Understanding the Essential Role of Monocytes in Atherosclerosis

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In recent years, research into the mechanisms of coronary atherosclerosis has progressed remarkably. Until the 1970s, extracellular cholesterol accumulation was thought to be the major determinant factor in human atherosclerosis. The concept of inflammation did not yet exist, and the majority of investigators thought that the mechanisms of the plaque formation might be related to the accumulation of lipoproteins in the arterial wall cells, such as endothelial cells, smooth muscle cells, and macrophages.

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In the 1990s, Ross developed the theory of the mechanism of atherosclerosis as “atherosclerosis: an inflammatory disease”, which proposed that atherosclerosis follows an excessive reaction of defense and the healing process caused by endothelial injury, thus damaging the endothelial barrier and resulting in increased ease of entry of lipoprotein into the intima.¹ When coronary risk factors such as dyslipidemia, diabetes, or hypertension were present, inflammation triggered the formation and progression of arterial atherosclerosis. Since the theory was proposed, many clinical studies have contributed to the concept that “atherosclerosis is a vascular chronic inflammatory disease”.²

Dyslipidemia, diabetes, hypertension, chronic kidney disease, and smoking are the major factors in the development of the inflammatory process,³ and increased levels of inflammatory cytokines, oxidative low-density lipoprotein, angiotensin II, reactive oxygen species, and advanced glycation endproducts. Vascular wall cells, such as endothelial cells and smooth muscle cells, adipocytes and blood cells, such as T cells, macrophages, and blood platelets, all behave as inflammatory leading actors. It is thought that various inflammatory coherence materials released by these cells develop the atherosclerosis process. Vascular endothelial cells, vascular smooth muscle cells, monocytes/macrophages, lymphocytes, mast cells, plasma cells, and dendritic cells have been identified as major cells contributing to human atherosclerosis.⁴

Nozawa et al have shown that the monocyte count might be an attractive surrogate biomarker for diagnosing coronary plaque progression.⁵ It is already known that leukocytes and monocytes contribute to acute inflammation and the onset of arteriosclerosis and subsequent development. When endothelial cells are injured they produce VCAM-1, which is an adhesion molecule that glues monocytes to the endothelial

cell surface and induces the monocytes to migrate into the base of the tunica intima.⁶ After migration through the endothelial barrier, monocytes transform into macrophages.

Taking in a large amount of intimal cholesterol, a macrophage becomes a foam cell and develops fatty streaks, which is the initial atherosclerotic lesion. Furthermore, smooth muscle cells, which migrated by tunica intima, secrete fibrous ingredients, such as collagen, that develop an advanced fibrous plaque. Thrombi may form in regions of bifurcation of coronary vessels where blood flow is turbulent and the atherosclerotic lesion becomes more complex.

Activated macrophages in the atherosclerotic lesion produce reactive oxygen species, cytokines and end peptidase. Some of the macrophages become apoptotic, and this enhancement of the fatty and necrotic core contributes to thrombogenesis and plaque deterioration. The inflammatory process of coronary artery disease is divided into acute and chronic stages. The acute stage accompanies the onset of acute coronary syndrome, with rupture of plaque and intravascular thrombogenesis. The markers that are reviewed and evaluated for the presence of the acute inflammatory process are high-sensitivity C-reactive protein (hsCRP), IL-6, serum amyloid A protein, pentaxin 3, neopterin, lipoprotein-associated phospholipase A2, tumor necrosis factor- α , white blood count, differential white blood count, soluble adhesion molecule, and myeloperoxidase, because they are related to atherosclerosis and thus cardiovascular events. In the patients with acute coronary syndrome, IL-6, an IL-1 receptor, hsCRP and serum amyloid A as inflammatory markers are increased in the circulatory blood system. However, the levels of these markers are not related to the seriousness of the atherosclerotic lesion, but contribute to prognosis. In addition, it is known that white blood cells contribute to the onset and development of atherosclerosis, as well as to acute inflammation.

In the daily clinical setting, cardiologists often find that patients with chronic coronary artery disease continuously show a slight increase in hsCRP, but the marker can not provide detailed information about the inflammatory process, risk factor control or the large spectrum of the vasculitis syndrome.

Can the monocyte count, as reported in this study, act as an effective marker of prognosis after acute myocardial infarction (AMI) and contribute to coronary plaque progression in the chronic stage? Fukuda et al have shown that the mono-

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cyte count increases after stent implantation and that the peak monocyte count is associated with the in-stent neointimal volume at follow-up.⁷ Chapman et al reported that the monocyte count was an independent predictor of common carotid atherosclerosis in a healthy community population.⁸ Other reports have demonstrated that circulating endothelial progenitor cells derived from bone marrow are incorporated into re-endothelialization after vascular injury.⁹ Nozawa et al have reported similar proof in the coronary artery.⁵ However, there are some problems: the monocyte count is affected by other infectious diseases and the total leukocyte count; for example, the value may be increased if an AMI patient has severe pneumonia. There is ample room to investigate whether the monocyte count increase in the acute phase correlates with the process of arterial atherosclerosis in the chronic stage, and further clinical studies are necessary.

Besides hsCRP, which is already available in the clinical setting, many factors, such as IL-6, serum amyloid A protein, monocyte chemo-attractant protein-1,^{10–12} tumor necrosis factor- α , solubility adhesion factor, myeloperoxidase and adipokine, related to arterial sclerosis and cardiovascular events have been reported by previous basic and clinical studies.^{13,14} However, these newer biomarkers are available in clinical cardiology, so it is necessary to gather detailed information about the character of the molecules participating in each stage of atherosclerosis, and to evaluate which biomarker will be appropriate for monitoring the process. Further study is expected because the monocyte count may be clinically available in the future as the factor that predicts atherosclerosis.

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