C-Reactive Protein Beyond Biomarker of Inflammation in Metabolic Syndrome

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The metabolic syndrome is characterized by low-grade inflammation. C-reactive protein (CRP), the best characterized biomarker of inflammation, is an independent predictor of future cardiovascular events, and elevated CRP level has also been implicated in the development of type 2 diabetes mellitus, a strong risk factor for cardiovascular disease. Recent reports have provided provocative evidence that high-sensitive CRP may impair insulin signaling. Accumulating evidence suggests a close association of CRP and the pathogenesis of metabolic syndrome. Therefore, it has been also proposed that high-sensitive CRP should be added as a clinical criterion for metabolic syndrome and for creation of a high-sensitive CRP-modified coronary heart disease risk score. However, it is still an enigma whether the increase in CRP contributes to the pathogenesis of metabolic syndrome, per se, or is a secondary response to inflammation in this disease state.

In this regard, Pravenec et al demonstrated increases in blood pressure, insulin resistance, microalbuminuria, and plasma triglyceride and reduced serum adiponectin in spontaneously hypertensive rats (SHRs) in which human CRP was transgenically expressed in the liver under control of the apolipoprotein E promoter. This transgenic rat showed enhanced inflammation and oxidative stress. As commented by the authors, one of the next important issues to be addressed is whether their observation is specific for this hypertensive model or not, because their studies on the metabolic effects of human CRP were performed in the SHR model, which is a strain known to be genetically susceptible to developing multiple features of the metabolic syndrome. Therefore, we speculate that other hypertensive models or strains might differ from SHRs in terms of the effect of CRP on the pathogenesis of metabolic syndrome. This kind of analysis is crucial, especially in terms of investigating the actual roles of CRP in the pathogenesis of metabolic disorders with elevated blood pressure. It would also be intriguing to address whether the possible increase in blood pressure by CRP induces multiple or specific features of metabolic syndrome and/or whether some CRP-mediated specific features of metabolic disorders, such as insulin resistance, act as a trigger for the increase in blood pressure (Figure). Moreover, it has to be clarified whether the state of high blood pressure is mandatory for the possible CRP-mediated pathogenesis of metabolic disorders, such as insulin resistance and adipocytokine dysregulation.

It is reported that chronic elevation of CRP is associated with a greater risk of hypertension, and Vongpatanasin et al reported that CRP transgenic mice showed an exaggerated blood pressure elevation in response to angiotensin II and a reduction in vascular angiotensin receptor subtype 2 expression with no change in angiotensin receptor subtype 1 and that the response to angiotensin II was reversed by an NO donor, which indicates a role for NO deficiency in the process. Schwartz et al reported that CRP downregulates endothelial NO synthase and attenuates reendothelialization in vivo in mice, and this action of CRP on endothelial NO synthase is mediated at the level of gene transcription. Angiotensin receptor subtype 2 receptor stimulation is also known to enhance the bradykinin/NO system in various organs including the vasculature, suggesting that CRP could cross-link the angiotensin receptor subtype 2 receptor with NO production, thereby regulating blood pressure (Figure).

In contrast, Kusche-Vihrog et al demonstrated recently that inhibition of the release of NO did not have an effect on CRP-induced stiffening of endothelial cells and that CRP enhanced the effects of aldosterone on the mechanical properties of the endothelium. Moreover, Zhang et al investigated the functional importance of human CRP in hypertensive cardiac remodeling by chronic infusion of angiotensin II into mice expressing human CRP and demonstrated that CRP promotes cardiac fibrosis and inflammation under high angiotensin II conditions, with enhanced upregulation of the angiotensin receptor subtype 1 and activation of the transforming growth factor-β/Smad and nuclear factor-κB signaling pathways. Taken together, these results suggest that possible cross-talk of the renin-angiotensin system and CRP plays a role in cardiovascular remodeling.

Pravenec et al also reported that transgenic CRP promotes insulin resistance in the SHR. The in vitro study by D’Alessandris et al suggested that human recombinant CRP may cause insulin resistance by increasing insulin receptor substrate 1 phosphorylation at Ser (307) and Ser (612) via c-Jun N-terminal kinase and extracellular signal–regulated kinase 1/2, respectively, leading to impaired insulin-stimulated glucose uptake, glucose transporter type 4 translocation, and glycogen synthesis mediated by insulin receptor substrate 1/phosphatidylinositol 3-kinase/Akt/glycogen syn-
thase kinase 3. Insulin resistance is well known to be closely associated with an increase in blood pressure, implying that the CRP-mediated blood pressure increase could be at least in part attributed to CRP-mediated insulin resistance (Figure). The metabolic syndrome is typically characterized by obesity associated with hypertension, hyperlipidemia, and hyperglycemia, and dysregulated adipose tissue functions appear to be important factors in exaggeration of the metabolic syndrome and the pathogenesis of cardiovascular disease. Furthermore, the reciprocal association of adiponectin and CRP levels in both human plasma and white adipose tissue in mice suggests that adipose tissue might participate in the development of atherosclerosis, and Pravenec et al. also observed reduced serum adiponectin in SHRs in which human CRP was transgenically expressed in the liver. It is interesting to speculate that the increase in CRP in adipose tissue in patients with abdominal obesity would dysregulate adipocytokine production, which would contribute to the pathogenesis of metabolic syndrome, eventually resulting in insulin resistance and diabetes mellitus and its associated cardiovascular events (Figure). It is also possible that an increase in CRP could impair the synthesis and secretion of insulin in the pancreas because of CRP-mediated inflammation and oxidative stress, and this possibility should also be addressed.

Elevated CRP is also a risk factor for the development of cardiovascular disease, irrespective of metabolic syndrome, mainly because of exaggeration of inflammation and oxidative stress. Given that CRP is a critical determinant of the exaggeration of cardiovascular disorders, including hypertension and metabolic disorders, not merely as a simple biomarker of these disease states, it is important to further examine the details of the signaling mechanism of CRP-mediated inflammation and oxidative stress and specific target organs of CRP and the localization of CRP receptors to understand the roles of CRP in the pathogenesis of metabolic syndrome and cardiovascular disease and to develop clinical interventions against CRP-mediated effects.

**Disclosures**

None.

**References**

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