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The role of interleukin-18 in the development and progression of atherosclerosis

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Atherosclerosis (AS) as a chronic inflammatory disorder of the cardiovascular system, is one of the leading cause of ischemic heart disease, stroke and peripheral vascular disease. There is growing evidence on the role of innate and adaptive immunity in the pathogenesis of atherosclerosis. Interleukin-18 is one of the novel proinflammatory cytokines involved in the atherogenesis, atherosclerotic plaque instability and plaque rupture. In this review, we overview the findings of the preclinical and clinical studies about the role and mechanism of action of IL-18 in the pathogenesis of AS, which could offer novel prognostic and therapeutic approaches.

Keywords: matrix metalloproteases; acute coronary syndromes; vascular smooth muscle cells; Polymorphism

Introduction

Atherosclerosis (AS) is a chronic inflammatory disease resulting from a complex interaction of multiple biological pathways leading to the formation and progression of lipid-laden plaques in the wall of the arteries. There is increasing evidence on the crucial role of innate and adaptive immunity underlying the pathophysiology of AS [1, 2]. Interleukin-18 (IL-18), which was initially known as an interferon (IFN)-γ–inducing factor [3], is one of the novel the T helper 1 (Th1) immune response and promotes the regulation of matrix metalloproteases (MMP) [4, 5] which is involved in atherosclerotic plaque instability and vulnerability. In this review, we overview the findings of various preclinical and clinical studies about the significant role and mechanism of action of IL-18 in the pathogenesis of AS which could offer potential novel prognostic markers and therapeutic approaches in patients with atherosclerotic conditions.

Atherosclerosis

The cholesterol carrying low-density lipoprotein (LDL) particles, particularly oxidized LDL (oxLDL) accumulates in the extracellular matrix of the intima of medium/large-sized muscular arteries and make them vulnerable to deleterious oxidative and enzymatic processes [6]. Phospholipids secreted from the LDL stimulate endothelial cells (EC) to express leukocyte inducible adhesion molecules, chemokines and cytokines [7] which in turn activates several types of cells including ECs, smooth muscle cells (SMCs), monocyte-derived macrophages (MDM) and T cells [8, 9]. Most of these T cells in the lesions recognize LDL as a local antigen belonging to the Th1 subtype and release proinflammatory cytokines contributing to local inflammation. Once adherent to the endothelial surface, leukocytes constitutively influx beneath the EC lining of the artery in response to various chemokines such as monocyte chemo-attractant protein-1(MCP-1),

regulated upon activation, normal T cell expressed and secreted (RANTES) and fractalkine [10]. MDM overexpress pattern recognition receptors which are scavenger receptors and toll-like receptors (TLR). Scavenger receptors mediate uptake of oxLDL, resulting in the formation of foam-cells.

On the other hand, TLR triggers a cascade of inflammatory molecules, secretion of vasoactive agents like nitric oxide (NO), endothelins, proteases and leukotrienes. The agents mentioned above cause distension of the intima, tissue remodeling, growth of fatty streak to larger fibro-fatty lesions [11] which subsequently become progressive plaques with a necrotic core covered by a fibrous cap which stabilizes dangerous plaques. The process of plaque development occurs together with the evolution of calcification to constitute fibrocalcific plaques which can be eroded during the time and can become fragile and eventually vulnerable to disruption. When the thick capped fibroatheromas ruptures, the necrotic core comes into physical contact with the blood flowing through the lumen launching the coagulation cascade which happens in response to the exposing of lipids and tissue factors existed in the core [12]. The resulting blood clot (thrombus) can obstruct the blood vessel lumen, leading to a significant decrement in the myocardial perfusion resulting in the development of acute coronary syndromes (ACS) [13].

Interleukin-18

Cytokines provide a framework for signaling proteins essential for the communication between cells [14]. The inflammation and the predominant Th1 cytokine pattern of acquired immune system responses are crucial in the pathogenesis of AS [15].

The IL-18 gene is located at the chr. 11q22.2 which belongs to the IL-1 superfamily cluster [16]. IL-18 is a 24-kDa non-glycosylated polypeptide and proinflammatory cytokine without

a classical signal peptide [3, 17]. Human IL-18 and IL-1β have 15% sequence homology have signaling pathways [18, 19]. IL-18 is produced as an inactive propeptide which undergoes proteolytic cleavage via the enzyme caspase-1 or cysteine proteinase IL-1β-converting enzyme to create a mature, biologically active, 18-kDa molecule (Figure 1) [17, 20]. However, a recent theoretical study showed that IL-18 is generated most often by caspase 1-independent pathway rather than a caspase 1-dependent pathway. Moreover, this pathway may be related to caspase 8 activity [21]. IL-18 is primarily expressed in Kupffer cells, ECs, keratinocytes, adipocytes, intestinal ECs, activated macrophages, dendritic cells (DCs) and human peripheral blood mononuclear cells or by the first line of the immune response in the central nervous system (CNS) [22, 23]. The IL-18 heterodimeric receptor complex composes of two receptor chains namely ligand-binding IL-18R chain (IL-18Ra) as well as signal-transducing IL-18R chain (IL-18Rb) [24]. These chains are essential for the functional signal transduction which initiates via the recruitment of the cytosolic adaptor molecule, myeloid differentiation 88 (MyD88), to the IL-18 complex and interaction with IL-1R-associated kinases (IRAKs) (Figure 1). Following autophosphorylation of IRAK, it separates from the IL-18 receptor complex and connects with tumor necrosis factor receptor-associated factor 6 (TRAF6) which motivates the sequential induction of NIK, IKK, and eventually NF-κB, p38 and c-Jun N-terminal protein kinase family of mitogen-activated protein kinases (JNK MAPKs) [25, 26].

There is an endogenous antagonist of IL-18 named IL-18 binding protein (IL-18BP) which binds to IL-18 and neutralize the activity of IL-18 as well as inhibits the IFN-γ production, leading to a decreased Th1 response. IL-18 can regulate the expression and production of proinflammatory cytokines, CC and CXC chemokines, adhesion molecules, Fas ligand (FasL) and tumor necrosis factor (TNF) receptor I (TNFR-I) [27-29]. Furthermore, IL-18

induced the expression of matrix-degrading enzymes, such as interstitial collagenases are responsible for the degradation of fibrillar collagen such as collagen type I and III, the main structure's biomechanical strength-bearing molecule of the plaque's fibrous cap [30].

Role of IL-18 in atherosclerosis

IL-18 as a proatherogenic, pleiotropic and proinflammatory cytokine which stimulates the production of TNF-α [31], which in turn increases the synthesis of IL-6 [32] and C-reactive protein (CRP) [33]. TNF can induce macrophages, T cells and other components of the atherosclerotic plaque, and thus accelerate the inflammatory response [34]. Circulating CRP by itself could lead to the worsening of the inflammatory cascade in human ECs along with the over-expression of IL-18 [35]. IL-18 contributes in AS via multiple potential mechanisms which are summarized in Table 1 [36]. Disruption of IL-18 activity decreases AS in mice [37].

IL-18 by stimulation of IFN-γ generation promotes the inflammatory responses and may cause thinning of the fibrous cap leading to vulnerable plaques which are susceptible to rupture [38]. IL-18 induces the amplification of MMP-1, -9, and -13 [4] within monocytes and vascular cells, that might play a role in plaque fragility [4]. IL-18 may worsen the pro-inflammatory cascade in the myocardium via up-regulation of EC adhesion molecules and generation of proinflammatory molecules associated with a reduction in myocardial contractility [39] and cardiomyocytes apoptosis [40, 41], such as TNF-α, IL-1β, IL-8, and inducible nitric oxide synthase (iNOs) [42]. IL-18 mRNA and protein are highly expressed by macrophages of atherosclerotic plaques; while IL-18R is regulated via macrophages, vascular SMCs (VSMCs) and ECs within atheromas [4]. Furthermore, over mRNA amplification of

IL-18 have been observed in unstable compared to stable atherosclerotic plaques, suggesting IL-18 render lesions susceptible to rupture and plaque instability [43]. Supporting evidence showed the overexpression of IL-18 in unstable coronary plaques obtained via directional coronary atherectomy from patients with unstable or stable angina[44].

It has been shown that serum levels of IL-18 positively correlated with brachial-ankle pulse wave velocity (baPWV) and carotid intima-media thickness (IMT) as indicators of systemic AS [45, 46].

Experimental evidence from in vivo studies

The homozygous apolipoprotein E–deficient (*apoE−/−*) mice is a particularly accepted AS experimental mouse model since it can spontaneously develop hypercholesterolemia and AS on a standard chow diet [47]. Experimental evidence demonstrated that the expression of IL-18 was significantly higher in the *apoE−/−* mice group compared to the control group [48]. Recently, Tang and co-researchers examined the association between the IL-18 concentrations and atherosclerotic plaques in *apoE−/−* mice. Results showed that the levels of IL-18 also was significantly higher in the stable and unstable plaque groups compared to the non-plaque group ($p<0.05$). In addition, IL-18 in the stable plaque group was remarkably reduced compared to the unstable plaque group [48].

It has been reported that IL-18−/−×apoE−/− mice have significantly reduced AS, local IFN-γ signaling and plaque rapture despite elevated serum cholesterol and triglyceride levels. These results demonstrate that IL-18 is as a proatherogenic cytokine which promotes the progression of IFN-γ secreting Th1 cells [49]. Suppression of the IL-18/Th1/IFN-γ pathway could be a promising approach for the AS therapy [50]. However, in IL-18−/−×apoE−/−

mice, reduced lesion size and lesion content were found to be independent of cholesterol, TG and IFN-γ release [49].

IL-18 administration increased the blood cholesterol and lipoprotein-cholesterol distribution in the mouse as well as activated inflammatory pathway via binding with IL-18Ra through NF-kB which plays a vital role in the progression and atherosclerotic plaques rupture in *apoE*−/− mice [51]. Additionally, blocking NF-kB inhibits the IL-18 signaling via down-expression of IL-18, IL-18Ra, scavenger receptor CD36, and MMP-9, thereby reducing inflammation and stabilises the plaque fragility by over-expression of liver X receptor alpha (LXR-α). LXR-α has an anti-inflammatory property and antagonizes the uptake of oxLDL and foam cell development, thereby inhibiting atheroma formation [51].

Wang et al. demonstrated that loss of the IL-18R does not impact on AS process in *apoE*−/− mice [52]. IL-18 binds with the transporter ion protein, Na-Cl co-transporter (NCC), which is high-regulated mainly in the kidneys and also atherosclerotic plaques [53] where it colocalizes with IL-18R. In *apoE*−/− mice, a combination of the absence of IL-18R and NCC shields mice from the development of atherosclerotic plaque. This study demonstrates that IL-18R and NCC in combination contribute to the atherogenesis and colocalize in VSMCs, ECs and macrophages. IL18-mediated NCC induction may also trigger downstream cell signaling through enhanced cell volume and alteration of intracellular Cl^- levels [54, 55].

Increased IL-18 expression results in a 44% reduction of intimal collagen and a 41% cap-to-core ratio ($p=0.002$) and eventually vulnerable plaque morphology in the *apoE*−/− mice. However, IL-18 did not influence the expression of collagen synthesis-associated genes. It was observed to increase the collagenolytic action of VSMCs *in vitro*, suggesting that the fewer collagen quantity is as a result of matrix degradation rather than reduced

synthesis. This evidence shed light on the role of IL-18 in the integration of extracellular matrix and in plaque stabilization, suggesting it a promising approach for targeted therapy [56].

It has been demonstrated that inhibiting IL-18 signaling in a mouse model of AS through IL-18BP administration significantly reduced plaque development and instability [57]. Also, in vivo suppression of IL-18 function by IL-18BP in mice induces tissue neovascularization after ischemic injury. Enhancement of post-ischemic neovascularization is associated with over-expression of VEGF and higher Akt phosphorylation. This study suggests that inhibition of IL-18 is a promising approach for the management of ischemic diseases [58].

Role of inflammatory cytokines

IL-18 promotes AS via stimulating an inflammatory response in an IFN-γ–dependent manner [59]. IL-18 by itself is a less potent inducer of IFN-γ release. IL-18 activities are synergistic with other co-inducers, especially IL-12, to trigger the secretion of IFN-γ generation via macrophages [60], T cells [61, 62], and NK cells [63]. The IL-12–IL-18–T-bet–IFN-γ cascade is a strong proinflammatory stimulus which enhance promotes and increases lesion development, and AS [64]. In addition, macrophages, NK cells and VSMC were the sources for the secretion of IFN-γ after the induction of IL-18 without the presence of T cells *in vivo* [65].

Cholesterol promotes AS and stimulates intact rat aortae to generate prostaglandin E2, an intense modulator of IL-23 which extends Th17. Pejnovic and colleagues examined the proatherogenic role for Th17 and whether cholesterol can stimulate the non-canonical Th17 pathway in *apoE*−/− mice with lower Th1 cells if they are received high lipid diet. It was found that Th17 is crucial for the progression to AS. VSMC generate IL-23 which is

important for expansion and activation of Th17 cells to produce IL-17 and IFN-γ. In the absence of IL-18, hypercholesterolemia aggravates AS which is correlated with higher IL-23 secretion with Th17 induction. It implies that in hypercholesterolemia, Th17 synthesis more IFN-γ than Th1 and IL-18 is not essential for the generation of IFN-γ in these lesions[66].

IFN-γ increases the expression of chemokine (C–X–C motif) ligand (CXCL)-16 within lesions in vivo [63]. On the other hand, IFN-γ also promotes the uptake of oxLDL in monocytes and SMCs through the CXCL16 scavenger receptor [50]. Tenger *et al*. reported that after IL-18 administration, a higher IFN-γ level was correlated with a remarkable increase of CXCL16 mRNA transcription in both lesions and spleens of the SCID/*apoE* knockout mice [65]. This indicates that the proatherogenic role of IL-18 could rely on IFN-γ mediated over-expression of CXCL16. Consistently, two studies have recently confirmed that IL-18 can stimulate CXCL16 in SMCs [50, 67].

MMPs have direct or indirect effect on actions of different cytokines which contribute to inflammation and repair processes, such as IFN-γ, TGF-β , IL-1 and TNF-α. Proteolysis of extracellular matrix via MMPs can lead to release of active transforming growth factors (TGF)-β from inactive complexes. The proinflammatory IL-1 and TNF-α activate a spectra of MMPs in vascular cells including MMP-1, -3, -8, and -9[68]. In particular, macrophages expressing pro-inflammatory cytokines can enhance the over-expression of MMPs participating in plaque instability [69]. The extracellular matrix metalloproteinase inducer (EMMPRIN) protein can activate the production of MMPs in fibroblasts, ECs, or cancer cells [83, 84]. EMMPRIN can also induce monocytes and SMCs to secrete MMPs and is implicated in the process of plaque destabilization. In one study IL-18 and EMMPRIN modulate the expression of each other in mononuclear cells.

Co-expression and cross-amplification of monocytic IL-18 and EMMPRIN boost the inflammatory cascade and enhance atherosclerotic lesions and plaque instability by over-expression of MMP-9 [85].

RANTES is a cytokine which selectively chemoattracts T cells, eosinophils, NK cells, and monocytes. The RANTES contributed in initiation of vascular inflammatory cell recruitment endothelial dysfunction, atherosclerotic plaque and neointima formation [70, 71]. RANTES is elevated in myocardial infarction (MI) patients, particularlly those with left ventricular heart failure (LVEF <35%)[72]. RANTES is also preserved in α-granules of the platelets and accumulated on the surface of damaged ECs post platelet activation. RANTES play a major role in this process, in which activated platelets enforce atherogenic recruitment of monocytes, which may aggrevate the atherosclerotic plaque development [73].

IL-6 is a distinctive pleiotropic cytokine presenting either pro- or anti-inflammatory features dependent on the target cell type. This cytokine strongly affects the expansion and induction of T lymphocytes [74]. IL-6 may have both pro- and anti-atherogenic impacts on processes related to formation and progression toward atherosclerosis. Pro-atherogenic impacts were induction of vascular SMC proliferation [75], as well as EC [76] and platelet activation [77], whereas atheroprotective effects encompass decreasing of plasma LDL through over-expression of LDL receptor [78].

IL-1 can enforce its gene amplification in multiple cell types, such as those contributed in atherogenesis. Cells in the atheroma generate IL-1 when encountered to inflammatory stimulus [79]. This cytokine changes the actions of cardiac myocytes beside those of cells in the blood vessel wall. IL-1 disturbs contractile function. IL-1 can promote ischemia-reperfusion injury and extensive cardiac remodeling post-experimental MI [80].

Role of oxidized LDL (oxLDL)

OxLDL which acts by binding several scavenger receptors such as lectin-like oxLDL receptor-1 (LOX-1) is a type II membrane protein which participates in ligand binding [81, 82]. These non-traditional receptors are mainly expressed on ECs, macrophages, monocytes, platelets, cardiomyocytes and VSMCs. LOX-1 is generally undetectable in physiological states, but it is over-expressed when exposed to different proinflammatory redox-sensitive transduction and proatherogenic stimulants and can be activated in vascular endothelial dysfunction [83-85]. Specific cell surface protease cleavages LOX-1 resulting in the release of soluble LOX-1 (sLOX-1) [86]. LOX-1 mRNA is closely associated with plaque instability and rupture [87, 88]. Moreover, it has been found that circulating sLOX-1 levels are increased in ACS and that sLOX-1 can be a potential biomarker for ACS. Interestingly, IL-18 has been found to be one of the stimuli contributing in sLOX-1 release in ACS and ADAM10, a protease belongs to the ADAM superfamily is also implicated in this process[89].

Role of IL-18 in other coronary events

Acute coronary syndrome

Increased levels of IL-18 were initially found in patients with MI [90]. Shortly after that, Mallat and co-workers [43] localized IL-18 in atherosclerotic plaque macrophages and demonstrated over-expression of IL-18R in plaque macrophages and ECs. Atherosclerotic plaque rupture is the reason of at least two out of three acute coronary events and the initiating factor in ACS. Atherosclerotic plaque rupture is closely associated with intracoronary local thrombosis activation and vessel occlusion [91]. The range of ACS varies

from ST-segment elevation myocardial infarction to non–ST-segment elevation myocardial infarction and UA [92].

There is growing evidence that the IL-18 concentrations are not only associated with acute events such as congestive heart failure (CHF), myocardial re-infarction and cardiovascular disease (CVD) death but also associated with long-term mortality in patients with ACS [93]. The plasma concentrations of IL-18 and IL-18BP were significantly elevated in patients with ACS compared to patients with stable angina pectoris and control groups [94].

Serum concentrations of IL-18 were significantly elevated in patients with acute MI compared to unstable angina patients[35]. In another study, among 446 MI patients and 477 normal controls, serum concentrations of IL-18 are increased in those who had previous MI, but revealed no relationship after adjustment for classical confounders (OR=1.07; 95%CI: 0.70–1.62)[95]. Mallat *et al.* reported that plasma levels of IL-18 were significantly elevated in unstable angina and MI groups than stable angina and control groups ($p < 0.01$) [96]. But, circulating IL-18 levels were not significantly different between patients with unstable angina, patients with non-Q wave MI or Q wave MI ($P>0.05$) [96].

Indeed, levels of IL-18 and ratio of IL-18/IL-18BP were increased in patients who had recent MI in comparison with those who did not, suggesting a significant association between unopposed IL-18 function and recent MI [97].

On the other hands, levels of IL-18 and IL-18BP were positively correlated with each other and with the values of CRP, left ventricular end-diastolic dimension (LVEDD) and *N*-terminal probrain natriuretic peptide (NT-proBNP) but inversely related with LVEF [94, 96]. Patients who had a troponin positive ACS had higher serum levels of IL-18 than those who suffer from severe coronary disease and did not experience a recent event.

The plasma IL-18 concentration is an independent predictive inflammatory marker of 30-day major adverse cardiac events and poor outcomes post-acute MI [98]. Indeed, circulating levels of IL-18 may be of potential use as an independent prognostic marker for estimation of atherosclerotic burden, even in general population. In two studies, within six months follow-up of patients with ACS post-hospital discharge, IL-18 serum levels were significantly increased in cases who develop adverse cardiovascular events compared to those who did not develop any adverse cardiovascular events independent of the clinical manifestations and markers of renal or cardiac dysfunction [99, 100]. In another survey, raised levels of IL-18 were correlated with higher incidence of major events (hazard ratio [HR]= 2.5; 95% CI: 1.1–5.5; P = 0.023)[99].

In short, evidence supports that IL-18 levels are significantly elevated in patients with ACS, acute MI or unstable angina. This suggests that IL-18 can be a potential predictive marker of future adverse cardiac events in ACS patients.

Abdominal aortic aneurysm and aortic dissection

IL-18 is involved in the pathogenesis of abdominal aortic aneurysm formation, through increasing osteopontin expression, macrophage recruiting and MMP induction [101]. The adipocyte and perivascular adipose tissue are also involved in the pathogeneisis of abdominal aortic aneurysm by releasing leptin and fatty acid-binding protein 4 (FABP4) that promote IL-18 levels and its activities [102].

Recently, increased levels of IL-18 was reported in aortic tissue and plasma sample of patients with acute aortic dissection (AD). Moreover, the plasma IL-18 concentratios were also positively related with the amounts of the M1 macrophage-associated cytokines IL-6 and IFN-γ[103]. This evidence indicates that IL-18 has a potential to be an independent risk factor for abdominal aortic aneurysm and AD.

Restenosis

IL-18 can activate Src kinase (Csk), PKC, p38 JNK MAPKs, Akt (protein kinase B), NF-kB (p50 and p65), activating protein-1 (AP-1), c-Fos, Fra-1 and stimulated expression of pro-inflammatory cytokines in VSMC contributing to AS [104, 105]. Beside, IL-18 can induce SMC migration possibly in an MMP9 (gelatinase B)-dependent manner. SMC migration is involved in normal angiogenesis, but also is actively involved in pathological vessel wall remodeling within atherogenesis, arteriosclerosis, and post-angioplasty restenosis [105]. ASC patients with high IL-18 levels have an increased risk of in-stent restenosis [106]. IL-18 plays a vital role in the intimal hyperplasia and migration, medial thickening, propagation and diffusion of VSMCs subsequent to injuries caused by balloon dilatation [107]. On the other hand, persistently raised levels of angiotensin (Ang) II was associated with the development of AS and restenosis [104]. Ang II triggers oxidative stress (OS), expression of pro-inflammatory cytokine, chemokine and adhesion molecules, EC death, SMC growth, colonization, and proliferation, and inflammatory cells infiltration to the arterial wall [108]. Exposure of VSMC with Ang II promoted IL-18-caused NF-kB activation and cytokine gene regulation. Notably, Ang II increased the IL-18Ra subunit at both transcription and translation levels. In addition, Ang II significantly induced transcription from IL-18Ra promoter including binding sites for signal transducers and activators of transcription (STAT) and AP-1. Therefore, Ang II promotes IL-18-caused inflammatory genes through over-expression of IL-18Ra [109].

Coronary heart disease and cardiocascular disease

The mean circulating levels of IL-18 in patients with ischemic heart disease without a specific traditional risk factor such as hypertension, dyslipidemia, diabetes and smoking were

significantly raised compared to healthy controls [110]. IL-18 stimulated lymphocytes from the circulation of CAD individuals to adhere to the endothelium with disrupted glycocalyx and enters the sub-intimal space promoting existing or initiating formation of new plaque within or immediately after coronary artery bypass grafting surgery [111].

However, in a prospective case–cohort study in middle-aged adults with 11 years follow-up, no significant association was seen between higher levels of IL-18 and incident of coronary heart disease (CHD) both in male (HR= 1.20; 95% CIs: 0.85-1.69), and in female (HR=1.25; 95% CI, 0.7-2.3) [112]. Consistently, in a prospective case–control study of apparently healthy women were followed for six-year, basal levels of IL-18 were remarkably higher in women who developed a CVD compared to controls (274.1 *vs.* 233.8 pg/mL, p<0.001), and were associated with future CVD (relative risk[RR] for highest *vs.* lowest quartile = 2.53; 95% CI: 1.5–4.3, p<0.001). After adjustment for most potential confounders, the RR of future CVD associated with the highest vs. lowest quartile of IL-18 was reduced to 1.6 (95% CI, 0.8–3.3, p = 0.13). However, women who have IL-18 levels >90th of the percentile of the target population (442 pg/mL) and increased total cholesterol levels are 6.3-times more at risk for future CVD events (95% CI, 2.0–19.7, *P* = 0.024) [113]. These reports are in contrast to two previous prospective cohorts [114, 115]. In a prospective cohort including 1229 CAD patients, blood levels of IL-18 were remarkably elevated in patients who had an adverse cardiovascular event compared to those who did not during median 3.9 years study period. Individuals in the highest quartile of IL-18 had a 3.3-times elevated risk of than those in the 1st quartile (95% CI: 1.3-8.4, P<0.01) [115]. In another prospective cohort with five-year follow-up, IL-18 levels were increased at baseline among those who developed coronary event (225.1 versus 203.9 pg/mL, p=0.005), and were related with future coronary events (RR for elevating tertiles of IL-18 1.4 [95% CI, 1.1–1.8, p=0.003]) [114].

Serum IL-18 level has the potential to be an important predictor of adverse cardiovascular events; although, it seems that when the follow-up was extended from 5 years, IL-18 levels were no longer predictive of the events, thereby challenging the importance of IL-18 as an independent determinant for subsequent CVD events.

Hypertention, strock and atrial fibrillation

It has been reported that IL-18 expression is increased to nearly 2-fold in patients with atrial fibrillation compared to healthy subjects and is associated with the incidence of atrial fibrillation [116]. Indeed, circulating and lung IL-18 concentrations are increased in pulmonary arterial hypertension (PAH) patients [117]. An animal experiment showed that IL-18 disruption could inhibit hypoxia-created PAH [118].

Recently, treated and untreated hypertensive patients have higher IL-18 levels compared to healthy subjects. IL-18 levels were also significantly decreased in treated hypertensive patients compared to untreated hypertensive cases [119]. The IL-18 levels were significantly higher in stroke patients compared to healthy controls. It has been speculated that high IL-18 levels are associated with stroke due to their relation to various inflammatory cytokines, which can cause alteration to atherosclerosis plaques, thrombosis, hyperlipidemia and hypertension, which all eventually leads to the development of stroke [120].

In relation to comorbidites

There is a strong association between accelerated AS in diabetes and high circulating amount of proatherogenic cytokine, IL-18. In patients with type 2 diabetes (T2DM), circulating IL-18 levels are higher compared to healthy controls. The fasting plasma glucose (FPG) was greater among patients with T2DM with increased IL-18 compared to those with normal IL-18 levels [121]. A strong association between IL-18 and insulin resistance was found in both patients

with T2DM and healthy controls [122]. The activation of protein kinase C (PKC)-β accelerates EC dysfunction through the aberrant expression of the IL-18/IL-18BP cascade, leading to a higher vascular cell adhesion molecule-1 (VCAM-1) expression, macrophage adhesion and trigger atherosclerotic plaque development in diabetes [123]. In addition, IL-18 levels is an independent risk marker of blood total homocysteine, which is correlated independently with atherosclerotic IMT [121].

Obstructive sleep apnea is described as recurrent episodes of entire or partial collapse and obstruction of the upper airway during sleep, leading to lower oxygen saturation and apneas or hypopneas [124]. There is a potent relationship between obstructive sleep apnea and CVD. Particularly, AS can occur in these patients independent of any other strong risk factors [124, 125]. In untreated patients who suffer from obstructive sleep apnea-hypopnea syndrome, carotid IMT and circulating IL-18 levels were positively correlated and were significantly increased compared to healthy subjects; the increments of IL-18 concentrations were correlated with the severity of disease [126]. The inflammatory response related to obstructive sleep apnea presumably associated with the development of AS through several mechanisms. Increasing levels of cytokines such as IL-1β, IL-6 and TNF-α can stimulate IL-18 [127]. Frequent nocturnal hypoxemia and increased oxidative stress in these patients can stimulate the release of IL-18 [127]. Also, a significantly raised IL-18 was found in hypoxic-ischemic brain tissue where possibly intermittent hypoxemia led to an elevation of IL-18 in obstructive sleep apnea-hypopnea syndrome cases [128].

Dawood and co-workers reported that women with polycystic ovary syndrome have higher circulating IL-18 levels rather than healthy women; as well IL-18 correlated positively with lipid accumulation product, insulin resistance and atherosclerotic CVD risk in these women.

IL-18 can be used as an indicator of adipocyte production in polycystic ovary syndrome consistent with the increased cardiovascular risk associated with this syndrome [129].

IL-18 predicts further major adverse CVD events in hemodialysis patients with 60% and 83% positive and negative predictive values, respectively. IL-18 was also elevated in patients with end-stage renal disease who developed CVD events compared to those who did not. These findings suggest the important role of inflammation as a novel prognostic factor in these patients [130].

In a large community-based study including apparently healthy subjects, increased plasma concentrations of IL-18 levels were associated with risk factors for AS and with the metabolic syndrome. But this association does not remain significant after adjustment for potential confounders. Therefore, IL-18 does not seem to be a potential diagnostic marker for the evaluation of atherosclerotic burden in the healthy population [131].

In conclusion, there is a significant association between higher levels of IL-18 and increased risk of developing AS or CVD in patients suffering from chronic disorders such as end-stage renal disease, diabetes, sleep apnea and polycystic ovary syndrome. Thus, IL-18 can be suggested as a potential prognostic marker for the developing of atherosclerotic CVD in this population.

Genetic evidence

There is growing evidence highlighting the relationship between blood IL-18 levels and the genetic variation of the IL-18 with coronary events. A functional single nucleotide polymorphism (SNP) -137 G/C (guanine to cytosine; rs187238) in the promoter region of IL-18 gene has been found to modulate the production of IL-18 from the circulating mononuclear cells [132]. Alteration of G to C in this locus influences the human histone H4 gene-specific transcription factor-1 (H4TF-1)-binding site. After induction, less promoter

activity has been detected for C alleles in these positions. The GG genotype of rs187238 revealed elevated transcriptional and translational activity, resulting in higher concentrations of the IL-18 protein compared to CC or GC genotypes [16, 133]. This functional variation can influence the mRNA expression of IL-18 and occurrence of CAD, proposing that IL-18 is causally contributed in the progression to AS and cardiac event [134].

In a large cohort study performed on 2,152 patients from the Finnish Cardiovascular Study, results from genotyping of five SNPs of the IL-18 gene (rs1946519, rs549908, rs360717, rs5744292 and rs4937100) showed that none of these variants showed any association with cardiovascular mortality. Only males harboring the agtA haplotype had a decreased risk for developing main branch CAD (OR=0.50, 95% CI 0.86–0.28, P = 0.04) [135].

Another study showed that the +183 G-allele (rs 5744292) was associated with lower serum levels of IL-18 compared to C-allele suggesting a functional role in the regulation of the transcription/translation process. The reduction of IL-18 levels associated with the +183 G-allele was 3-4 times more pronounced in patients with diabetes and MS in comparison with those free of these conditions. As the position of the +183 A/G variation is within the 3'UTR of the gene, an interference with the mRNA stability or the translation process is plausible and also an interaction with the 5' end in the regulation of transcription activity [136]. The IL-18+183 G-allele was associated with a 35% lower risk of clinical events in stable CAD cases. Moreover, the co-existence of the IL-18+183 AA and MMP-9-1562 CT/TT genotypes significantly correlated with higher risk of clinical events (OR = 1.9; 95% CI = 1.1–3.1, p_{adj} = 0.015) [137]. Increased expression and circulating levels of MMP-9 have been associated with the development and progression of AS. The significance of the MMP-9 gene, in particular, the functional promoter−1562 C/T SNP is demonstrated in the laboratory and clinical settings [138, 139]. Both IL-18 and MMP-9 are crucial mediators during the

development of CVD, and the genetic polymorphisms of IL-18 and MMP-9, may assist the diagnosis of very-high risk patients.

Zhang et al. explored the relationship of the two functional variants in the IL-18 gene promoter, [C−607A (rs1946518) and G−137C (rs187238)], with the risk of developing ischemic stroke (IS) in a Chinese population including 423 patients and 384 age- and sex-matched controls. The results revealed that the C allele at position−607C was associated with a 1.4 odds of IS as well as the having the G allele of rs187238 SNP was associated with 1.6 times more elevated risk of IS specifically in patients with AS of large arteries. Patients carrying the haplotype −607C/−137G had a significantly enhanced risk of IS versus controls. This finding provides evidence that IL-18 expression is associated with IS so that potentially novel therapeutic approaches aimed to reduce IL-18 protein genesis or function might be feasible for the prevention and therapy of IS [140]. G−137C polymorphism is also a major predictor of sudden cardiac death from any cause in cases with and without CHD [141]. In addition, the −137G/C variation of the IL-18 promoter has also been correlated with the CVD mortality and a trend towards correlation with all-cause mortality, in patients with diabetic nephropathy[142]. In a recent meta-analysis of published data, −137G/C is associated with a signifiant reduced risk of CAD in the dominant model (OR=0.85) and heterozygous model (OR=0.88). For -607C/A, the overall OR related with a decreased risk of CAD in different genetic models including allelic (OR=0.8), recessive (OR=0.7) dominant (OR=0.7), homozygous (OR=0.6), and heterozygous models (OR=0.7). Additionally, IL-18 polymorphisms were associated with MI and multivessel (MV) disease [143]. Overall, genetic variation of the IL-18 can regulate the production of IL-18 and could potentially predict future coronary events.

Conclusions and Perspectives

There is growing evidence that immune system and proinflammatory cytokines play a predominant role in the pathogenesis of AS. Various in vivo experiments suggest that disruption of the IL-18 gene results in reduced development of atherosclerosis in animal models of AS[49, 57]. Notably, exogenous administration of IL-18 not only promotes atherosclerosis in mouse but also enhances the progression of diabetes and metabolic syndrome [59, 65, 144].

Despite the theoretical association between IL-18 with subclinical atherosclerosis, concerning the use of IL-18 as a predictive biomarker in patients with CAD, contrasting results have been yielded. In addition, there was no association between polymorphisms in the IL-18 related genes and CVD risk in the European prospective cohort [145]. Probably these conflicting results are based on prospective studies evaluating a different heterogeneous patient and healthy cohorts with different risk factors, suggesting variability in the findings. The potential of IL-18 as a predictive marker for future coronary events warrant further investigations. Larger study population, serial measurement of the circulating IL-18, use of standardized and reproducible assays for IL-18 and assessment of long-term clinical outcome in a series of prospective studies could potentially reduce the heterogeneity in the studies and make the results more reliable.

IL-18 is also can be a useful marker in healthy individuals, but it should be adjusted for traditional cardiovascular risk factors such as HDL-C. Previous evidence demonstrated that inflammation and hyperlipidemia act distinctively in the pathophysiology of AS and that combination of high concentrations of inflammatory and lipid markers is associated with a higher risk of cardiovascular events compared to increased values of either biomarker separately.

Regarding the mediator role of IL-18 in acute cardiac effects or chronic cardiac alterations such as fibrosis, it is rational to suggest that IL-18 inhibition has the potential to be an effective approach in the management of acute and chronic cardiac conditions. Blocking of IL-18 activity through neutralizing antibodies such as IL-18BPa, or caspase-1 inhibitors may prevent the development of atherosclerotic plaque and progression, providing the basis for further investigations of this cytokine. IL-18 acts in synergy with many cytokines implicated during atherogenesis such as IL-6 and IL-12 and it possibly serves to amplify ongoing inflammatory responses. Blocking this could thus be advantageous by inhibiting the activation of numerous proinflammatory cascades therein.

Preclinical studies using targeted treatments with IL-18BP/IL-18Ab given during AS or at the time of atherosclerotic plaques rupture are lacking. If such studies were able to show a protective effect of IL-18 inhibition that is continued over time and not related with plaque instability in preclinical AS modes, then pilot clinical trials in AS patients may be needed. However, there are several pitfalls about using of IL-18 blocking agents. The most noticeable concern is associated with the importance of IL-18 in immune responses against infectious pathogens and, therefore, a potential higher susceptibility to infections after the loss of IL-18 activity. Another issue that should be taken into account is the role of this cytokine in tumour surveillance. In brief, IL-18 has been implicated in immune surveillance of many solid and haematopoietic cancers. This characteristic is mainly because of the ability of IL-18 to increase the cytotoxicity in NK and CD8 T cells [146]. It is plausible that long-term effect IL-18 blocking affects tumorigenesis which should be taken with caution.

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Figure legend:

Figure 1. Role of inteleukin-18 and other proinflammatory cytokines in atherosclerosis. This cytokine is expressed as a precursor, pro-IL-18, which is inactive until cleaved by caspase-1. Once secreted, IL-18 is bound and inactivated by IL-18BP, and only the free fraction can induce a signal transduction via the β-chain of the IL-18R. IL-18 act synergistically with IL-12 to induce a Th1 response with generation of IFN-γ. The IL-12–IL-18–T-bet–IFN-γ cascade is a strong proinflammatory stimulus which enhance promotes and increases lesion development, and atherosclerosis. Adipocyte also promote IL-18 levels and activities via releasing of leptin and FABP4. IL-18 binds to a heterodimeric receptor (IL-18Rα and IL-18Rβ), which in turn mediates signaling by the canonical IL-1R superfamily signaling axis which includes MyD88, IRAK, TRAF-6 to NF-κB.

Abbreviations: fatty acid-binding protein 4 (FABP4), IL-18 binding protein (IL-18 BP), IL-18 receptor (IL-18R), IL-18 complex and interaction with IL-1R-associated kinases (IRAKs), smooth muscle cells (SMCs), chemo-attractant protein-1(MCP-1), normal T cell expressed and secreted (RANTES), interferon (IFN), matrix metalloproteases (MMP), myeloid differentiation 88 (MyD88), oxidized LDL (oxLDL), tumor necrosis factor receptor-associated factor 6 (TRAF6).

Table 1. Role of IL-18 in developing cardiovascular disease.			
Condition	**Experiment model/participants**	**outcome**	**Ref.**
Atherogenesis	−human vascular endothelial cells −SMC −macrophages	−over-expression of IL-18 by macrophages of atherosclerotic plaques	[4]
Carotid atherosclerosis	-366 patients without histories of cardiovascular accidents	−IL-18 positively correlated and carotid IMT	[45]
Atherosclerotic lesions	-SMC	−IL-18 stimulate scavenger receptor CXCL16	[50]
Atherosclerotic plaques	- *apoE*−/− mice -male C57BL/6 mice	−over-expression of IL-18 in the *apoE*−/− mice *vs.* control	[48]
Atherosclerosis in the aortic root of the offspring	-old *apoE*−/− mice	−slow-down of arthrosclerosis in *IL-18*−/−×*apoE*−/− mice	[49]
Atherosclerotic lesion	-*apoE*−/− mice	−higher IL-18 expression causes to decrements in intimal collagen and cap-to-core ratio in *apoE*−/− mice	[56]
Myocardial dysfunction	- 11 patients with UA and negative troponin I - 21 patients with acute non-Q wave MI - 21 patients with acute Q wave MI -9 patients with stable angina -11 controls	−IL-18 levels significantly associated with reduced LVEF in ACS patients	[96]
Recent MI	84 unselected patients who had coronary artery disease	−increments the levels of IL-18 and ratio of IL-18/IL-18BP in patients with recent MI *vs.* who did not	[97]
ACS	-35 patients with acute coronary syndrome	−increments the levels of IL-18 in patients with acute MI *vs.* unstable angina patients	[35]
AAA formation	- male C57BL/6J WT mice - IL-18$^{-/-}$ mice	−IL-18 induces higher osteopontin expression, macrophage recruiting, and MMP induction	[101]
In-stent restenosis	-198 patients with ACS underwent coronary drug-eluting stent implantation	− high IL-18 levels related to increased risk of in-stent restenosis in ASC patients	[106]
Neointimal hyperplasia after balloon injury	- male NZW rabbits	− vital role of IL-18 in intimal hyperplasia and migration, medial thickening, propagation, and diffusion of VSMCs subsequent injury	[107]
ACS	-112 ACS	−higher levels IL-18 related with higher incidence of major coronary events	[99]
CHD	-382 case subjects with incident CHD - 1980 non-cases	−higher levels of IL-18 were not related to incident of CHD	[112]

CVD	-253 participants who developed CVD - 253 healthy controls	−higher baseline levels of IL-18 in woman who developed a CVD compared *vs.* controls	[113]
Acute MI	- 20 patients with acute MI -20 patients with SAP	−co-expression of monocytic IL-18 and EMMPRIN boost the inflammatory cascade and enhance atherosclerotic lesions and plaque instability by over-expression of MMP-9	[147]
ACS	-HEK-293T cells - C57BL/6 mice	−higher circulating sLOX-1 amounts are in ACS	[89]
CHD	-10,600 healthy European men	−IL-18 levels were increased at baseline among those who developed coronary event and were related with future coronary events	[114]

Abbreviations: abdominal aortic aneurysm (AAA); apolipoprotein E–deficient (*apoE−/−*); acute coronary syndromes (ACS); brachial-ankle pulse wave velocity (baPWV); chemokine (C–X–C motif) ligand (CXCL); coronary heart disease (CHD); cardiovascular disease(CVD); extracellular matrix metalloproteinase inducer (EMMPRIN); interleukin (IL); intima-media thickness (IMT); soluble lectin-like oxLDL receptor-1 (sLOX-1); left ventricular ejection fraction (LVEF); metalloproteases (MMP); New Zealand white (NZW); smooth muscle cells (SMCs); stable angina pectoris (SAP); unstable angina (UA); vascular SMCs (VSMCs); wild-type (WT).