21, 27, 29, 30].

STAT3 Signaling Pathway

Overall, STAT3 pathway mediates anti-inflammation, cell growth, cell differentiation, and cell cycle transition signal from G1 to S. Following the binding of IL-27 to its receptor, activation of STAT3 promotes differentiation of naive T cells into Treg cells type one, which secret IL-10 cytokine to suppress excessive Th1 pro-inflammatory re-

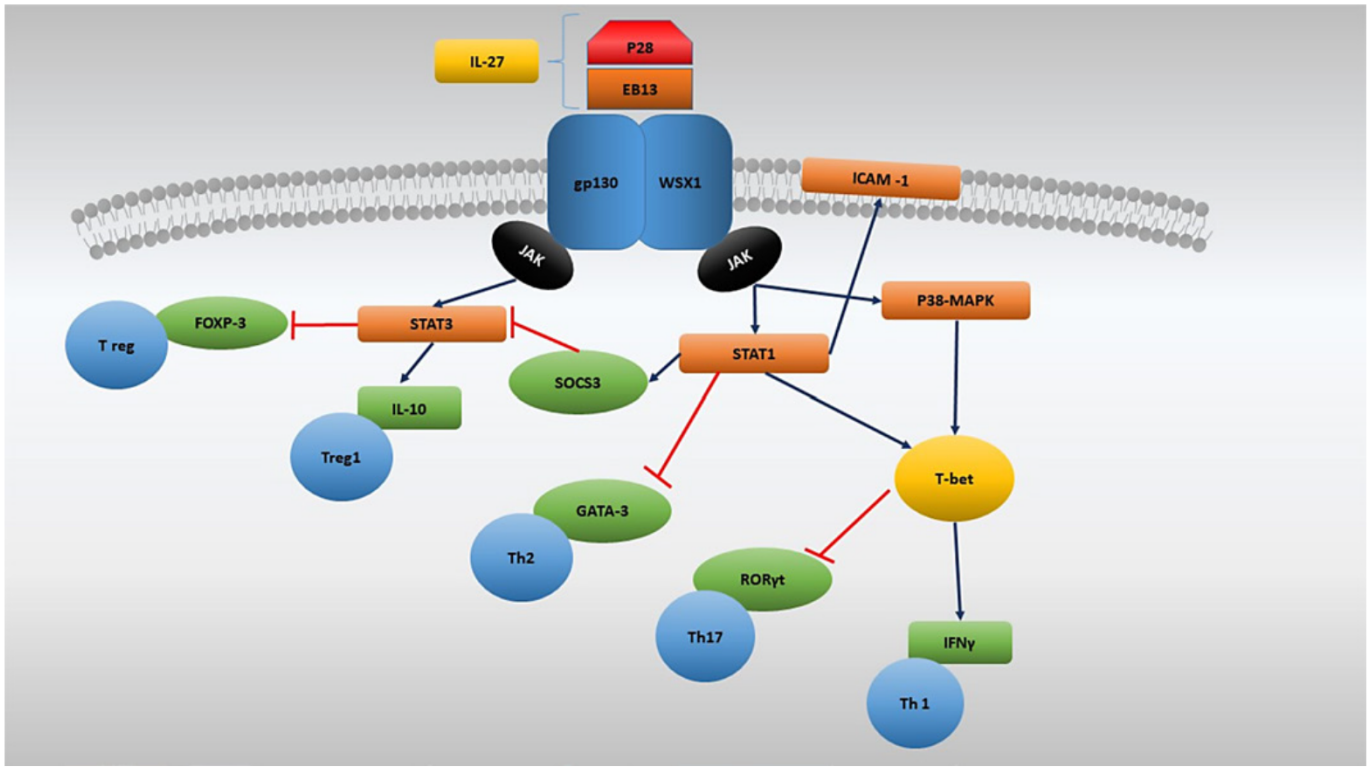

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Fig. 1. IL-27 signaling.

sponses [31]. Besides, STAT3 has an inhibitory effect on FOXP3, which is a factor for the differentiation of Treg cells. Furthermore, suppressor of cytokine signaling 3 (SOCS3), a protein that can be increased by IL-27, has negative effects on STAT3. The net effect of SOCS3 protein is a pro-inflammatory effect [29].

Moreover, some studies have shown that IL-27 mediates endothelial differentiation in cardiac stem cells through STAT3/Pim-1 signaling pathway [32]. Pim is a proto-oncogene that was first described in T-cell lymphomas and functions as a target for gp130-mediated STAT3 signal [33].

IFN-γ promotes the influx of inflammatory cells via increased expression of monocyte chemoattractant protein-1, ICAM-1, and vascular cell adhesion molecule 1 from the ECs [29, 34]. IL-27 alone could also significantly promote the release of chemokine CXCL10 [35].

Effect of IL-27 on Th17 Cell Differentiation

Th17 cells are pro-inflammatory T cells that secret IL-17 and IFN-γ and express IL-23 receptor. The differentiation of Th17 cells requires exposure to IL-1β and IL-23, or IL-6 [36]. As previously mentioned, T-bet inhibits Th17 differentiation via the transcription factor ROR-gamma t [24, 25, 36]. On the other hand, IL-27 shows inhibitory effects on IL-23 [18, 24], which induces IL-17 production from Th17 cells [34]. Several studies demonstrated that in ischemic heart disease, the number of circulating Th17 cells and its related cytokines (IL-17 and IL-23) increase significantly [34, 37]. The determining factors for IL-27 effect on Th17 may depend on the level of IL-27 and the type of cytokines released by Th17 cells. In summary, the role of IL-27 in increasing or suppressing the inflammation may vary among diseases [25, 38].

Effect of IL-27 on NLRP3 Inflammasome and IL-1β

The NLRP3 inflammasome has an important role in inflammation and in atherosclerosis. One of the key components of NLRP3 signaling is the caspase-1 enzyme. Caspase-1 exists in human macrophages in atherosclerotic plaques and activates IL-1β. IL-1β has been known as a central pro-inflammatory cytokine for a long time [1, 39].

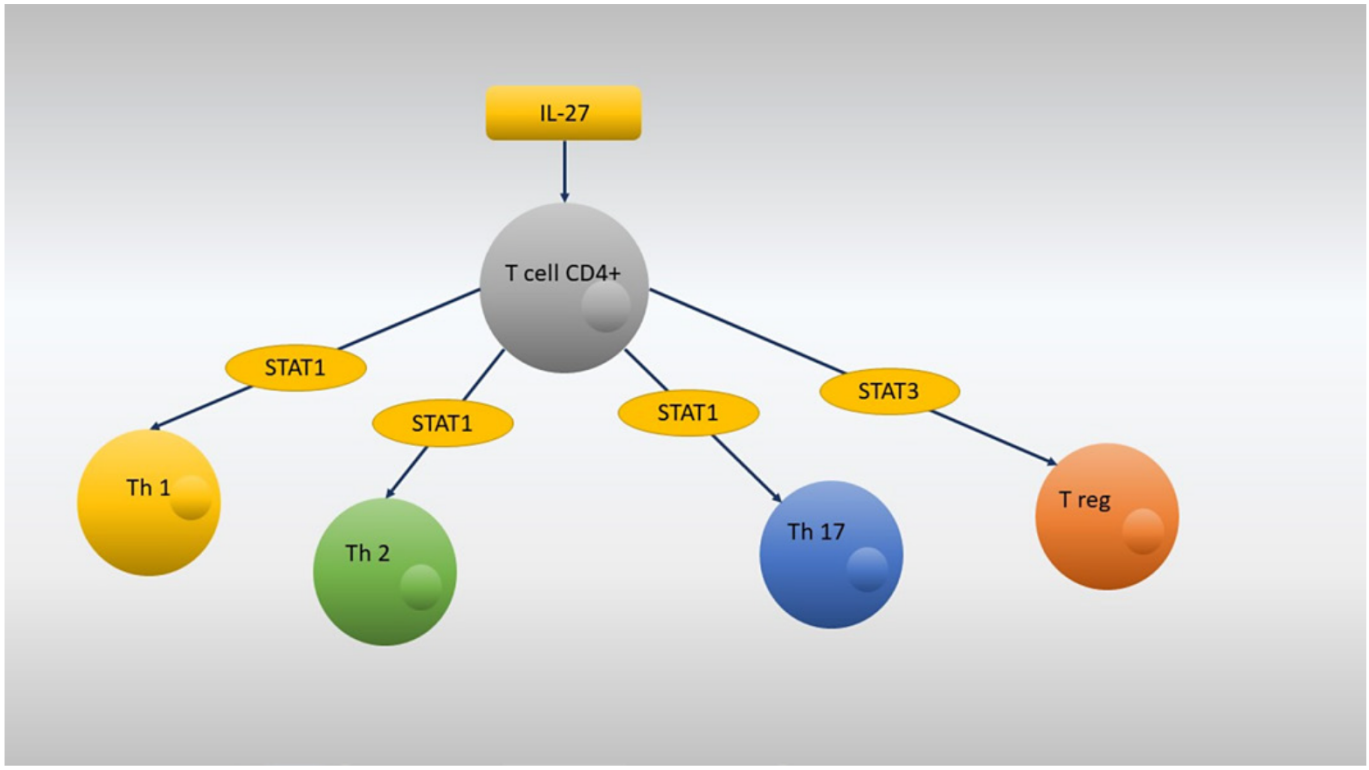

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Fig. 2. IL-27 effects on T cell differentiation.

Activation of NLRP3 inflammasome is regulated via a 2-step pathway, a priming signal and a second signal [40, 41]. Priming is a process through which stressor molecules recognized by TLRs and cytokines, such as TNF-α, induce the activation of nuclear factor-kappa B, thereby increasing the expression of NLRP3 and the production of pro-IL-1β (the biologically inactive precursor of IL-1β). The second signal leads to the formation of NLRP3 inflammasome and IL-1β release [24].

IL-27 has an important pro-inflammatory role in Th1 cells, macrophages [42], and human peripheral blood mononuclear cells (PBMCs) [43], as it increases the level of IL-1β through induction of LPS-ATP via NLRP3-dependent [42] and NLRP3-independent pathways [43]. IL-27 may act as a priming signal for NLRP3 inflammasome activation from an increased pro-IL-1β expression triggered by LPS. Furthermore, IL-27 may serve as the second signal by enhancing ATP effects, caspase-1 activity, and IL-1β induction [42, 43]. IL-27 can also activate TLR4 and induce relocalization of CD14-TLR4, which subsequently results in activation of STAT3-nuclear factor-kappa B pathway and thereby mediating LPS response in monocytes [43, 44]. A study by Gregersen et al. [43] confirmed that IL-27 enhances LPS/ATP-induced IL-1β and LPS-induced TNF release from PBMCs, indicating that IL-27 mediates inflammation via LPS in 2 ways: NLRP3 inflammasome-dependent or independent.

It is noteworthy that in the CANTOS trial that randomized 10,061 patients with a history of myocardial infarction and elevated hsCRP levels (a biomarker for IL-1β-driven inflammation), patients who received canakinumab at the dosage of 150 mg once every 3 months had a 15% lower risk of recurrent myocardial infarction, stroke, or cardiovascular death [45]. These findings support that NLRP3 inflammasome may be a therapeutic target for the secondary prevention of atherosclerosis. In light of the relationship between IL-27 and inflammation induced by LPS, it is plausible to speculate that IL-27 may be a potential marker for atherosclerosis.

IL-27 and Atherosclerosis

In vitro Studies

Several in vitro studies on human and mice cell cultures have suggested mechanisms through which IL-27 may be able to affect atherosclerosis (Table 1). In 2012, Jin et al. [46] examined the association of IL-27 and

Table 1. In vitro studies

Author	Cell culture and variables	Findings
Jin et al. [46]	Monocyte-derived DCs	Ox-LDL dose-dependently enhanced secretion of IL-27 from DCs
Fu et al. [47]	Cell culture of foam cells	IL-27 decreases lipid content inside THP-1 macrophage-derived foam cells by:
		increasing cholesterol efflux to THP-1 cells
		inducing ABCA1 expression through the JAK2-STAT3 signaling pathway
Phan et al. [52]	Cardiomyocyte-like H9c2 cells culture	IL-27 decreases cell injury caused by high glucose, high salt, or cholesterol alone
		GSC decreases the expression of gp130 of IL-27 receptor but does not have any effect on the expression of WSX-1 of IL-27 receptor
		IL-27 does not have any effect on the expression of gp130 and WSX-1 of IL-27 receptor
		IL-27 activates STAT3 signaling and reduces cell injury by protecting cells from cytochrome c activation
		IL-27 does not have any effect on LDH release
		Stattic, a selective STAT3 inhibitor, reduces STAT3 activity and cardioprotective feature of IL-27
Tanaka et al. [32]	Cardiac Sca-1+ cells from wild type C57BL/6 mice	IL-27 enhances the expression of the endothelial marker genes, such as VE-cadherin and CD31, which leads to endothelial differentiation in cardiac Sca-1+ cells
		IL-27 dose-dependently upregulated the expression of Pim-1 by phosphorylation of STAT3
		Dominant negative Pim-1 inhibits endothelial differentiation in cardiac Sca-1+ cells by IL-27
Qiu et al. [35]	HCAECs	WSX-1 and gp130 mRNA of IL-27 receptor are expressed in HCAECs
		The combination of IL-27 and TNF-α significantly increases expression of ICAM-1, VCAM-1, IL-6, CCL5, and CXCL10 in HCAECs, which is suppressed by treatment with neutralizing monoclonal antibodies against the TNFRII
		IL-27 does not have any effect on the IFN-c-mediated upregulation of ICAM-1
		JNK inhibitor, p38 MAPK inhibitor, and NF-κB signaling pathways suppress the release of IL-6 from HCAECs
Gregersen et al. [43]	Human monocytic cell line THP-1, primary monocytes, and PBMCs	IL-27 increases release of IL-1β from monocytes through NLRP3 expression
		IL-27 stimulates IL-1β release in LPS/ATP exposed THP-1 monocytes
		IL-27 upregulates LPS signaling in monocytes
		IL-27 enhances STAT1 and STAT3 pathways in THP-1 monocytes
		IL-27 increases inflammatory responses in PBMCs through inflammasome-dependent and independent inflammatory effects
		IL-27 release in PBMCs is not increased following LPS or LPS/ATP activation
		NLRP3 inflammasome components are upregulated in carotid atherosclerotic plaques
		IL-1β and NLRP3 expression in carotid artery plaque tissue are positively correlated with IL-27r

CCL5, chemokine (C-C motif) ligand 5; CXCL10, C-X-C motif chemokine 10; DCs, dendritic cells; gp130, glycoprotein 130; GSC, high glucose, high salt, and cholesterol combination; HCAEC, human coronary artery endothelial cells; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; JNK, Jun N-terminal kinase; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain containing 3; ox-LDL, oxidized low-density lipoprotein; PBMC, peripheral blood mononuclear cell; Pim-1, proto-oncogene serine/threonine-protein kinase; Sca-1+, stem cells antigen-1; STAT, signal transducer and activator of transcription; THP-1, human monocytic cell; TNF-α, tumor necrosis factor alpha; TNFRII, tumor necrosis factor alpha type II; VCAM-1, vascular cell adhesion molecule 1.

oxidized low-density lipoprotein (ox-LDL) using monocyte-derived DCs. They found that ox-LDL stimulates DCs by upregulating the mRNA expression of both IL-27 subunits (p28 and EBI3) in a dose-dependent manner.

Another study in 2014 by Fu et al. [47] showed that IL-27 reduced the accumulation of lipids in Th1 cells and macrophages. It was revealed that IL-27 increased ATP-binding cassette transporter A1 (ABCA1) expression in Th1 cells via STAT3 pathway and subsequently promoted cellular cholesterol efflux. ABCA1 is primarily expressed on macrophages and has an important role in the control of cholesterol efflux [47–49]. Several other studies have reported upregulation of ABCA1 via STAT3 pathways [50, 51].

Phan et al. [52] suggested that pretreatment with IL-27 may have a cardioprotective effect in high glucose, salt, and cholesterol environment using cardiomyocyte-like (H9c2 cells) cell culture. They showed that H9c2 cells expressed mRNA for both IL-27 subunits, gp130 and WSX-1. In addition, IL-27 binding to its receptor on the H9c2 cells induced STAT3 activation and protected cells from cytochrome c activation and subsequent cell damage. Moreover, they found that the potential cardioprotective role of IL-27 could be inhibited by the STAT3 inhibitors.

In 2015, Tanaka et al. [32] evaluated the effect of IL-12 family cytokines on the trans-differentiation of cardiac Sca-1+ cells into cardiac cells. It was concluded that (1) IL-27 receptor a (IL-27Ra) was expressed in the cardiac Sca-1+ cells; (2) IL-27 expression was elevated in murine hearts in cardiac injury models; (3) stimulation of IL-27 for 14 days led to expression of the EC marker genes via phosphorylation of STAT3; and (4) IL-27 upregulated the expression of Pim-1, but the overexpression of dominant negative STAT3 inhibited the increase of Pim-1 by IL-27. As the net effect, the results suggest a neovascularization role for IL-27 via induction of the EC differentiation in cardiac stem cells through the STAT3/Pim-1 signaling pathway.

In 2016, Qiu et al. [35] investigated the potential role of IL-27 in vascular inflammation in a study on human coronary artery ECs. The authors found that

1. mRNAs of IL-27 receptor subunits (WSX-1 and gp130) were upregulated in human coronary artery ECs.
2. IL-27 alone may significantly induce CXCL10 release, and this effect can be augmented in the presence of TNF-α.
3. IL-27 significantly increased the TNF-α-mediated cell expression of ICAM-1, vascular cell adhesion molecule 1, IL-6, and chemokines CCL5 and CXCL10.
4. IL-27 could enhance the TNF-α-mediated activation of human coronary artery endothelial cells via the activation of the p38 MAPK, JNK, and NF-κB pathways.

CXCL10 is a chemokine that increases T cell adhesion into ECs [53]. It has been shown that CXCL10 levels positively correlate with restenosis after percutaneous coronary interventions [54]. The main role of CXCL10 in atherosclerotic lesions may be modulating the local balance between the effector and regulatory immune system through the induction of Treg cells in the aorta [55].

In 2017, Gregersen et al. [43] studied the in vitro effect of IL-27 on human Th1 cells, primary monocytes, and PBMCs. IL-27 was shown to increase NLRP3-dependent release of IL-1β via LPS signaling in a dose-dependent manner. In PBMCs, IL-27 activated the NLRP3 inflammasome in both first and second signal pathways. Furthermore, the expression of IL-1β and NLRP3 in carotid plaques was increased. These results suggest an inflammatory effect for IL-27 in atherosclerosis.

Animal Studies

The results from animal studies are summarized in Table 2. In a study by Koltsova et al. [56], atherosclerosis-prone $Ldlr^{-/-}$ mice transplanted with $Il27ra^{-/-}$ bone marrow and were fed Western diet for 16 weeks showed an increase in the size of the atherosclerotic lesion. IL-27R deficiency was found to result in atherosclerosis development through an increase in the accumulation of T cells in the aorta of $Ldlr^{-/-}$ mice. Also, ablation of IL-27 receptor induced Th17 activation and release of IL-17A, IL-6, and TNF in the atherosclerotic aortas, followed by an increased expression of various chemokines such as CCL2. Upregulation of CCL2 was demonstrated to mediate the increased accumulation of CD11b+ CD11c+ inflammatory macrophages and DCs in the aorta. Thus, confirming the hypothesis that IL-27 has anti-inflammatory actions.

In 2013, Hirase et al. [57] studied the effect of recombinant IL-27 three times weekly on $Ldlr^{-/-}$ mice fed with high-cholesterol diet over 16 weeks. Mice lacking the IL-27 receptor were found to be more susceptible to atherosclerosis due to macrophage activation in arterial walls. Additionally, IL-27 treatment leads to decreased lipid accumulation in the atherosclerotic plaques and inhibited foam cell formation. As a result, it was suggested that IL-27 treatment may inhibit atherosclerotic lesion development.

In 2015, Ma et al. [58] examined the effects of IL-27 on rat hearts after 40 min of coronary ligation for 7 days. The levels of IL-27 receptor subunit gp130 mRNA but not subunit WSX-1 mRNA decreased in post-ischemic hearts.

Table 2. Animal studies

Author	Characteristics	Findings
Koltsova et al. [56]	Atherosclerosis-prone $Ldlr^{-/-}$ mice transplanted with $Il27ra^{-/-}$ bone marrow following 16 weeks of Western diet	IL-27R deficiency causes atherosclerosis by increasing T cells in the aorta of $Ldlr^{-/-}$ mice
		Blocking IL27r signaling pathway leads to enhancement of Th17 immune response in $Ldlr^{-/-}$ atherosclerotic mice
		Blocking IL27r signaling pathway leads to decrease in immunosuppressive Treg and Th1 cells in peripheral lymphoid organs in $Ldlr^{-/-}$ atherosclerotic mice
		IL27ra deficiency causes increased production of IL-17 and TNF, which leads to increase of various chemokines in mouse aortas, including CCL2
		CCL2 from IL-17 increases accumulation of CD11b + CD11c + inflammatory macrophages and DCs in aorta
Hirase et al. [57]	$Ldlr^{-/-}$ mice following 16 weeks of high-cholesterol diet	Mice lacking IL-27 receptors are more susceptible to atherosclerosis due to macrophage activation in arterial walls than wild type
		There is no difference between Ly6Chi monocytes levels in wild-type mice and mice lacking IL-27 or IL-27 receptor
		IL-27 treatment decreases lipid accumulation in the atherosclerotic plaques and inhibits foam cell formation
Ma et al. [58]	Rat hearts following 40 min of coronary ligation and release for 7 days	IL-27 is upregulated in post-ischemic hearts
		Expression of gp130 and WSX-1 mRNA
		IL-27 protects neonatal cardiomyocytes against SH and increases STAT3 activity
		IL-27 protects H9c2 cells against SH-mediated cell damage and activates STAT3
		Blocking gp130 abolishes the effects of IL-27
		The gp130-neutralizing antibody attenuates IL-27-mediated STAT3 activation
		IL-27 protects hearts against acute IR in an ex vivo perfused model
Peshkova et al. [59]	$Apoe^{-/-}$ mice	$Apoe^{-/-}$ mice or $Apoe^{-/-}$ $Il27ra^{-/-}$ mice have larger atherosclerotic lesions compared to control group
		Production of pro-inflammatory cytokines is higher in IL-27R-deficient mice
		IL-27R signaling decrease atherosclerosis development in $Apoe^{-/-}$ mice
		Chemokines and adhesion molecules are increased in $Apoe^{-/-}$ $Il27ra^{-/-}$ mice
		IL-27R deficiency increases accumulation of immune cells in the aorta

Apoe, apolipoprotein E; CCL2, chemokine ligand 2; DCs, dendritic cells; gp130, glycoprotein 130; IL, interleukin; IL-27R, interleukin 27 receptor; LDLr, low-density lipoprotein receptor-negative; STAT3, signal transducer and activator of transcription 3; Th1, T helper 1; Th17, T helper 17; TNF, tumor necrosis factor; Treg, T regulatory.

It was concluded that during myocardial recovery, increased IL-27 production may occur in order to compensate downregulation of its receptor. Moreover, IL-27 administration 5 min before reperfusion appeared to protect the myocardium against reperfusion injury and improve cardiomyocyte recovery through the STAT3 signaling.

In another study on $Apoe^{-/-}$ mice, Peshkova et al. [59] showed that IL-27R suppressed atherosclerosis development. Moreover, deficiency of the IL-27 receptor led to the accumulation of immune cell in the aorta, activation of myeloid cells with increased local antigen presentation, and expression of pro-inflammatory cytokines.

Human Studies

The role of IL-27 in atherosclerosis in humans has been investigated in several studies (Table 3). Liu et al. [60] investigated the serum levels of IL-27 and other risk factors in 264 patients admitted for coronary angiography based on clinical symptoms. They showed that serum levels of IL-27, NT-proBNP, hsCRP, myeloperoxidase, and creatine kinase-muscle/brain were significantly high-

Table 3. Human studies

Author	*N*	Design	Population	Findings
Liu et al. [60]	264	Case-control	264 hospitalized patients who underwent coronary angiography following chest pain	Serum levels of IL-27, NT-proBNP, hsCRP, MPO, and CK-MB were significantly higher in positive CAD compared to control group For IL-27: OR = 0.074 (95% CI = 0.007–0.820)
Jafarzadeh et al. [34]	180	Case-control	60 patients with AMI, 60 patients with UAP, and 60 healthy controls	IL-27 level is higher in patients with AMI and UAP compared to control group IL-27 is higher in patients with certain risk factors (including HTN, DM, dyslipidemia, and smoking) There was no significant difference between serum IL-27 level in patients with AMI or UAP
Jin et al. [46]	165	Cohort	Patients who underwent coronary angiography following chest discomfort	IL-27 levels are higher in patients with CAD than in control group IL-27 levels are higher in AMI and UAP than in SAP Ox-LDL levels are higher in AMI than in UAP, SAP, or control group. However, levels of ox-LDL are higher in UAP or SAP group than in control group Gensini score is higher in AMI than in patients with UAP, SAP, or control group IL-27 levels have positive correlation with ox-LDL and Gensini score ($p < 0.01$) IL-27 levels have positive correlation with the severity of coronary artery stenosis In vitro: ox-LDL dose-dependently enhanced secretion of IL-27 from DCs
Lin et al. [61]	208	Case-control	Patients who underwent coronary angiography following chest discomfort into 4 groups 43 SAP patients 62 UAP patients 56 AMI patients 47 chest pain syndrome patients as a control group	IL-27 levels are higher in AMI and UAP groups than in SAP and control groups No differences between IL-27 levels in control group and the healthy students No difference in IL-27 levels following treatment with aspirin and clopidogrel IL-27 levels have weak negative correlation with LVEF in CAD patients
Gregersen et al. [43]	140	Cohort	Patients with ≥70% internal carotid stenosis underwent endarterectomy or carotid angioplasty with stenting. Tissue samples are from atherosclerotic carotid plaques during carotid endarterectomy. In vitro experiments: human monocytic cell line THP-1, primary monocytes, and PBMCs	IL-27 levels are higher in patients with carotid atherosclerotic disease compared to healthy control group IL-27R components including p28, EBI3, and IL-27RA are higher in carotid atherosclerotic plaques In vitro results: IL-27 increases release of IL-1β from monocytes through NLRP3 expression IL-27 stimulates IL-1β release in LPS/ATP exposed THP-1 monocytes IL-27 upregulates LPS signaling in monocytes IL-27 enhances STAT1 and STAT3 pathways in THP-1 monocytes IL-27 increases inflammatory responses in PBMCs through inflammasome dependent and independent inflammatory effects IL-27 release in PBMCs is not increased following LPS or LPS/ATP activation NLRP3 inflammasome components are upregulated in carotid atherosclerotic plaques IL-1β and NLRP3 expression in carotid artery plaque tissue are positively correlated with IL-27r
Si et al. [63]	81	Case-control	81 children with KD 80 children with an acute febrile infectious disease and 90 healthy children were selected	Serum levels of IL-27, IL-6, IL-1β, and TNF-a were significantly higher in the KD patients than in control groups No significant differences between group of KD and controls, in age, sex, WBC, platelet, RBC, HB, CRP, ESR, PCT, IL-17A, and IL-10 Levels of WBC, CRP, PCT, IL-10, IL-17A, IL-6, IL-1β, and TNF-α levels had positive correlation with IL-27 in patients with KD ($r = 0.185$, $p = 0.037$; $r = 0.291$, $p = 0.000$; $r = 0.400$, $p = 0.000$; $r = 0.454$, $p = 0.000$; $r = 0.618$, $p = 0.000$; $r = 0.263$, $p = 0.044$; $r = -0.130$, $p = 0.401$; $r = 0.372$, $p = 0.013$, respectively)

Table 3 (continued)

Author	*N*	Design	Population	Findings
Miura et al. [62]	274	Cross-sectional	274 consecutive patients who underwent elective coronary angiography for suspected CAD 177 had CAD and 177 had stable ACS	Higher IL-27 and hsCRP in CAD group Independent risk factors for CAD: IL-27 level >0.25 ng/mL (OR = 1.83, 95% CI: 1.01–3.32, $p < 0.05$) and hsCRP level >1.0 mg/L (OR = 3.40, 95% CI: 1.78–6.50, $p < 0.001$) IL-27 was not an independent risk factor for ACS, but high hsCRP level was a risk factor for ACS (OR = 3.84, 95% CI: 1.57–9.38, $p < 0.005$)
Posadas-Sánchez et al. [8]	1,162	Cohort	Four IL-27p28 gene polymorphisms in 1,162 premature CAD cases and 1,107 control IL-27 levels in 450 controls and 450 cases	IL-27 plasma levels significantly higher in cases than in controls IL-27p28 gene polymorphisms are associated with premature CAD and with some metabolic parameters IL-27 plasma levels were not associated with IL-27p28 polymorphisms

AMI, acute myocardial infarction; CAD, coronary artery disease; CK-MB, creatine kinase-muscle/brain; DC, dendritic cell; DM, diabetes mellitus; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; IL, interleukin; KD, Kawasaki disease; LVEF, left ventricular ejection fraction; MPO, myeloperoxidase; NALP3, NACHT, LRR, and PYD domain-containing protein 3; NT-proBNP, N-terminal pro b-type natriuretic peptide; ox-LDL, oxidized low-density lipoprotein; PBMC, peripheral blood mononuclear cells; SAP, stable angina pectoris; STAT, signal transducer and activator of transcription; THP-1, human monocytic cell; TNF, tumor necrosis factor; UAP, unstable angina pectoris.

er in patients with coronary artery disease (CAD) compared with no CAD group.

Jafarzadeh et al. [34] investigated the serum levels of IL-27 in 60 patients with acute myocardial infarction (AMI), 60 patients with unstable angina (UA), and 60 healthy controls. While there was no significant difference between AMI and UA groups, the IL-27 levels in AMI and UA patients were both higher than those in the healthy controls.

In 2012, in a cohort study by Jin et al. [46], 165 patients with the clinical diagnosis of CAD were found to have elevated serum levels of IL-27, ox-LDL, and Gensini score compared with the control group. Also, there was a positive correlation of IL-27 levels with ox-LDL and Gensini score. Furthermore, they investigated in vitro IL-27 level in response to ox-LDL, and they showed that IL-27 protein and IL-27p28 and EBI3 mRNA were expressed in a dose-dependent manner in response to ox-LDL.

Another case-control study by Lin et al. [61] included a total of 208 patients, among which 43 had stable angina pectoris, 62 had unstable angina pectoris (UAP), and 56 had an AMI. They showed that plasma IL-27 levels significantly increased in the UAP and the AMI group compared with the stable angina pectoris group.

In a cross-sectional study by Miura et al. [62], 274 patients (177 with CAD and 97 without CAD) who underwent elective coronary angiography for suspected CAD were followed for 4 years. Blood samples for plasma levels of IL-27 and hsCRP were obtained. IL-27 and hsCRP levels in patients with CAD were significantly higher than those in the group without CAD. Also, IL-27 levels were not statistically different across the types of CAD (ACS, stable CAD, and CAD), or NSTEMI versus UAP. Greater hsCRP levels were observed in ACS and stable CAD patients versus CAD. Also, among patients with CAD, both IL-27 and hsCRP levels tended to increase with the number of coronary vessels affected by CAD. The correlation with the severity of stenosis and the Gensini score was weak for IL-27 (rs = 0.15 and rs = 0.16, $p < 0.02$) but was significant for hsCRP (rs = 0.35 and rs = 0.31, $p < 0.001$). There was no significant correlation between IL-27 and hsCRP levels. In a multiple logistic regression model, IL-27 and hsCRP were both identified as independent risk factors for CAD (IL-27 > 0.25 ng/mL: OR = 1.83 [95% CI: 1.01–3.32], $p < 0.05$; hsCRP >1.0 mg/L: OR = 3.40 [95% CI: 1.78–6.50], $p < 0.001$). IL-27 was not an independent risk factor for ACS, but the high hsCRP level was a risk factor for ACS (OR = 3.84 [95% CI: 1.57–9.38], $p < 0.005$).

In 2017, a cohort study by Gregersen et al. [43] included 140 patients with more than 70% internal carotid stenosis admitted for endarterectomy or carotid angioplasty with stenting. Plasma levels of IL-27 and expression of IL-27 and IL-27R in plaques were increased in patients with carotid atherosclerosis. In the human monocytic cell line, IL-27 was shown to induce NLRP3-dependent release of IL-1β from monocytes in a dose-dependent manner. Specifically, IL-27 was found to enhance LPS/ATP-induced release of IL-1β and TNF. Furthermore, there

was a strong correlation between the expression of IL-1β and NLRP3 in the carotid atherosclerotic plaques through STAT1 and STAT3 pathways.

In 2017, a case-control study by Si et al. [63] included 81 children with Kawasaki disease (KD), 80 children with an acute febrile infectious disease, and 90 healthy children. Serum levels of IL-27, IL-17A, IL-10, IL-6, IL-1β, and TNF-α were measured. Patients with KD were demonstrated to have higher levels of IL-27, IL-6, IL-1β, and TNF-α than the control groups. Of note, serum levels of IL-27 were positively correlated with WBC, CRP, PCT, IL-10, IL-17A, IL-6, IL-1β, and TNF-α levels among KD patients.

In 2017, Posadas-Sánchez et al. [8] studied 4 IL-27p28 gene polymorphisms in 1,162 premature CAD cases and 1,107 control subjects. IL-27p28 gene polymorphisms were associated with premature CAD and metabolic parameters. IL-27 plasma levels were significantly higher in premature CAD cases than in controls. Also, the authors found that plasma levels of IL-27 were not associated with IL-27p28 polymorphisms in these patients.

In 2020, Ye et al. [64] evaluated the association between IL-12 family in patients with hypertension and its association with carotid atherosclerosis. They included 430 patients in the hypertensive group and 70 patients in the control group. They found that IL-27 was substantially increased in all hypertensive patients compared to the control group. Also, the authors found that IL-27 was related to the development of carotid atherosclerotic plaque in patients with hypertension.

Discussion

IL-27 was first described in 2002 by Pflanz et al. [10] as a member of the IL-12 family. Its structure, receptor, and the signaling pathways have been explored. The biphasic role of IL-27 in inflammation has been suggested in various autoimmune and inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, allergic rhinitis, atrial fibrillation, and ITP [16, 65–68]. In the study of osteoclastogenesis in animal models, Park et al. [69] described an inhibitory effect of IL-27 in association with IFN-γ production, whereas Seita et al. [70] found a hematopoiesis role for IL-27 in the proliferation and differentiation of hematopoietic stem cells.

Atherosclerosis, a type of chronic inflammation, is the most common cause of CAD. In general, pro-inflammatory cytokines and Th1 cells induce progression of atherosclerosis [71], while the anti-inflammatory cytokines and Treg cells have anti-atherogenic effects [1, 72]. Of note, Th2 cells have both pro- and anti-atherogenic properties. Previous studies have identified various inflammatory mediators involved in the progression of atherosclerosis including IL-1, IL-6, IL-18, IL-17, IL-12, and monocyte chemoattractant protein 1 [1, 73–76]. In atherosclerotic plaques, the level of IL-27 is increased and the concentration of its receptor subunits is upregulated [6, 43]. Moreover, human studies have demonstrated that IL-27 levels are high in the patient with positive CAD [46, 60, 62], premature CAD [8], AMI and unstable angina [34], significant internal carotid stenosis [43], and KD [63]. Additionally, in the atherosclerotic plaques, ox-LDL is taken up by macrophages and induces the release of inflammatory products and cytokines [4]. IL-27 levels were positively associated with oxidizing LDL levels based on in vitro studies [46]. Also, in the atherosclerotic setting, in vitro IL-27 induces both pro-inflammatory and anti-inflammatory pathways via STAT1 and STAT3 [43]. In an animal study of IL-27 receptor-deficient mice by Koltsova et al. [56], the production of inflammatory cytokines such as IL-17, IL-6, and TNF was increased in aortas in the absence of IL-27 receptor. Collectively, these suggest evidence for an anti-atherogenic effect of IL-27R signaling in atherosclerosis. Also, other animal studies have confirmed that IL-27-deficient mice are more susceptible to atherosclerosis [57, 59].

On the other hand, other animal studies showed that IL-27 treatment decreases lipid accumulation and therefore inhibits atherosclerotic lesion development [47]. Cardioprotection and regeneration effects of IL-27, via activation of STAT3 pathways, Pim-1, and ABCA1 have been found in vitro studies [32, 47, 52, 77] and post-MI animal models [58].

Several studies discussed above have shown a regulatory role of IL-27 via STAT3 system. Besides, considering peaked levels of IL-27 after MI and regenerative properties of IL-27 on cardiac resident stem cells, it may be suggested that IL-27 is associated with tissue repair and the termination of inflammatory phase in atherosclerosis [32]. Accordingly, in the rat study by Ma et al. [58], IL-27 injection could prevent reperfusion injury. During myocardial recovery, increased IL-27 production could have occurred in order to compensate downregulation of its receptor.

Peak expression of IL-27 levels is 7–14 days after MI [32], whereas the IL-6 family cytokines increase in the hearts immediately after MI [78]. Also, studies have demonstrated an increase in IL-27 levels during MI and UA. Taken together, it can be suggested that IL-27 levels will increase after a cardiovascular event and upregulate its

receptor, leading to repair and regeneration, compensating the inflammatory responses of other mediators. The heterogeneous effects of IL-27 seem to be determined by the local environment, activated mediators, and cell types. The exact immunomodulatory effects of IL-27 on human atherosclerosis need to be investigated by future studies especially in vitro animal models and human clinical setting studies.

Conclusion

IL-27 is a pleiotropic cytokine that can have immunomodulatory effects on atherosclerosis via interaction with various T cell subsets through STAT1/STAT3 pathways. Anti-atherogenic role of this cytokine in the animal models has been observed, and increased blood levels of IL-27 have been shown in several human studies of atherosclerosis. Animal studies have confirmed the anti-inflammatory actions of IL-27; yet, studies on human subjects associate circulating IL-27 levels with CAD. This depicts that IL-27 can have both pro- and anti-atherogenic effects. Thus, the definitive role of IL-27 in clinical settings should be further investigated.

Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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