

Expanded Network of Inflammatory Markers of Atherogenesis: Where Are We Now?

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Abstract: Inflammatory biomarkers play a pivotal role in atherosclerotic lesions. The plasma levels of these markers are predictive of adverse outcomes such as myocardial infarction and cardiovascular death. The immune system is involved at all stages of atherogenesis *via* activation of monocytes/macrophages and T lymphocytes. Circulating proinflammatory cytokines and chemokines produced by these cells interact with specific receptors on various cells and activate specific signaling pathways, leading to inflammation-induced atherosclerotic lesions. Recent studies have focused on predictive value of inflammatory biomarkers such as C-reactive protein and interleukin-6. These biomarkers were shown to be associated with poor quality of life and predictive of adverse events in coronary atherosclerosis and left ventricular dysfunction. Vascular predictive value of other numerous inflammatory markers is being investigated. We herein analyze the role of several mediators of inflammation, affecting vascular functions and leading toward atherosclerotic lesions.

Keywords: Inflammation, Atherosclerosis, Cytokines, C-reactive protein.

INTRODUCTION

Inflammatory biomarkers play a pivotal role in the initiation and propagation of atherosclerosis. Inflammation accompanies coronary artery spasm, impaired coronary blood flow, myocardial ischemia and restenosis after angioplasty [1-3]. Surprisingly, the first inflammatory characteristics of atherosclerotic lesions were presented by European surgeons almost two centuries ago [4]. However, atherosclerosis was categorized to inflammatory diseases by Russell Ross in 1999 [5].

Vascular endothelial dysfunction and lipoprotein retention in the arterial intima are the earliest events in atherogenesis that promote the release of cytokines and chemokines, both of which are responsible for leukocyte recruitment. These events followed by activation of T lymphocytes, particularly T helpers, which facilitate cascade of events related to oxidized low density lipoproteins (LDL) [6, 7]. Circulating pro-inflammatory cytokines produced by monocytes/macrophages and T lymphocytes interact with platelet derived inflammatory and prothrombotic agents and activate specific signaling pathways, initiating cells adhesion, apoptosis and increased permeability of the endothelium. These cytokines are also responsible for oxidative stress [8].

Recent studies have demonstrated vascular predictive value of several inflammatory markers [9-11] and association of these markers with established cardiovascular risk factors, such as dyslipidemia, cigarette smoking, hypertension,

diabetes, obesity [12-16]. Oxidation of LDL and modification of other lipoproteins induce overexpression of inflammatory cytokines and other mediators of inflammation in vessels [17-20]. Studies on the link between hypertension and inflammation have also shown that angiotensin II can lead toward hypertension through activation of inflammatory cascades and atherogenesis [21]. It is also known that hyperglycemic profiles in diabetes are associated with overproduction of pro-inflammatory cytokines by vascular endothelial cells [22]. In obese subjects, the adipose tissue can synthesize cytokines (e.g., tumor necrosis factor alpha [TNF- α] and interleukin-6 [IL-6]) and, thus, promote inflammatory atherogenesis [23].

Recent studies have also shown that suppression of diverse inflammatory mediators may retard atherosclerotic process. Interestingly, evidence indicates that knockout of interferon- γ (IFN- γ) [24] and interleukin-18 (IL-18) [25, 26] is crucial for retardation of atherosclerosis. Established cardiovascular risk factors modification can reduce levels of circulating inflammatory markers and improve endothelial function [27]. The atherogenic role of inflammation has also been confirmed within the frames of chronic low- and high-grade inflammatory disorders such as diabetes, periodontal disease, familial Mediterranean fever, lupus, antiphospholipid syndrome, rheumatoid arthritis, systemic sclerosis, end-stage renal disease [28-32].

We herein analyze the role of several mediators of inflammation, affecting vascular functions and leading toward atherosclerotic lesions.

C-REACTIVE PROTEIN (CRP)

Acute-phase reactants are produced in response to trauma, tissue necrosis, infections and inflammation. There

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are two important sources of CRP implicated in atherothrombosis: local production in atherosclerotic plaques and in adipose tissue [33]. CRP is able to stimulate production of plaque-destabilizing matrix metalloproteinases (MMPs) and monocyte chemoattractant protein 1 (MCP-1). It also can decrease activity of endothelial nitric oxide synthase (eNOS) and impair endothelium-dependent vasodilation [34].

High sensitivity CRP (hs-CRP) levels have been proved to be strongly predictive of cardiovascular events and potentially associated with the severity of coronary atherosclerosis [35-39]. Utility of this biomarker for cardiovascular risk stratification in populations with and without established cardiovascular disease is supported by strong evidence [40]. In particular, it was shown that survival rate following percutaneous coronary intervention in patients with angina was significantly low in those with high CRP levels [41]. Not less importantly, very high levels of CRP were associated with poor quality of life, high incidence of depressive symptoms and physical inactivity [42]. Associations were also found between hs-CRP and ischemic heart disease, left ventricular ejection fraction, congestive heart failure [43, 44].

Four CRP polymorphisms were associated with 64% increase in CRP levels, resulting in predicted increased risk of ischemic heart disease and ischemic cerebrovascular disease by 32% and 25%, respectively [45].

FIBRINOGEN

Fibrinogen contributes to atherosclerosis through several mechanisms: 1. propagation of atherosclerosis *via* adhesion of white blood cells to the endothelium, stimulation of smooth muscle cells (SMCs) proliferation and release of endothelium-derived growth factor; 2. aggregation of platelets; 3. increase of plasma viscosity [46, 47]. Fibrinogen may play an active role in the development and destabilization of atherosclerotic plaques. Several prospective trials have demonstrated strong vascular predictive value of this biomarker [48-52]. In one study, adjusted hazard ratio for atherosclerosis progression for the highest quartile of baseline fibrinogen was 2.45 [53]. It was also suggested that this hazard ratio can be especially high in younger patients [54]. Population studies allowed to suggest that high prevalence of cardiovascular disease can be genetically determined and linked to locus in the 7th pair of chromosome encoding fibrinogen [55]. Findings have also indicated that high fibrinogen levels and genetic variation in fibrinogen- α and fibrinogen- γ genes may be associated with arterial stiffness [56].

SERUM AMYLOID A (SAA)

SAA belongs to the family of apolipoproteins. SAA is produced by liver and reticuloendothelial tissue in response to inflammatory stimuli, and circulates in complex with high density lipoprotein (HDL). It has been suggested that SAA can stimulate pro-inflammatory cytokines production by monocytes/macrophage and thereby contribute to the pro-inflammatory state in coronary artery disease [57]. Furthermore, the role of SAA in the prediction of cardiovascular events has been proved [58].

TUMOR NECROSIS FACTOR ALPHA (TNF- α)

TNF- α is a secretory product of macrophages that activates endothelial cells, stimulates angiogenesis, and induces proliferation of SMCs. The expression of TNF- α in both intimal and medial SMCs and macrophages is associated with the progression of atherosclerosis [59]. Significant correlation was found between TNF- α and severity of coronary artery disease assessed by the number of obstructed coronary vessels and the Gensini severity score [60].

TNF- α is actively involved in the progression of atherosclerosis [61-63]. It was demonstrated that elevated soluble TNF receptor 1 (sTNF-R1) can predict cardiovascular mortality in patients with chronic heart failure [64]. Activity of TNF and its receptor may also has additive role in atherosclerosis induced by homocysteine in patients with diabetes [65].

MONOCYTE CHEMOATTRACTANT PROTEIN-1 (MCP-1)

MCP-1 is a member of the CC chemokine superfamily that activates monocytes at acute stage of inflammation. MCP-1 induces migration of monocytes/macrophages, as well as CD4⁺ and CD8⁺ T lymphocytes into the sub-endothelial space [66-69]. MCP-1 expression can be induced by IL-1b and TNF-alpha through the activation of nuclear factor-kB [70, 71]. MCP-1 facilitates oxidation of cholesterol and through it contributes to the development of fatty streaks in hypercholesterolemia [72]. Interestingly, MCP-1 inhibition in apolipoprotein-E knockout mice prevents atherogenesis [73].

INTERLEUKIN-6 (IL-6)

IL-6 is a well-known risk marker of cardiovascular disease associated with obesity, type 2 diabetes and myocardial infarction. The relationship between IL-6, the Gensini severity score and >70% stenosis of coronary vessels has been already proved [74, 75]. IL-6 levels are also independently associated with subclinical atherosclerotic lesions [76, 77], and proved to be predictive of ischemic events [78].

IL-6 induces secretion of other inflammatory markers, particularly CRP. IL-6 activates cell-surface signaling *via* the assembly of IL-6, its receptor (IL-6R) and signaling receptor gp130 [79]. Haddya *et al.*, demonstrated positive correlation between IL-6, TNF- α and CRP in parents and their offsprings. Furthermore, they found negative relationship between IL-6 and HDL-cholesterol [80].

INTERLEUKIN-8 (IL-8)

IL-8 is another cytokine, mediator of angiogenesis in coronary atherosclerosis, inducing migration and proliferation of endothelial cells and smooth muscle cells [81]. Recently, macrophages from atherosclerotic plaques were found to express the IL-8 receptor (CXCR2). This expression is pro-atherogenic. CXCR2 deficiency retards progression of atherosclerosis in animal models [82]. Besides, elevated levels of IL-8 are associated with an increased risk of coronary artery disease [83].

INTERLEUKIN-1 (IL-1)

IL-1 is a pro-inflammatory cytokine that increases production of other cytokines and induces expression of adhesion molecules on endothelial cells. In addition, IL-1 contributes to the tissue damage by stimulating cell proliferation and release of matrix metalloproteinases. Overexpression of IL-1 receptor antagonist (IL-1Ra) inhibits the development of atherosclerotic lesions. Moreover, inhibition of IL-1 β decreases severity of atherosclerosis through the increased expression of VCAM-1 and MCP-1 [84, 85].

INTERLEUKIN-4 (IL-4)

Deficiency of IL-4 can reduce atherosclerotic lesions [86]. This cytokine increases the number of cell-surface binding sites for LDL. IL-4 can have profound effect on the macrophage lipid metabolism within atherosclerotic lesions [87].

INTERLEUKIN-10 (IL-10)

The role of IL-10 in the inflammatory process is dual, pro- and anti-inflammatory [88]. Cumulative incidence of coronary artery disease was significantly greater in individuals with IL-10 concentrations ≥ 1.04 pg/ml and one standard deviation increase in baseline IL-10 concentration was associated with a 34% greater risk of this event [89]. This interleukin is expressed in human atherosclerotic plaques, and it can modulate local inflammatory response by preventing excessive cell death in the plaque [90]. In a study on animal models, increased T-cell infiltration, abundant interferon-gamma expression and decreased collagen content were shown in the atherosclerotic lesions of IL-10-deficient mice. IL-10 appeared to be crucial for protection against the effect of environmental pathogens on atherosclerosis [91].

INTERLEUKIN-12 (IL-12)

Recent data suggest that IL-12 plays an active role in regulating immune response during initial atherosclerotic changes in animal models. Daily administration of IL-12 was shown to increase serum levels of antibodies against oxidized LDL [92]. IL-12 can also induce T lymphocytes recruitment into atherosclerotic plaque [93].

INTERLEUKIN-15 (IL-15)

Plasma levels of IL-15 were found to be high in patients with coronary artery disease, compared to those without coronary artery disease [94]. This cytokine is up-regulated in atherosclerotic lesions, where it stimulates recruitment of T lymphocytes [95]. The expression of IL-15 is found almost exclusively in fibrolipid and lipid-rich plaques in complex foam cells [96].

INTERLEUKIN-18 (IL-18)

IL-18 is a pro-inflammatory cytokine secreted by mononuclear cells. The serum concentrations of this cytokine have been shown to be predictive of mortality in coronary artery disease [97]. Patients in the highest quartile for this marker had greater risk of cardiovascular death, compared to those in the lowest quartile [98]. Recent findings have indicated a role of IL-18 in progression of atherosclerosis at its early

and late stages [99]. It has also been shown that, despite increased activity of T lymphocytes and increased serum levels of cholesterol, there is no progression of atherosclerosis in the absence of IL-18 [100]. Pro-atherogenic effect of IL-18 is strongly dependent on IFN- γ produced by T lymphocytes, macrophages, natural killer cells and vascular cells [101].

INTERLEUKIN-33 (IL-33)

IL-33 is a member of the IL-1 family that induces differentiation of T lymphocytes and is involved in T-cell mediated immune responses. IL-33 regulates production of IL-5, IL-4, IL-13 and can decrease levels of IFN- γ in the serum and lymph nodes [102]. It is also involved in the production of antibodies against oxidized LDL [103].

INTERCELLULAR ADHESION MOLECULE-1 (ICAM-1)

ICAM-1 is a member of the immunoglobulin superfamily. Its role relates to leukocytes migration into tissues. ICAM-1 can contribute to inflammatory responses within the blood vessel wall by increasing endothelial cell activation and augmenting atherosclerotic plaque formation. Its expression is up-regulated in atherosclerotic plaques in human coronary arteries [104, 105]. Besides, it was shown that soluble ICAM-1 is correlated with the severity of atherosclerosis, that its inhibition can retard atherogenesis [106-108] and that ICAM-1 can serve as a predictor of vascular events [109].

VASCULAR CELL ADHESION MOLECULE-1 (VCAM-1)

VCAM-1 facilitates adhesion of most inflammatory cells (monocytes, lymphocytes, eosinophils etc.) to the vascular wall and monocytes recruitment into atherosclerotic sites [110].

METALLOPROTEINASES (MMPs)

Monocyte/macrophage-derived MMPs are zinc-dependent endoproteases with collagenase and/or gelatinase activity [111]. These agents damage the endothelium and collagen fibrils in atherosclerotic plaques, thus accelerating the process of atherothrombosis [112-116].

CONCLUDING REMARKS

Clinical implications of inflammation in atherosclerosis have been acknowledged in the past decade. Diverse markers of inflammation have been associated with adverse vascular events and inefficiency of primary and secondary cardiovascular prevention [117]. The concept that inflammation contributes to atherosclerotic cardiovascular disease has had a remarkable impact on our understanding of atherothrombosis that is no longer considered as a reflection of lipid disorders, but rather as a disorder characterized by low-grade vascular inflammation.

Population-based studies have proved that elevated levels of several inflammatory mediators have predictive values for future coronary vascular events. In particular, some prospec-

tive studies have demonstrated increased vascular risk associated with increased baseline levels of pro-inflammatory cytokines (IL-6 and TNF- α) [118], cell adhesion molecules (ICAM-1, P-selectin, E-selectin [119] and acute-phase reactants (CRP, fibrinogen, serum amyloid A) [120]. It has recently been suggested that hs-CRP is a well validated biomarker with predictive value. Benefits of hs-CRP for stratifying the risk of atherosclerotic events have been confirmed. It is the most useful predictive marker of recurrent adverse events, including death, myocardial infarction and restenosis after cardiac revascularization [121].

In contrast to cytokines, CRP has a long half-life with stability of levels with no observable circadian variation [122]. In addition, there are well validated assays for detection of CRP in freshly frozen and stored plasma [123]. The American Heart Association and the Centers for Disease Control and Prevention have published a joint scientific statement on the use of inflammatory markers, particularly hs-CRP in clinical and public health practice. According to the statement, subjects with hs-CRP levels <1.0 mg/L are at low risk, those with hs-CRP of 1.0-3.0 mg/L at moderate risk, and those with hs-CRP >3.0 mg/L at high risk of vascular events. Furthermore, subjects with unexplained, sustained elevation of hs-CRP (>10.0 mg/L) should be evaluated to exclude non-cardiovascular causes [124-126].

In one study, circulating levels of CRP were found to be significantly increased in patients with unstable angina, particularly in those who later develop an adverse vascular event. In this study, the relative risk of adverse events associated with the highest tertile of CRP levels was 5.2 [127]. In another study, CRP levels were associated with an increased incidence of major adverse cardiac events in patients with acute myocardial infarction [128]. Also, it was shown that CRP levels greater than 10 mg/L independently predict the presence of significant coronary lesions [129]. Patients with hs-CRP >3.5 mg/L had 11-fold increased risk of cardiac events, compared with those with lower levels [130].

Elevated hs-CRP levels are associated with poor quality of life, depression, physical inactivity [42], and are predictive of poor outcomes in coronary atherosclerosis and left ventricular dysfunction [43].

The role of anti-inflammatory drugs in prevention of atherosclerotic events has not been fully elucidated. Some studies have demonstrated that anti-inflammatory drugs can be useful in prevention of scar formation after catheter procedures and vascular surgery [131]. Importantly, anti-inflammatory actions of statins have been linked to their favorable effects on atherosclerosis [132]. Several other therapeutic agents with anti-inflammatory properties are being investigated in studies with experimental and clinical models of inflammation-associated atherosclerosis.

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