Vulnerable plaque is closely related to cardiovascular events and their prognosis. Coronary angiography, coronary CT and coronary magnetic resonance are the main tools used for imaging diagnosis of vulnerable plaque, but they have not become established because methods for screening of vulnerable plaque must be rapid, simple, non-invasive, highly sensitive and specific. In this issue of the Journal, Kimura et al focus on the systemic pentraxin-3 (PTX3) level in patients with ST-elevation acute myocardial infarction (AMI).^{1}

As biomarkers of instability and rupture of plaque, lipid-related factors such as oxidized low-density lipoprotein (LDL)^{2} and lipoprotein-associated phospholipase A2, oxidative stress-related factors such as glutathione peroxidase-1 and myeloperoxidase, proteolytic enzymes such as matrix metalloproteinase, acute inflammation-related factors, and regulators of white blood cells and platelets have been reported.^{3} However, for patients with acute coronary syndrome, particularly those who have received reperfusion therapy with percutaneous coronary intervention (PCI), a useful clinical biomarker to predict prognosis associated with plaque instability has not been established.

Acute-phase proteins such as the PTX family proteins have been expected to be sensitive and specific biomarkers for vulnerable plaque because inflammation plays a key role in the

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development and progression of atherosclerosis. The PTX protein family is divided into 2 subfamilies: “short” PTXs (25 kDa), such as C-reactive protein (CRP) and serum amyloid P (SAP), and “long” PTXs (40–50 kDa), such as PTX3. PTX3 has a long unique domain at the N-terminus in addition to the PTX domain as in the case of CRP and SAP (Figure). CRP and SAP are mainly produced in the liver by stimulation with interleukin-6 in response to primary inflammatory stimuli. Serum levels of high-sensitivity CRP show a significant correlation with the occurrence of the cardiovascular events of atherosclerotic disease, indicating that it is a useful biomarker for predicting cardiovascular event risk and prognosis in patients with coronary artery disease. However, high-sensitivity CRP is not a specific biomarker for vulnerable coronary plaque because CRP is produced by local inflammation at various sites other than the vascular system and by minor infection.

In contrast, PTX3 is produced by stimulation of interleukin-1β, tumor necrosis factor α or oxidized LDL in cells involved in the pathogenesis of cardiovascular diseases, such as vascular endothelial cells, vascular smooth muscle cells, monocytes, macrophages, dendritic cells, adipocytes and white blood cells. Rolph et al. reported that PTX3 was expressed mainly in vascular endothelial cells and macrophages in advanced atherosclerotic plaques. Savchenko et al. demonstrated that foam cells expressed PTX3 in coronary arterial thrombi containing an atherosclerotic plaque component in both patients with AMI and human aortic tissues from autopsy cases. Thus, PTX3 is an inflammatory marker that is thought to be more specific than CRP to local inflammation in atherosclerotic lesions.

As a function of PTX3, Rovere et al. reported that it binds to dying cells and regulates their clearance by antigen-presenting dendritic cells. Several studies have shown that PTX3 inhibits angiogenesis and activation of smooth muscle cells in vitro through binding to fibroblast growth factor-2. Interestingly, Norata et al. showed that atherosclerotic and inflammatory lesions of the aorta were significantly increased in double-knockout mice lacking PTX3 and apolipoprotein E compared with those in apolipoprotein E-knockout mice. In addition, Salio et al. reported that tissue mRNA expression and circulating levels of PTX3 were increased in a mouse model of AMI caused by coronary artery ligation and reperfusion. They also reported that PTX3-deficient mice showed a larger infarct area than null mice in association with a greater no-reflow area. These findings suggest that PTX3 has an atheroprotective effect through modulation of the immunoinflammatory balance in the cardiovascular system and that it plays a cardioprotective role against acute myocardial ischemia. Thus, because the PTX3 system is a defense mechanism in the cardiovascular system in vivo, the circulating level of PTX3 is expected to more specifically reflect coronary plaque instability, the extent of myocardial damage in AMI and its prognosis.

Kumira et al. clearly demonstrate that the group with high PTX3 levels pre-PCI had higher frequencies of thin-cap fibroatheroma and plaque rupture and poorer post-PCI myocardial perfusion than those in the group with low pre-PCI PTX3 levels. The pre-PCI PTX3 level may reflect local inflammatory status and plaque instability such as plaque rupture or a large necrotic core at the coronary culprit site, causing impaired post-PCI myocardial perfusion associated with distal embolization and leading to severe myocardial damage. Therefore, the systemic pre-PCI PTX3 level may be a reliable predictor of outcome in patients with ST-elevation myocardial infarction. As an indication of the clinical significance of PTX3, Koga et al. also demonstrated that higher levels of systemic PTX3 are associated with thin-cap fibroatheroma, suggesting that the systemic PTX3 level is a useful inflammatory marker reflecting coronary plaque vulnerability. Inoue et al. established a highly sensitive plasma ELISA assay system for detecting PTX3 using monoclonal antibodies and showed that the levels of plasma PTX3 were increased in patients with arterial inflammation, especially those with unstable angina. Latini et al. also reported that PTX3 was elevated in the acute phase of AMI and had prognostic significance in those patients.

In conclusion, as with brain natriuretic peptide as a biomarker of severity and a predictor of prognosis in patients with congestive heart failure, PTX3 is expected to become a novel biomarker for the diagnosis of vulnerable coronary plaque and a reliable predictor of prognosis in patients with AMI.

Disclosures
The author has no conflict of interest directly relevant to the content of this article.

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