High-sensitivity C-reactive protein: still need for next-generation biomarkers for remote future cardiovascular events

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This editorial refers to ‘C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians’, by K.-C. Sung et al., on page 1809.

Inflammation in the vessel wall plays a crucial role in the pathophysiology of atherogenesis, progression of atherosclerosis, and plaque instability. Atherosclerosis is initiated by dysfunction of endothelial cells (ECs), leading to expression of adhesion molecules for inflammatory cells.1,2 Vascular inflammation leads to an oxidizing environment due to activation of macrophages that secrete cytokines/chemokines as well as growth factors,3 all of which contribute to the progression of atherosclerosis.1,2 Therefore, the interactions among ECs, vascular smooth muscle cells (VSMCs), and inflammatory cells are substantially involved in the development of cardiovascular diseases.3 ECs produce nitric oxide and prostacyclin, which protect against vascular remodeling.5 Activated VSMCs produce proinflammatory cytokines and chemokines, which are stimulated by oxidative stress.6–8

No causality of C-reactive protein for the development of atherosclerosis

High-sensitivity C-reactive protein predicts cardiovascular events in the remote future.10–12 However, this has been inappropriately conflated with causality of atherogenesis. Many of the known causative factors (e.g. circulating cytokines/chemokines and growth factors) for atherosclerosis induce CRP synthesis in the liver (Figure 1). However, genetic epidemiology studies have never supported a pathogenic role for CRP. Recently, Lane et al. investigated the effects of infusion of pure natural human CRP into healthy adult human volunteers.14 They used comprehensively characterized, pharmaceutical grade, endotoxin-free, purified CRP, prepared to GMP (Good Manufacturing Practice) standard from pooled normal human donor plasma.14 Importantly, the human CRP molecule itself did not exert any proinflammatory effects in the volunteers, suggesting that circulating CRP is not a proatherogenic factor but just a reflection of inflammation.14 Similarly, many animal studies also revealed that CRP is not directly involved in atherogenesis.15

Biomarkers for existing cardiovascular diseases

High-sensitivity C-reactive protein is useful for prediction of cardiovascular events in the general population.10–12 Currently, most...
hospitals in the world are well equipped for the measurement of hsCRP. However, hsCRP is not a biomarker that is used daily for differential diagnosis of existing cardiovascular diseases. In the outpatient clinic, no specialist relies on the use of hsCRP for emergent assessment of patients with possible symptoms of coronary artery disease (CAD). This is because hsCRP has a limited ability to diagnose existing cardiovascular diseases (e.g., severe coronary artery stenosis or unstable plaque).

The use of biomarkers, such as cardiac troponin T, enables us to diagnose patients with myocardial infarction. However, even with these biomarkers, it is difficult to diagnose patients with severe CAD or unstable atherosclerotic plaque, which will cause myocardial infarction in the near future. In the actual clinical settings, what we really need is a practical biomarker that enables us to identify patients at risk before cardiovascular events occur. Therefore, the development of a biomarker for existing CAD or cardiovascular diseases is required.16

**Novel biomarkers for the diagnosis of coronary artery disease**

There are several reports on the role of circulating biomarkers for prediction of existing CAD.17,18 Circulating CRP is produced mainly by the liver and reflects the elevated cytokines/chemokines caused by inflammation (Figure 1). In contrast, pentraxin 3 (PTX3) is produced at the site of vascular inflammation by various cell types, including macrophages, ECs, and VSMCs.17 The role of circulating PTX3 for the diagnosis of patients with CAD has recently been demonstrated.17 Additionally, we also have recently demonstrated that plasma cyclophilin A (CyPA) is a novel biomarker for CAD (Figure 1).18 Multivariable analysis demonstrated that in addition to the established risk factors (e.g., age, sex, smoking, hypertension, and diabetes), CyPA at >15 ng/mL was significantly correlated with CAD.18 Importantly, excluding patients with high hsCRP did not significantly change the results. In patients with hsCRP values of <1000 mg/L, the adjusted odds ratio for CAD in the fourth quartile of CyPA, as compared with the first quartile, was 13.2 (P < 0.001). Our analysis revealed that the number of stenotic coronary arteries was slightly increased in the fourth quartile of hsCRP.18 However, the P-value for the trend was small (P = 0.107) as compared with the quartiles of CyPA (P < 0.001).18 Moreover, quartiles of hsCRP did not show any significant correlation with the requirement for cardiovascular intervention.18 Importantly, there was no significant difference in the angiographic findings or the requirement for cardiovascular intervention between high and low hsCRP groups. In contrast, in both the subgroups with low and high hsCRP, CyPA levels were significantly higher in patients with severe CAD than in those without it.18

**Figure 1** C-reactive protein (CRP): a reflection of elevated circulating cytokines. Plasma CRP is a biomarker for the assessment of remote future cardiovascular events. The synthesis of CRP in the liver is increased by circulating inflammatory cytokines [e.g., interleukin-6, interleukin-1β (IL-1β), IL-6, monocyte chemoattractant protein-1 (MCP-1), or tumour necrosis factor-α (TNF-α)].
Lessons to be learnt

The development of biomarkers has contributed to medical progress in the world. However, we still do not have a biomarker that is truly useful to identify patients at risk before cardiovascular events. Although hsCRP may be useful for the prediction of cardiovascular events in the distant future, we should focus on the development of next-generation biomarkers for existing CAD or cardiovascular diseases with a high accuracy and simplicity.

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