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 is a crucial, especially in terms of investigating the actual roles of pathogenesis of metabolic syndrome. This kind of analysis is different from SHRs in terms of the effect of CRP on 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, Kutsche-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 e-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-
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atherosclerosis,10 and Pravenec et al3 also observed reduced adiponectin and CRP levels in both human plasma and white adipose tissue in mice suggests the reciprocal association of adiponectin and CRP in the pathogenesis of cardiovascular disease. Furthermore, the reciprocal association of adiponectin and CRP in both human plasma and white adipose tissue in mice suggests that adipose tissue might participate in the development of the metabolic syndrome.673

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.10 and Pravenec et al3 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 the metabolic syndrome, eventually resulting in insulin resistance and type 2 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.

Figure. Possible roles of CRP in pathogenesis of metabolic syndrome and cardiovascular disorders.

Disclosures

None.

References

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