

Novel inflammatory biomarkers in acute coronary syndrome

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See Article on Page 165-173

Acute coronary syndrome (ACS) is multifactorial and is caused by plaque rupture and subsequent thrombosis [1]. Inflammation in the plaques is one of the driving forces triggering a cascade of events leading to plaque rupture and acute coronary occlusion.

C-reactive protein (CRP) is increased after ACS, particularly in association with myocardial necrosis, reflecting the level of inflammation in the myocardium. CRP levels following acute myocardial infarction (MI) peak at 2 to 4 days, then subside to baseline levels over 8 to 12 weeks. Clinical trials have yielded conflicting results on the predictive value of CRP after acute MI. Elevated serum CRP obtained within 12 to 24 hours of symptom onset in a study of 448 patients with acute MI (ST-elevation MI, 76%) was associated with larger echocardiographic infarct size, higher 30-day mortality rate, and development of heart failure [2]. In contrast, CRP measured within 6 hours of symptom onset in 483 patients with acute ST-elevation MI was not associated with 30-day mortality rate or development of heart failure [3]. Similarly, CRP measured 2 months after acute MI in a study of 957 patients was not a predictor of cardiac death or recurrent

nonfatal MI during a 2-year follow-up [4]. These discrepancies may be explained, in part, by the timing of CRP measurement, suggesting that the peak CRP level after acute MI may predict early clinical outcome. In addition to CRP, a number of novel biomarkers of inflammatory activity are emerging for clinical use.

Myeloperoxidase (MPO) is a hemo-protein abundantly expressed by polymorphonuclear neutrophils, which has potent proinflammatory properties. MPO is found in atheromatous plaques and may activate metalloproteinases and inactivate plasminogen activator inhibitor contributing directly to tissue injury [5]. MPO levels after acute MI peak early, then decrease over time and are not correlated with cardiac troponin levels or neutrophil counts. Only a small number of clinical studies have addressed the prognostic role of MPO in patients with ACS, and the results indicated that high MPO levels predicted an increased risk for subsequent death and MI at 1 year [6,7]. Further investigations regarding the actual role of MPO and its clinical significance for patients with ACS are needed.

Pregnancy-associated plasma protein A (PAPP-A) is a proatherosclerotic zinc-binding matrix metalloproteinase (MMP), highly expressed in vulnerable plaques. Circulating PAPP-A

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is increased following ACS and has been shown to be associated with adverse cardiovascular events. One study in 136 ACS patients negative for cardiac troponins indicated that PAPP-A was a strong independent predictor of ischemic cardiac events and need for revascularization during 6-month follow-up [8]. However, current evidence for PAPP-A as a novel marker of atherosclerotic plaque activity is insufficient, and further studies are needed to validate its clinical value.

Matrix metalloproteinases (MMPs) may degrade myocardial extracellular matrix (ECM) leading to left ventricular dilatation and heart failure. The structural integrity of myocardial ECM is dependent on endogenous zinc-binding MMPs, which are regulated by tissue inhibitors of metalloproteinases (TIMPs), in particular TIMP-1. MMP 9 and TIMP1 are known to be predictive of cardiovascular death and heart failure [9]. MMP3 is also elevated after acute MI, and associated with left ventricular dysfunction, adverse left ventricular remodeling, and prognosis [10]. In this issue of *The Korean Journal of Internal Medicine*, Guzel et al. [11] report an association between elevated levels of MMP-9, TIMP-1, and decreased levels of interleukin-33 (IL-33), indicating their potentially crucial role in the development and progression of ACS. In 55 patients with non-ST-elevation ACS, serum levels of IL-33, MMP-9, TIMP-1, and CRP were measured on admission, and at 12, 24, 48, and 72 hours after the initial evaluation. Serum levels of IL-33 were decreased in ACS groups, as compared to controls, whereas levels of MMP-9 and TIMP-1 were higher in ACS groups. IL-33 levels were negatively correlated with MMP-9 and CRP levels, supporting the anti-inflammatory and atheroprotective actions of IL-33 in the course of ACS.

Although there are many emerging biomarkers of inflammation, their roles in the development and progression of ACS and their clinical utility remain unclear. Currently available biomarkers have not been instrumental in guiding treatment strategies, and current evidence still favors the need for further investigation into the mechanisms through which these inflammatory biomarkers may exert prognostic impact in patients with ACS. Large-scale randomized trials based on the use of a biomarker or of combined biomarkers would prove beneficial in tailoring therapy as well as providing more compelling evidence on their

utility as surrogate markers of disease severity and inflammatory activity in ACS.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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