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Perspective

Current advances in circulating inflammatory biomarkers in atherosclerosis and related cardio-cerebrovascular diseases

Jun-Xuan Lv, Qi Kong, Xin Ma*

Department of Neurology, Xuanwu Hospital of Capital Medical University, National Clinical Research Center for Geriatric Disorders, Clinical Center for Cardio-cerebrovascular Disease Capital Medical University, Beijing 100053, China

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Abstract

Atherosclerosis (AS) is a systemic chronic disease affecting both the coronary and cerebral arteries. Inflammation plays a key role in the initiation and progression of AS, and numerous inflammatory factors have been proposed as potential biomarkers. This article reviews recent research in studies on major circulating inflammatory biomarkers to identify surrogates that may reflect processes associated with AS development and the risk of AS-related vascular events, such as Von Willebrand factor, lectin-like oxidized low-density-lipoprotein receptor-1, soluble urokinase plasminogen activator receptor, regulated upon activation, normal T-cell expressed and secreted, and microparticles, which may provide new perspectives for clinical AS evaluation and risk stratification.

Keywords: Atherosclerosis; Plaques; Inflammatory biomarkers; Risk factors

Atherosclerosis (AS) is among the most common pathological changes in ischemic cardiovascular and cerebrovascular disease.[1] Since Ross et al presented the "Response to Injury Hypothesis" in 1973,[2] a large number of studies has indicated that AS is a progressive chronic inflammatory vascular disease. Early AS lesions show characteristic low-density lipoprotein (LDL) accumulation and modification in the subendothelial area. Thus, endothelial cells are activated and up-regulate their adhesion molecule expression to enhance leukocyte recruitment and infiltration into the AS lesion, where they generate a series of cytokines to initiate and perpetuate inflammation.[3] Phagocytes in these inflammatory foci, mainly including macrophages and vascular smooth muscle cells, ingest modified LDL and are converted into foam cells, which further fuel lesion progression. Moreover, inflammation is closely related to AS lesion vulnerability and subsequent cardio-cerebrovascular events, partially by producing matrix metalloproteinase that may degrade the extracellular matrix and weaken the fibrous cap.[4]

Although the involvement of inflammation in atherosclerosis has been known for more than 100

* Corresponding author.
E-mail address: maxin118@hotmail.com (X. Ma).

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years, the molecular mechanisms have only recently been clarified. Numerous circulating inflammatory factors have been found to serve as surrogates that may reflect processes associated with AS development and the risk of AS-related events. We critically reviewed current major studies to identify relevant inflammatory biomarkers to promote better risk stratification and optimal management.

Von Willebrand factor—endothelial injury-induced inflammation fuels AS development

Von Willebrand factor (VWF) is a large plasma adhesive glycoprotein with a multimeric structure of varying size (up to 20,000 kDa) and is selectively produced in megakaryocytes and endothelial cells.[5] VWF plays a key role in repairing vascular injury. It can rapidly bind to exposed fibrillar collagen type I and III and immobilizes at sites of vascular damage. VWF can also combine with platelet glycoprotein Ibα to participate in platelet decelerating, rolling, and arresting, facilitating hemostasis and thrombus formation.[6]

Recently, it was suggested that VWF also functions in inflammatory processes. *In vitro* analysis demonstrated that VWF mediated leukocyte adhesion as a ligand for P-selection glycoprotein ligand 1 and β2 integrin on leukocytes.[7] Petri et al found that VWF also facilitates interaction between leukocytes and the endothelium, leading to extravasation of leucocytes into inflamed tissues, which is a key process in early AS.[8] Methia et al discovered that VWF-deficient mice had smaller aortic fatty streak and fibrous plaques, as well as fewer macrophages in the lesions, compared to normal mice.[9] It has also been confirmed that VWF can directly stimulate the proliferation of smooth muscle cells (SMCs), which constitute the major cell component of atherosclerotic plaques.[10] Several anti-VWF antibodies tested in animal models, such as 82D6A3, GPG-290, and AJW200, primarily showed both anti-thrombotic and anti-inflammatory effects.[11]

Clinical studies have also indicated the potential role of VWF in reflecting AS severity, risk of cardiovascular events, and adverse outcomes. A study including 318 patients with acute coronary syndrome and 263 patients with stable angina pectoris showed that a high plaque burden in coronary angiography or intravascular ultrasound virtual histology imaging was associated with higher VWF levels, and VWF levels predicted the adverse cardiovascular outcome and death during one-year follow-up.[12] A multi-ethics and multi-centers study also found that levels of VWF were increased significantly in patients with first ST-elevation myocardial infarction compared to in healthy controls.[13] Recently, studies on VWF as a biomarker in cerebrovascular disease have been conducted. In patients with chronic cerebrovascular disease, plasma VWF levels were clearly higher than those in healthy individuals, but lower than in acute ischemic stroke and transient ischemic attack (TIA) patients.[14]

These laboratory and clinical findings reveal the importance of VWF in triggering inflammation, which may give rise to AS progression and the occurrence of AS-related vascular events. The therapeutic potential of regulating VWF levels has been suggested by primary experiments. However, additional studies are needed to determine whether VWF can be used as a reliable biomarker or an efficient treatment target in clinical practice.

Lectin-like oxidized LDL (oxLDL) receptor-1 (LOX-1)—recognition of oxLDL mediates its proatherosclerotic inflammatory effects

LOX-1, a 50-kDa transmembrane glycoprotein in the C-type lectin family, was initially identified in bovine aortic endothelial cells and later found to be expressed in other cell types, such as human coronary artery endothelia cells, macrophages, platelets, fibroblasts, SMCs, and cardiomyocytes.[15,16]

In early AS lesions, monocyte-derived macrophages bind and engulf oxLDL deposited in the subendothelial area to form foam cells, which is mediated by numerous scavenger receptors (SRs) on its surface, such as SR-AI, SR-BI, LOX-1, and CD36.[17] LOX-1 is nearly undetectable under normal physiological conditions, but is significantly up-regulated in vascular cells under atherogenic conditions, and thus is considered to be a key receptor binding oxLDL in AS development. Additionally, there appears to be positive feedback between LOX-1 expression and oxLDL accumulation.[18] Subsequent studies supported the involvement of LOX-1 in AS processes, such as endothelial dysfunction, recruitment of monocytes in arterial intima, foam cell formation, endothelial cell and SMC apoptosis, and plaque rupture.[18,19]

Animal studies suggested that expression of LOX-1 was up-regulated after a short time of coronary artery occlusion followed by reperfusion, and in rat model of the focal cerebral transient ischemia, expression of LOX-1 was up-regulated by 10-fold at the ischemic lesion site.[20] Injection of LOX-1 antibody before

ischemia occurrence reduced inflammation, oxidative stress, and apoptosis, as well as infarct size in a coronary artery occlusion-reperfusion model.[21] LOX-1$^{-/-}$ mice showed higher survival rate because of myocardial injury attenuation and cardiac function improvement in model mice with permanent coronary artery ligation.[22] Various natural compounds and synthetic formulations, such as tanshinone II-A, curcumin, gingko biloba extract, small chemical inhibitors of LOX-1, and LOX-1 antibodies, were shown to reduce inflammation in AS through LOX-1-mediated pathways.[23]

Specifically, LOX-1 can be cleaved from the cell membrane by proteolytic enzymes to become soluble LOX-1 (sLOX-1), which may represent the expression level of LOX-1.[24] A human biomarker study demonstrated that high LOX-1 ligand activity was a risk factor for ischemic stroke and increased sLOX-1 levels in stroke patients.[24] Recently, a genetic case–control study of 526 patients with stroke and 640 healthy controls showed that the minor allele of rs1050283 was associated with higher sLOX-1 levels and higher risk of atherosclerotic cerebral infarction in a Chinese population.[25]

A growing body of evidence supports that LOX-1 is an attractive marker for AS risk evaluation and potent target for AS prevention and treatment. However, additional studies are needed to determine whether sLOX-1 reflects the expression level of LOX-1 on the cell membrane, and if the sLOX-1 level is elevated systemically rather than adjacently to AS lesions, which may further facilitate its clinical translation.

Urokinase-type plasminogen activator receptor (uPAR)—coagulation system interacts with inflammatory system in atherosclerotic lesion progression

uPAR is a membrane-linked protein widely found in various cell types, including immunologically active cells and vascular endothelial cells.[26] As a molecule with multiple biological functions, uPAR is involved in many pathophysiological processes of AS, such as plasminogen activation, modulation of cell adhesion, migration, and proliferation.[26,27] Stimulated by inflammation, uPAR can be cleaved from the membrane of endothelial cells, macrophages, and other cells to become soluble as soluble uPAR (suPAR).[28]

In the MONIKA study, after adjusting for age, gender, smoking, and physical activity in 2273 individuals, suPAR was found to be relevant to endothelial dysfunction and AS.[29] Another cross-sectional study of 1126 randomly sampled middle-age individuals showed that coronary artery calcification score was increased by 16% when plasma suPAR concentrations were increased by 1 ng/ml. When suPAR was added to the Systematic Coronary Risk Evaluation model, its efficacy for predicting remarkable AS, which was defined as a coronary artery calcification score >100, was significantly elevated.[30]

More recently, it was shown that plasma suPAR levels in symptomatic carotid stenosis were remarkably higher than in asymptomatic carotid stenosis, and suPAR levels were associated with the vulnerable inflammatory plaque in immunoassay.[31] A prospective population-based cohort study including 569 healthy individuals demonstrated that elevated blood suPAR levels were associated with an increased incidence of cardiovascular and cerebrovascular events during a mean follow-up of 14.1 years.[32]

Thus, uPAR may reflect the interaction between the coagulation system and inflammatory system in AS development, and inflammation in turn increases the level of suPAR, which may be a promising biomarker not only for reflecting AS severity, but also for improving risk prediction of cardio-cerebrovascular events. Additionally, suPAR shows high stability during storage and repeated freeze-thaw circles,[33] suggesting that it may be more feasible for clinical applications.

Regulated on activation, normal T cell-expressed and secreted (RANTES)—inflammatory chemokine plays a complicated role in AS processes

CC chemokine ligand-5, or RANTES, a soluble 7.8 kDa protein, is a chemokine secreted by many different cell types, such as activated T cells, macrophages, platelets, endothelial cells, and smooth vascular cells.[34]

RANTES is mainly involved in chemotaxis and activating leucocytes such as monocytes, T cells, and eosinophilic/basophile granulocytes.[35] *In vivo* and *in vitro* studies confirmed that RANTES in flow facilitated monocyte recruitment and infiltration in the subintimal area.[36] Additionally, studies on human and murine models demonstrated a key role of RANTES in the formation of atherosclerotic plaque and pathological advancement of AS lesions.[37]

In the Atherosclerosis Risk In Communities study, by performing gadolinium-enhanced magnetic resonance imaging of the carotid artery and measuring the plasma RANTES levels of 1901 participants, positive associations between RANTES and carotid wall

thickness and lipid core volume of AS plaque were discovered, suggesting that high RANTES level is correlated with the severity of carotid stenosis and vulnerability of plaque.[38]

However, other studies showed contradictory results. A study on 389 males found that low RANTES levels in the plasma were associated with severe AS lesions in coronary angiography, and low baseline RANTES levels predicted acute myocardial infarction and cardiac mortality during a follow-up of 24 months.[39] Another coronary angiography study of 62 patients with AS in the coronary artery also concluded that the mean plasma RANTES level was significantly higher in patients with lower AS severity than in patients with severe coronary artery disease.[40]

Thus, additional studies are needed to clarify the ambiguity of RANTES in mediating AS development, as well as the detailed relationship of RANTES with the severity of AS and risk of AS-related ischemic events, before using this molecule as a reliable clinical biomarker.

Microparticles (MPs)—budding of plasma membrane with various phenotypes participates in multiple inflammatory pathways of AS

MPs are submicron fragments of cell membranes (measuring from 50 nm to 1 μm in diameter) made up of oxidized phospholipids and specific proteins that may reflect the originating cells.[41] Several types of inflammatory and physical stimulation may result in asymmetry and disruption of the lipid membrane through different signaling pathways, leading to cellular activation and apoptosis, in turn inducing budding of the plasma membrane and release of MPs.[42]

MPs in circulation are derived from different types of cells such as erythrocytes, granulocytes, monocytes, lymphocytes, platelets, and endothelial cells.[41] MPs are detectable in healthy people, but their phospholipid composition, surface marker, interior protein structure, and genetic information may vary under different physical and pathological conditions.[43] Recently, studies showed that excess production of MPs was involved in many diseases such as cardiovascular disease, tumor, infection, and pathological pregnancy. The association between MPs and AS is mediated by multiple mechanisms including inflammatory response, endothelial dysfunction, angiogenesis, and coagulation.[44,45]

Research has confirmed that platelet microparticles (PMPs) and endothelial microparticles (EMPs) induce the expression of proinflammatory interstitial cell adhesion molecule-1 (ICAM-1), while monocyte microparticles increase the expression of ICAM-1 and interleukin-8.[46] A clinical study of healthy volunteers also suggested a positive correlation between PMPs and interleukin-6.[47] Biasucci et al found that EMPs and PMPs were related to high sensitive C-reactive protein levels in patients who underwent percutaneous coronary intervention after acute coronary syndrome.[48] A clinical study indicated that levels of CD_{45}^{+}-panleukocyte MPs and CD_{45}^{+}/CD_{3}^{+}-lymphocyte MPs were significantly higher among familial hyperlipidemia patients with lipid-rich atherosclerotic plaques than in those with fibrous plaques, indicating that MPs are associated with plaque vulnerability.[49] It has also been found that plasma levels of several phenotypes EMPs were significantly elevated in acute ischemic cerebrovascular patients compared to in healthy controls, including $CD144^{+}CD41a^{-}$, $CD31^{+}CD41a^{-}$, $CD62E^{+}$, and Annexin $V^{+}CD62E^{+}$.[50]

As shown in previous studies, MPs may phenotype-specifically take part in various inflammatory processes of AS, and testing them in combination may be a more sensitive and specific method for evaluating and predicting AS and AS-related diseases. However, as an emerging biomarker, more standardized methods for detecting MPs and additional studies on how MPs exert their biological functions are urgently needed.

Conclusion

Inflammation is a basic pathogenic element in the development of AS and related cardio-cerebrovascular events. Several inflammatory factors have been proposed as potential biomarkers for improving the evaluation of AS and optimizing the identification of high-risk patients. Circulating biomarkers involved in various inflammatory processes appear to be particularly promising because of their better clinical feasibility. However, much work is needed before their wide clinical use, including more mechanism and translational studies to improve their sensitivity, specificity, and reproducibility.

Conflict of interest

The authors declare that they have no conflict of interest.

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