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Interleukin-18 and Atherosclerosis: Mediator or Biomarker

Kunal Mahajan*

Department of Cardiology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

***Corresponding author:** Kunal Mahajan, Department of Cardiology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India-171001, Tel- +918628864820; Email- kunalmahajan2014@yahoo.com

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Abstract

Atherosclerosis, a progressive disorder of the vessel walls with the formation of plaques throughout the arterial system, is an essential pathological process in the development of various Cardiovascular Diseases (CVDs). Inflammation has been demonstrated to play an inevitable role in all the stages of atherosclerosis though its pathogenesis is complicated and still remains enigmatic. Interleukin-18 (IL-18) is a pleiotropic pro-inflammatory cytokine, which belongs to the Interleukin-1 (IL-1) family. This pro-inflammatory cytokine is among the more recently recognized cytokines to be involved in the development of various cardiovascular diseases and their related manifestations. At one end, studies indicate that IL-18 is a key player that orchestrates the inflammatory cascade associated with the pathogenesis of atherosclerosis, whereas others showed circulating levels of IL-18 to be a prognostic marker. Present article summarizes the scientific rationale which highlights the signatures of interleukin-18 as a mediator in the pathogenesis as well as a diagnostic marker.

Keywords: Interleukin-18; Atherosclerosis; Biomarker

Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity worldwide [1-3]. Atherosclerosis is the major underlying cause of various CVDs including Coronary Artery Disease (CAD), myocardial infarction etc. Multiple risk factors coordinate in an intricate network for the progression of atherosclerosis. Inflammation has been demonstrated to play a pivotal role in the genesis of atherosclerosis though its pathogenesis is extremely complicated [2,4,5]. It is generally accepted that a complex endothelial dysfunction induced by free radicals, low-density lipoproteins (LDL), infectious microorganism, shear stress, toxins, hypertension or a combination of these and other factors lead to the development of atherosclerosis. Besides implication of inflammation and immune reactions in this process, a wide range of circulating markers of inflammation has also been demonstrated to predict cardiovascular event in a variety of clinical settings [1,3,4,6-8].

Interleukin-18, a member of the IL-1 superfamily, has several biological activities that initiate and promote host defence and inflammation [9]. IL-18 is biologically and structurally related to IL-1β [10-12]. It is a pro-inflammatory cytokine with multiple biological functions. Cells known to express IL-18 include macrophages, Kupffer cells, keratinocytes, and glucocorticoid-secreting adrenal cortex cells. There have been several reports relating the up regulation of IL-18 in human inflammatory and autoimmune diseases, including rheumatoid arthritis, type I diabetes, atherosclerosis, chronic heart failure, and idiopathic thrombocytopenic purpura [11,13-15].

Clinical and experimental studies have demonstrated an association of elevated IL-18 levels with increased CVD risk. However, question still remain unanswered whether this observation is indicative of IL-18 being causal in plaque rupture, or whether rupture prone plaques release IL-18 into the circulation, or this association is nothing but a co-incident. Present article summarized the scientific rationale which highlights the importance of Interleukin-18 as biomarker and as a mediator in the pathophysiology of atherosclerosis.

Expression and synthesis of Interleukin-18

Interleukin-18 was first identified as an interferon-γ (IFN-ϒ)-inducing factor in the sera of endotoxin injected mice [12]. As stated earlier, IL-18 belongs to the IL-1 superfamily, thus sharing structural and functional properties with IL-1β. IL-18 also shares the same signalling cascade with IL-1 β. IL-18, like IL-1β, is produced as a 24-kD inactive precursor lacking a signal peptide (pro-IL-18). Pro-IL-18 is cleaved by the endoprotease IL-1β-converting enzyme (ICE; caspase-1) to generate a biologically active, mature 18-kD moiety of IL-18 molecule [16,17]. However, proteinase-3 can also generate biological active IL-18 from pro-IL-18 [18,19]. IL-18 is normally regulated via the naturally occurring IL-18-binding protein (IL-18BP). IL-18BP specifically binds to IL-18 with high affinity [20]. A potent stimulus for IL-18 expression remains under investigation however lipopolysaccharide (LPS) and Fas L (Fas ligand) are known and well-studied stimuli [21]. To initiate IL-18 intracellular signalling, mature IL-18 is required for the assembly of IL-18Rα and IL-18Rβ [22,23]. (Detailed signalling and structural details reviewed in Ref. [12,20,23]).

Interleukin-18 as a mediator in the pathophysiology of Atherosclerosis

Although, originally identified as a factor capable of inducing IFN-γ production by murine splenocytes, the effect or role of IL-18 is rapidly expanding in different pathological settings. There are now strong experimental data supporting the hypothesis that a novel pathway for signalling in atherogenesis and plaque vulnerability involves the IL-18 and its interaction with receptor [15,24,25]. IL-18 has been first identified in human atherosclerotic lesions with significantly higher levels of mRNA in unstable plaques [26]. Furthermore, Gerdes et al. (2002) demonstrated that in vitro stimulation of the IL-18 receptors on endothelial cells or smooth muscle cells triggers atheroma-associated

processes such as stimulation of the pro-inflammatory cytokines like IL-6 and IL-8 and expression of adhesion molecules and matrix metalloproteinases [27]. Whitman et al. (2002) in their study reported that, administration of IL-18 leads to an increase in lesion size and induce the number of lesion-associated T-lymphocytes in animal models. Both effects were abolished in IFN-γ deficient mice, which strongly suggested the importance of the IFN-γ dependent pathway [28]. Moreover, inhibition of IL-18 signalling by IL-18 binding protein has been shown to reduce lesion progression and change in the plaque composition towards a stable feature which include a decrease of inflammatory cells and lipid content and an increase of smooth muscle cells and collagen [26]. These studies clearly pinpointed, IL-18 to be an excellent candidate linking local vascular wall pathology with the inflammation.

Experimental studies have shown that IL-18 enhances atherosclerosis through release of interferon gamma (IFN-γ) [28] and induces expression of inflammatory cytokine IL-6 in the vascular endothelial and smooth muscle cells [27]. In apolipoprotein E-knockout mice IL-18 deficiency has been shown to reduce the extent of atherosclerosis [29]. Adhesion molecules plays important role in the pathophysiology of atherosclerosis and its related manifestations [14,30]. IL-18 has also been demonstrated to increase expression of vascular cell adhesion molecule -1 (VCAM-1) and intracellular cell adhesion molecule-1 (ICAM-1) in endothelial cell and synovial fibroblasts [31,32]. Reducing IL-18 activity with either IL-18 BP or a caspase-1 inhibitor, the functional impairment of the ischemia reperfusion injury found to be significantly reduced [33]. Moreover, a neutralizing antibody to IL-18 resulted in near prevention of endotoxin-induced myocardial suppression in mice [34]. In addition, in animal model, IL-18 administration has been demonstrated to result in ventricular hypertrophy and elevated left ventricular diastolic pressure [35,36].

IL-18 was found to be highly expressed in human carotid atherosclerotic plaques, predominantly co-localized with macrophages [26]. In an another study, the myocardium of patients with ischemic heart failure express the alpha chain of the IL-18 receptor and have elevated levels of circulating IL-18 levels and has been shown to be correlated with death [15]. Very recently, Pigarevskii et al. (2014) [37] have demonstrated role of interleukin 18 in destabilization of the atherosclerotic plaque in humans. These authors have precisely demonstrated the location of IL-18 in the cellular and tissue elements of unstable and stable atherosclerotic plaques, whereas no IL-18 was observed in control vascular tissue. Intracellular (endotheliocytes, macrophages/monocytes) and diffuse extracellular IL-18 was shown to be located mainly in unstable lesions [37], which clearly demonstrated the importance of IL-18.

In a search for IL-18-inducible genes, Kim and colleagues (2005) identified a novel cytokine IL-32 [38]. IL-32 is constitutively and inducible expressed by monocytes and by epithelial cells within multiple human inflammatory tissues, and expression has now been described in a variety of pathologies [39]. Further studies will be needed to elucidate the correct signalling pathway(s) for IL-32 to allow development of rational approaches to intervention and are beyond the scope of present article.

Interleukin 18 as Biomarker in Atherosclerosis

With the recognition that inflammation plays significant role in CVD pathophysiology, studies have shown that circulating inflammatory markers could be predictive of cardiovascular diseases [1,14,40,41]. As discussed in previous section, it become clear that IL-18 plays a significant role in orchestrating the cytokine cascade and accelerates atherosclerosis and plaque vulnerability. However, epidemiological data evaluating the role of IL-18 levels in atherosclerosis in humans is still needed.

One of the earlier studies, by Mallat et al. [26] and Yamagami et al. [42] has shown the importance of IL-18 as biomarker of the disease. In their study, they demonstrated association of higher serum IL-18 levels with greater carotid intima- media thickness (IMT) (as evaluated by B-mode ultrasound), suggesting a link between IL-18 and atherosclerosis. In addition, findings of Yamagami et al. (2005) reported a positive association of serum IL-18 with other predictive risks like age and BMI in subjects with coronary heart disease [42].

There is much evidence that matrix metalloproteinases (MMPs) are involved in the balance between the breakdown and synthesis of extracellular matrix, which determines the risk of rupture of plaques and subsequent disease events [7,43]. MMPs and their inhibitors (TIMPs) have already been demonstrated as potential factors in the pathophysiology of various disease settings [43-46]. Extracellular Matrix Metalloproteinase Inducer (EMMPRIN), a trans membrane glycoprotein, is capable of inducing MMPs through direct cell-cell interaction [46,47]. Xie et al. (2014) have demonstrated that EMMPRIN and IL-18 together form a mutually reinforcing response mechanism that contributes to atherosclerotic plaque destabilization [24].

IL-18 provides powerful information for future fatal cardiovascular events across the entire spectrum of patients with stable coronary artery disease (CAD) and patients with unstable CAD. The relation between IL-18 and future cardiovascular events was independent of other risk factors and clinical features such as ejection fraction and remained unaffected by various markers of inflammation such as C-reactive protein (hsCRP), fibrinogen, or IL-6 [9,13]. Human heart tissue contains preformed IL-18 in macrophages and endothelial cells [33]. In another study, myocardial tissue steady-state concentrations of IL-18, IL-18R, and IL-18 BP mRNA and their respective proteins were measured in patients with end-stage heart failure. Both circulating plasma and myocardial tissue concentrations of IL-18 were found to be higher in the heart failure patients than in the age-matched controls. Additionally, plasma IL-18 concentrations were significantly higher in the patients who died than in survivors [15].

Human atherosclerotic plaques from the coronary arteries exhibit higher concentrations IL-18 and IL-18 receptors than found in non-diseased segments of the same artery [27]. (For detailed prospective studies and systematic review readers can read Ref. [48,49]). Zirlik et al. (2007) summarized the results from Dallas Heart study demonstrated that IL-18 associates with several CVDs risk factors, including many components of the metabolic syndrome, in a large population based cohort of apparently healthy subjects. Although IL-18 associates with subclinical atherosclerosis in invariable analysis, this association does not persist after adjustment for traditional CV risk factors. These authors concluded that IL-18 does not appear to add to currently accepted risk markers as a diagnostic tool for assessment of atherosclerotic burden in a community-based population [48]. On the contrary, another large population-based study mainly with healthy middle-aged men; baseline IL-18 levels were positively correlated with CHD risk [49]. These results were corroborated with other studies by Mallat et al. (2001) and Gerdes et al. (2002) [26,27].

Looking at immunological aspects, IL-18 induces high immunoglobulin E expression by B cells and in combination with IL-2, anti-CD3, and anti-CD28, markedly enhances IL-4 production by CD4+ T cells. When cultured alone or in combination with IL-4, IL-18 induced T cell Th2 differentiation in mice [50]. In addition, direct effects on macrophages and DC have also been reported. Stimulation of bone marrow-derived macrophages or splenic DC with IL-12 and IL-18 resulted in IFN-γ production [51]. All these events lead to inflammatory rich milieu. IL-18 acts as an important regulator of both innate and acquired immune responses. It is an important cytokine in myocardial ischemia reperfusion injury, a model of acute infarctions, where it functions to decrease the contractile force of the heart.

IL-18 Polymorphism and Atherosclerosis

Functional effects of biologically important gene polymorphisms on transcription and circulating enzyme levels have been identified and, associated with severity of several diseases. In a haplotype study by Tiret et al. [10], the genetic variability of the IL-18 gene was shown to associate with serum IL-18 levels and cardiovascular mortality in CAD patients. The association between angiographically proven CAD and IL-18 gene polymorphism has been studied by Liu W et al. [23], and they demonstrated that the IL-18 promoter -137 G⁄C polymorphism influences IL-18 levels and the occurrence of angiographically verified CAD.

IL-18 promoter -137G/C polymorphism influences IL-18 levels and the occurrence of coronary artery disease, suggesting that IL-18 is causally involved in the development of atherosclerosis. The variation of the IL-18 gene was not found to associate significantly with mortality for cardiovascular causes during follow-up in a patient population undergoing exercise tests [52]. Occlusion of one of the main branches of the coronary arteries is more likely to cause severe complications than does occlusion of smaller arteries. Among the men undergoing coronary angiography, the carriers of the agtA haplotype (and thus also the carriers of the t allele +127 C⁄ T polymorphism) seemed to have a lower risk for main branch CAD. Another study carried by the same group, previously shown that among men, carriers of the c allele of the 137 (G⁄C) polymorphism are at a lower risk for sudden cardiac death and that hypertension is a key element conveying the risk [53].

A combination of multiple biomarkers that best predict the disease from controls is the need of hour. Both IL-18 and MMP-9 are considered as important mediators during the development of CVD. Importance of the MMP-9 gene, especially the functional promoter -1562 C/T polymorphism, is documented in both experimental and clinical studies. The IL-18+183 A/G polymorphism another polymorphism studies in CAD patients [54,55]. Opstad et al. (2013), in search of combined genetic influence of IL-18 and MMP-9, observed additional risk for the combined genetic influence of both IL-18/ MMP-9 loci suggests the superiority of screening more than one marker to identify patients at high risk [54]. In another study, Liu et al. (2013) have demonstrated a significant association of -137 G/C polymorphism of IL-18 with the incidence of in-stent restenosis after percutaneous coronary intervention in Chinese population [56].

Conclusion

In this article, the roles of IL-18 are summarized with respect to the atherosclerosis primarily from the viewpoint that it is a cause or a biomarker of the disease. Based on the review of literature, IL-18 cannot be applied for the routine diagnostic of CVDs yet and the clinical utility remains to be established. Nevertheless, IL-18 appears able to modulate inflammation at multiple checkpoints, acting not only on initiation and expansion of an inflammatory response but also have direct effects on multiple cellular targets, including macrophages, lymphocytes, and target host tissue cells-endothelial cells and fibroblasts. Therefore, IL-18 can be considered, as a potential target for future therapeutic strategies using selective inhibitors. A better understanding of cytokine biology over the last two decades has allowed the successful development of cytokine inhibitors. The introduction of these therapies should be considered a breakthrough in the management of several vascular diseases.

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