ARTICLE IN PRESS

+ MODEL

Available online at www.sciencedirect.com

ScienceDirect

Chronic Diseases and Translational Medicine xx (2017) 1–6

www.keaipublishing.com/en/journals/cdtm/

www.cdatm.org

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

Received 9 August 2017

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).

Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.cdtm.2017.09.002

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

Please cite this article in press as: Lv J-X et al., Current advances in circulating inflammatory biomarkers in atherosclerosis and related cardio-cerebrovascular diseases, Chronic Diseases and Translational Medicine (2017), https://doi.org/10.1016/j.cdtm.2017.09.002