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Inflammation in Ischemic Heart Disease

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Abstract

Advances in understanding the pathobiology of atherosclerosis have implicated inflammation as a central contributor to its initiation and progression. Several risk factors were known to promote atherosclerosis, and various biomarkers were shown to identify patients at risk for Coronary Artery Disease (CAD). One of the major subset of mediator contributing in the interaction between inflammatory cells and endothelial and smooth muscle cells and the subsequent perpetuation of the inflammatory reaction are cytokines. C-reactive protein (CRP) is the best studied of the inflammatory biomarkers in CAD and increasing evidence suggests the localization of CRP in the atherosclerotic plaque and its role in the inflammatory process of atherosclerosis. Higher levels of Pentraxine-3 were found in patients with cardiovascular disease and its levels seem to be more closely related than CRP. Novel interesting biomarkers that was recently extensively studied is soluble RAGE: its serum levels correlate positively with occurrence and severity of CAD, underlining their central role in the pathogenesis of atherosclerosis. In addition, Lectinlike oxidized low-density lipoprotein receptor-1 was demonstrated to favoring the formation of atheroma. Finally, the most recent evidences demonstrated that miRNAs can be detected in serum and in plasma in stable form and may be useful as biomarkers for disease. However, the influence of endothelial activation and atherosclerotic disease, as well as the influence of current vasculoprotective therapy, on levels of circulating miRNAs is still unknown. The aim of the present review was to systematically report current evidence on the possible new promising biomarkers recently found as associated with coronary artery disease.

Keywords: Coronary Artery Disease; Soluble RAGE; miRNAs; CRP; Cytokines

Abbreviations

ACS: Acute Coronary Syndrome; AGEs: Advanced Glycation End products; CAD: Coronary Artery Disease; cRAGE: cleaved-RAGE; CRP: C-Reactive Protein; esRAGE: endogenously secreted RAGE; IFN: Interferon; IL-1: Interleukin 1; IL-6: Interleukin 6; LDL: Low-Density Lipoprotein; LOX-1: Lectinlike Oxidized low-density lipoprotein receptor-1; MI: Myocardial Infarction; M-CFS: Macrophage Colony-stimulating Factor; MCP-1: Monocyte Chemo attractant Protein-1; PTX3: Pentraxin-3; RAGE: Receptor for Advanced Glycation End-products; SMI: Silent Myocardial Ischemia; sRAGE: soluble RAGE; TNF: Tumor Necrosis Factor.

Introduction

Coronary Artery Disease (CAD) is still one of the leading causes of death in the Western world. Endothelial activation is considered the first step of atherosclerotic lesion development, followed by invasion of proinflammatory cells and proliferation and dedifferentiation of smooth muscle cells [1]. New understanding in pathobiology of atherosclerosis has implicated inflammation as a central contributor to initiation and progression. Chemoattractant cytokines, such as monocyte chemoattractant protein-1 (MCP-1), mediate transmigration of inflammatory cells into the sub endothelial space and macrophage colony-stimulating factor (M-CSF) contributes to differentiation of monocytes into macrophages were transformed into foam cells, key element of the fatty streak [2]. Mononuclear cells release cytokines, which recruits further inflammatory cells, resulting in further uptake and oxidation of low-density lipoproteins (LDLs) [3].

Therefore, inflammation and biochemical modifications, causing endothelial and smooth muscle cells to proliferate, produce extracellular matrix molecules, and form a fibrous cap over the developing atheromatous plaque. Plaques lead to clinical symptoms by producing flow-limiting stenoses (causing stable angina) or by provoking thrombi that interrupt blood flow on either a temporary basis (causing unstable angina) or a permanent one (causing myocardial infarction) [4].

Several risk factors were known to promote atherosclerosis, and various biomarkers were shown to identify patients at risk for CAD. Some studies found an association among inflammatory biomarkers and cardiovascular diseases suggesting their utility to identify the risk of an acute ischemic event and the detection of vulnerable plaques.

C-reactive Protein

C-reactive protein (CRP) is the most studied CAD inflammatory biomarkers. It is a pentraxin, composed of five subunits that may increase in various pathological situations; it synthesized mainly in the liver, but it also produced by leukocytes and adipocytes [5]. Increasing evidence suggest the CRP localization in the atherosclerotic plaque and its role in inflammatory process of atherosclerosis [6]. Seems that CRP had also an important role on plaque vulnerability, as well as restenosis after coronary intervention [7].

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The association between CRP circulating levels and numerous cardiovascular risk factors, such as blood pressure, serum triglycerides, fasting blood glucose and obesity [8], underline the CRP roles as useful biomarkers for short-term prognosis and long-term risk assessment after a cardiovascular event. Its association with long-term risk assessment in patients with stable CAD or after an Acute Coronary Syndrome (ACS) has been extensively investigated. In particular, it was reported that high CRP levels at baseline was associated with 45% increase in the relative risk of nonfatal myocardial infarction or sudden cardiac death over 2 years of follow-up [9].

The Canadian Cardiovascular Society suggested that CRP evaluation in patients at intermediate risk could represent a predictive risk of cardiovascular event from 10% to nearly 20% within the subsequent 10 years observation. Equally, the National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines and the American College of Cardiology Foundation-AHA Task Force on Practice Guidelines affirmed that evaluation of CRP levels was acceptable for patients at intermediate risk [10].

Pentraxin-3

Pentraxin-3 (PTX3), a member of the pentraxins superfamily characterized by a long N-terminal domain, results as an important player in immunity and inflammation [11]. Dendritic cells, macrophages and endothelial cells in response to interleukin 1 (IL-1) and tumor necrosis factor (TNF) produced PTX3 [12]. Higher plasma PTX3 levels were found in patients with cardiovascular disease and its levels seem to be more closely related than CRP in acute phase of cardiac damage [13]. Soluble PTX3 seems too increased in the early phase after ischemic heart events and PTX3 mRNA and protein expression enhanced in the ischemic area of the heart [14]. It was also demonstrated that PTX3 was strongly expressed on the surface of lumen and within the atherosclerotic plaque both in humans and animal models [15]. These evidences suggest the PTX3 role as a specific prognostic indicator. In addition, PTX3 resulted to be more specific than cardiac troponin I in patients with unstable angina pectoris within the six hours of the chest pain [16].

Cytokines

Cytokines are pleiotropic proteins that have been extensively implicated in the inflammation process. Cytokines are one of the major subset of mediators that contribute to the interaction between inflammatory, endothelial and smooth muscle cells and the subsequent perpetuation of the inflammatory reaction. Several studies indicated that serum levels of MCP-1, tumor necrosis factor (TNF)-α and interferon (IFN)-γ correlate positively with occurrence and severity of CAD, underlining their central role in the pathogenesis of atherosclerosis [17].

Interleukin 6 (IL-6) may increase plaque instability driving expression of matrix metalloproteinases, TNF-α, and MCP-1 [18]. Previous studies showed that IL-6 levels were significantly higher in patients with ACS than in patients with clinically stable angina pectoris, and those elevated levels of IL-6 were associated with higher mortality [19-20] and increased risk for future myocardial infarction, independently of CRP [21]. However, the application of IL-6 as a biomarker is limited by large circadian variations and lack of confirmatory studies.

The pathogenesis of atherosclerosis was found to be linked to the interleukin 1 family, particularly by IL-1β. Plasma concentrations of IL-1β are elevated in patients with hypercholesterolemia and it seems that statin therapy may have lower IL-1β levels [22]. However, the relationship between IL-1β and atherosclerotic clinical events is not fully understood at this moment and further data from clinical studies are needed for this assessment. Findings that atherogenic fatty acids induce IL-1α to promote vascular inflammation identify a key role for this less-well-studied cytokine [23].

Through its effects on endothelial function, coagulation, insulin resistance and lipid metabolism, the proinflammatory cytokine TNF-α could be involved in cardiovascular pathophysiology [24]. TNF-α has also been implicated in myocardial dysfunction and remodeling after acute coronary events [25].

Mainly inflammatory cells and endothelial cells express MCP-1 and its expression level is upregulated after proinflammatory stimuli and tissue injury [26]. An association between MCP-1 levels and the extent of coronary atherosclerosis [27] and an increased risk of death for Myocardial Infarction (MI) after 10 months, even after adjustment for traditional risk factors is known [28].

These data suggest that cytokines roles in the prediction of cardiovascular risk is still controversial, or, at least, we do not know yet, which one is better as a prognostic biomarker and probably a therapeutic target in CAD.

Eotaxin

Eotaxin is a chemokine produced by the fat tissue. The eotaxin family comprises three distinct peptides (eotaxin, eotaxin-2 and eotaxin-3), which are implicated in eosinophilic inflammation. Eotaxin binds with high affinity and specificity the chemokine receptor CCR3 and plays an important role in the pathogenesis of allergic disease. Eotaxin belongs to CC chemokines with selective activity for eosinophils and basophils and it is important in extrinsic asthma, inflammatory disorders [29]. Moreover, a large study on patients with documented CAD showed that reduced levels of circulating eotaxin-3 might represent a potentially powerful biochemical marker for predicting future adverse cardiovascular events such as death from cardiovascular causes and nonfatal myocardial infarction [30].

Receptor for Advanced Glycation End-products

Advanced Glycation End-products (AGEs) are a heterogeneous and complex group of biochemical modifications, which play an important role in development of chronic disease processes [31]. AGEs cause a wide range of deleterious effects, which are mediated by cellular receptor, especially RAGE (Receptor for Advanced Glycation End-products) [32,33]. RAGE, a multi-ligand member of the immunoglobulin superfamily, is a ubiquitous receptor present on epithelial, neuronal, vascular and inflammatory cells, usually expressed at low levels in homeostasis and to increased degrees at sites of stress or injury [34]. RAGE acts as a pattern recognition receptor for ligands released by inflamed, stressed and damaged cells [35]. Increased expression of both cell-surface RAGE and accumulation of its ligands was observed in a range of disorders characterized by chronic inflammation, such as inflammatory bowel disease,

rheumatoid arthritis, atherosclerosis, amyloidoses, Alzheimer's disease and the vascular complications of diabetes [36].

RAGE is composed of a large extracellular part, a transmembrane domain and a 43-amino-acid-long cytoplasmic tail [37]. The extracellular domain includes a short signaling sequence for the cell membrane binding and two C-type and one V-type immunoglobin-like domains. The ligand-binding site is into V-domain, whereas the cytosolic tail mediates intracellular signaling. More recently, it has been suggested that RAGE may form dimers and multimers for ligand binding to occur [37].

A range of splice variants of murine and human RAGE has been identified; most of these lead to removal of the transmembrane domain to produce soluble variants. RAGE has a C-truncated secretory isoform that circulates in plasma and which at least two variants: one secreted from cells, endogenously secreted RAGE (esRAGE), and another one, which formed by proteolytic cleavage, by matrix metalloproteinases from the cell-surface, cleaved-RAGE (cRAGE) [35]. The soluble isoform (sRAGE) acts as a decoy receptor for RAGE ligands, and is thought to afford protection against inflammation [38,39].

The RAGE–ligand interaction triggers activation of NF-κB and other signaling pathways through stimulation of p21ras, ERK (extracellular signal-regulated kinase) 1/2, p38 MAPK, SAPK (stress-activated protein kinase)/JNK (c-Jun n-terminal kinase), Rho GTPases, PI3K and JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathways. Subsequently, expression of inflammatory cytokines increased, leading to an inflammatory response with associated cellular migration and proliferation [9]. Ligation of RAGE causes a positive feed-forward loop, in which inflammatory stimuli activate NF-κB, which induces RAGE expression, followed again by NF-κB activation [40]. NF-κB up-regulates multiple cellular signaling cascades and determines increased production of numerous growth factors and cytokines [41].

The complexity of the role of RAGE in the biological setting is also evident from human studies in different vascular disease states [42]. In patients with heart failure, higher sRAGE concentration and RAGE -374T/A polymorphism in RAGE gene promoter was associated with heart failure severity [43,44]. On the other hand, many studies have pointed out that decreased sRAGE levels are associated with increased extent of CAD and with higher incidence of cardiovascular events, such as myocardial infarction. Falcone C et al. in 2005 [45], showed that low plasma levels of sRAGE were independently associated with the prevalence of CAD in non-diabetic men. Recent data from the Dallas Heart Study [46] confirm that lower levels of sRAGE are independently associated with a greater prevalence of coronary atherosclerosis. More recently, Falcone et al., demonstrated that sRAGE plasma levels were significantly lower in patients with ACS than in patients with stable angina, suggesting that sRAGE can be considered an indicator of destabilization of vulnerable plaque [47]. In addition, it shown that CAD patients presenting with peripheral artery disease have lower sRAGE levels than CAD patients without peripheral atherosclerosis, showing that stable atherosclerotic lesions in different vascular districts are inversely related to soluble decoy receptor sRAGE [48]. Moreover, it was shown that certain polymorphisms in the RAGE gene (-374T/A, -429T/C, G82S) are strongly associated with higher sRAGE levels [49], implicating a complex genetic regulation of sRAGE levels and suggesting that sRAGE may not be a marker of a disease state but also a potential target in the pathobiology of the atherosclerotic process. The correlation between the RAGE gene polymorphisms and CAD was extensively investigated and several studies demonstrated that -374A allele might reduce susceptibility to CAD exerting a protective effect on coronary risk [50]. In a study of Falcone C et al, the mean number of injured vessels was significantly lower in AA genotype than AT or TT genotype patients and it would seems to indicate that this polymorphism is one of the likely determinants candidate for genetic variance of disease phenotype in coronary atherosclerosis [51]. Another study by the same research group indicated that -374T/a polymorphism could be also associated with a reduced risk of in-stent restenosis after coronary stent implantation [52]. These findings clearly illustrate the need for further studies of the complex involvement of RAGE in the development of vascular disease states.

Lectin-like Oxidized Low-density Lipoprotein Receptor-1

Lectinlike oxidized low-density lipoprotein receptor-1 (LOX-1) allows the passage of oxidized lipids in the cells and may cause endothelial dysfunction/apoptosis, inflammation, and the increase smooth muscle cell number favoring the formation of atheroma [53-56]. Moreover, LOX-1 increment observed to be associated with cardiovascular risk factors like hypertension and metabolic disorder. Clinical studies have demonstrated that well-known coronary risk factors, including metabolic diseases, hypertension, obesity and smoking, are associated with oxidative stress. When the LDLs are exposed to oxidative stress, they are caught and oxidized in the vessel, forming ox-LDL that promotes the synthesis of a large variety of cytokines and chemokines by the endothelium [57].

Recent study observed that the circulating levels of sLOX-1 are very high in ACS and that the plateau value reached before troponin T, highlighting the instability of the plaque [58].

miRNA Levels

MicroRNAs (miRNAs) are small (~22-nucleotide) noncoding RNAs regulating gene expression on the post-transcriptional level by binding the target mRNA, leading either to degradation or to translational repression [59]. MiRNAs control is critically involved in many biological processes in health and diseases including cardiovascular diseases [60]. *In vitro* studies showed that several specific miRNAs stimulate of inhibit angiogenesis in endothelial cells [61]. In particular, miR-126 was shown to be highly enriched in endothelial cells, and its expression is essential for vascular development [62,63]. In addition, members of the miR-17-92 cluster were shown to modulate angiogenesis [64]; miR-143 and miR-145 are highly expressed in smooth muscle cells and they can alter the cell maintenance [65,66]. In cardiomyocytes, miR-1 and miR-133 control myogenesis, cardiac development, and hypertrophy [67,68].

Recent studies demonstrated that miRNAs be detected in serum and in plasma in stable form and may be useful as biomarkers for disease [69]. Although, the mechanism of how circulating miRNAs are released into the circulation is unclear; evidence suggests that miRNAs are actively secreted in micro vesicles [70,71]. For these

reasons, that circulating myocardial-derived miRNAs might be useful as potential biomarkers. However, the influence of endothelial activation and atherosclerotic disease, as well as the influence of current vasculoprotective therapy, on levels of circulating miRNAs is unknown.

It proved that miR-155 could be a new component of inflammatory signal transduction pathways in the pathogenesis of atherosclerosis.

Of interest is miR-155, which proved a new component of inflammatory signal transduction pathways in the pathogenesis of atherosclerosis. In fact, the expression of miR-155 considered a prospective marker for CAD prognosis predicting, since it mainly found in patients with CAD compared to healthy subjects [72].

Coenzyme Q10

Coenzyme Q10 is a lipid-soluble benzoquinone, key component of the mitochondrial respiratory chain for adenosine triphosphate (ATP) synthesis [73. Coenzyme Q10 is an intracellular antioxidant that protects membrane phospholipids, mitochondrial membrane protein and LDLs from free radical-induced oxidative damage [74]. Patients with lower coenzyme Q10 concentration might have compromised mitochondrial function and correlating to the severity of the disease [75]. Recent studies showed that subjects with higher coenzyme Q10 concentrations had a significantly lower risk of CAD [76] and demonstrated that coenzyme Q10 supplementation reduces oxidative stress and increase antioxidant enzyme activity in patients with CAD [77]. Few studies have investigated the relationship between plasma coenzyme Q10 and racial differences, especially in Asian population. However, significantly lower Q10 plasma levels reported in Indian males than Chinese ones [78]. This observation may explain the higher susceptibility of this ethnic group to CAD and it be linked to the racial differences in lifestyle and nutrition.

Coenzyme Q10 and tocopherols are the mayor circulating lipid-phase micronutrients know to help mitigate oxidative damage and prevent chronic disease, possibly by preventing damage from chronic inflammation [79]. Many biological effects of γ-tocopherol have observed *in vitro*, with potentially important biological and health consequences, including inflammation [80] and immune function [81]. Previous epidemiological studies have suggested the anti-inflammatory role of γ-tocopherol and its protective association with heart disease [82].

Conclusion

Recently, changed the attitude of the physician as regards both the primary and secondary prevention. To traditional risk factors, including hypertension, diabetes, smoking, obesity, dyslipidemia, and positive family history of CAD, that have always been considered implicated in ischemic heart disease, should be added new innovative markers. Adequate risk assessment remains the most challenging in the classification of individuals into low or intermediate risk categories.

Inflammation plays a key role in the initiation and promotion of atherosclerosis and may lead to ACS by induction of plaque instability. For this reason, numerous inflammatory markers have extensively investigated as potential candidates for the enhancement of cardiovascular risk assessment. Indeed, inflammation provides the pathway that links alterations in traditional risk factors and modification in the biology of the artery wall that give rise to atherosclerosis and its complications. Although, recent data demonstrate that there is a close association between inflammatory biomarkers and CAD, further studies must be carried out taking into account also some important criteria typically used in the selection of a new biomarker: discrimination, calibration and reclassification, i.e. the ability of a test to discern between those that will face the disease from those that will be free, the assessment of the risk factor predicted and observed, classification in categories of low, intermediate and high risk for CAD.

Inflammatory biomarkers may be useful to identify apparently healthy individuals, without known CAD, who may be at a higher risk than estimated by traditional risk factors. They also may have prognostic value for future cardiovascular risk among subjects at high risk or with documented cardiovascular disease.

The 10-20% of middle-aged and elderly subjects with no apparent heart disease presented Silent Myocardial Ischemia (SMI), and is associated with higher risk for cardiovascular mortality. There is a particular biochemical pattern of inflammatory system activation that explains the lack of anginal symptoms. Several observations suggest that inflammatory cytokines orchestrate nociception and suggest their role in the perception of pain. Particularly, pain perception may result from micro environmental balances between pro-infiammatory and anti-infiammatory cytokines [83]. In addition, recent study by Mouridsen et al. [84] showed that, in asymptomatic subjects with SMI, hs-CRP adds significant prognostic information after adjustment for conventional risk factors. They identified a cut off value for risk stratification among subjects with SMI in order to define low-risk subgroup and patients with relatively poor prognosis. Moreover, Guzel et al. showed higher IL-6, leptin and osteoprotegerin values in diabetic patients with SMI, as compared to diabetic patients without SMI [85].

To date, many therapies reduce the risk of initial and recurrent cardiovascular events, but many patients go against one of many events due to the failure of conventional therapies to adequately address the inflammation. Drugs that inhibit different inflammatory pathways involved in atherosclerosis are subject of current research, such as antioxidants, phospholipase A2 inhibitors, leukotriene pathway inhibitors, IL-1 inhibitors and p-selectin inhibitors. Some of these drugs being investigated in Phase III clinical trials of atherosclerosis. Improved access to currently available therapies like statins would decrease the burden of cardiovascular disease worldwide. Several trials investigate the relationship between statins and CRP levels. These studies indicate that statin therapy lowers CRP levels, independently of lipid levels, and appear to eliminate the excess of mortality associated to increase CRP, supporting the possibility that statins have anti-inflammatory effects [86]. In Physicians' Health Study was also evaluating the role of aspirin in prevention of first MI [87]. This study showed that aspirin related with a significant risk reduction indicating also that aspirin is more efficacious in the prevention of first vascular events. However, statins and aspirin only delay the progression of atherosclerotic disease. It is therefore clear that the next generation of therapeutic strategies directly treat the inflammation at the base of the formation and modification of the atherosclerotic plaque.

However, being atherosclerosis a chronic disease, the long-term systemic use of anti-inflammatory drugs involves the risk of complications resulting from immunosuppression. To add correctly immunosuppressive drugs in the treatment of patients, it is necessary to increase the knowledge about the inflammatory pathogenesis of atherosclerosis, and find safe and effective compounds that can directly suppress plaque inflammation.

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