C-reactive protein (CRP), composed of 5 23-kDa subunits, was traditionally viewed as one of the acute phase reactants. More recently, CRP has risen in stature to subsume the role of the “best” marker of inflammation useful in the prediction of future cardiovascular risks. However, the clinical utility of CRP measurement in cardiovascular risk prediction is still not well defined. Furthermore, there is an intense debate on whether CRP is merely a marker of inflammation or a direct participant. The finding reported by Dr. Janos Filip’s group in this issue of Circulation Research provides additional insights into the current CRP debate. In this editorial, I will focus my discussion on 2 main issues. Where is CRP produced? And, is CRP biologically active?

Where Is CRP Produced?
CRP was traditionally thought to be produced by the liver in response to inflammatory cytokines. Several recent studies, however, clearly showed that CRP can be produced by nonhepatic tissues. Two studies have shown that both epithelial cells of the respiratory tract and renal epithelium can produce CRP under certain circumstances. Moreover, neuronal cells also seem to be capable of synthesizing acute phase reactants involved in the pathogenesis of neurodegenerative disease such as Alzheimer disease. These new sources of CRP production pointed to a more systemic generation of CRP in our body. However, these new sources provided only tenuous link to atherosclerosis. CRP has been shown to colocalize with the terminal complement complex in atherosclerotic plaques. Moreover, neuronal cells also seem to be capable of synthesizing acute phase reactants involved in the pathogenesis of neurodegenerative disease such as Alzheimer disease. These new sources of CRP production pointed to a more systemic generation of CRP in our body. However, these new sources provided only tenuous link to atherosclerosis. CRP has been shown to colocalize with the terminal complement complex in atherosclerotic plaques. Furthermore, Yasojima et al reported that mRNAs for CRP and the classical complement components C1 to C9 could be detected in both normal artery and plaque tissue. We recently showed that human coronary artery smooth muscle cells, but not human umbilical vein endothelial cells, could synthesize CRP after stimulation by inflammatory cytokines. This locally produced CRP may directly participate in the pathogenesis of atherosclerosis. Moreover, we have also shown that human adipocytes could produce CRP after stimulation by inflammatory cytokines and by a specific adipokine, resistin. Production of CRP by adipocytes may partially explain why CRP levels are elevated in patients with metabolic syndrome (Figure).

Does CRP Have Biological Activities?
In recent years, there has been a proliferation of reports demonstrating direct biological activity of CRP on vascular cells and monocytes/macrophages. For example, several laboratories reported CRP could directly activate endothelial cells to express adhesion molecules, chemokines, and cytokines. CRP was also shown to inhibit nitric oxide (NO) production and stimulation of NO release via downregulation of endothelial NO synthase. CRP unregulated angiotensin receptor-1 (AT1-R) protein expression, increased AT1-R number on vascular smooth muscle cells, and promoted vascular smooth muscle migration and proliferation in vitro. CRP functioned as a chemottractant for monocytes and was able to induce tissue factor expression in macrophages. Furthermore, soluble CRP and immobilized CRP have been demonstrated to mediate uptake of native LDL into macrophages. Many of the studies cited above used recombinant CRP obtained from commercial sources that are contaminated by lipopolysaccharides (LPS) or by sodium azide. Thus, many of the reported biological effects could be due to either LPS or sodium azide contamination.

To avoid the potential artifact caused by LPS or sodium azide contamination, we have to turn to the results of in vivo animal models. Because mouse CRP is not an acute phase reactant, a model using expression of a human CRP-transgene has been employed. Two of these studies support the theory that CRP is proatherogenic and prothrombotic, but the other 3 studies reported negative results. First, human CRP created a prothrombotic phenotype as evidenced by higher rates of thrombotic occlusion after arterial injury. Second, by crossing CRP-tg mice with ApoE−/− mice, CRP increased atherogenesis in vivo. These CRP-tg/ApoE−/− mice displayed accelerated aortic atherosclerosis, which was associated with increased complement deposition and elevated expression of angiotensin type 1 receptor, vascular cell adhesion molecule-1, and collagen within the lesions. Crossing the human CRP transgenic mice with the apolipoprotein E*3-Leiden transgenic mice, however, failed to show a role of CRP to the development of early atherosclerosis lesions. The CRP level in the apolipoprotein E*3-Leiden mice is lower than those in the ApoE−/− mice. Another study crossing rabbit CRP transgenic mice into apoE knockout mice also did not augment atherogenesis at 20 weeks and at 52 weeks. Hirschfield et al also showed that transgenic expression of human CRP had no effect on development, progression, or
severity of spontaneous atherosclerosis, or on morbidity or mortality, in male apolipoprotein E (ApoE)-deficient C57BL/6 mice up to 56 weeks, despite deposition of human CRP and mouse complement component 3 in the plaques. However, among human CRP transgenic mice, the circulating CRP concentration was higher in ApoE knockouts than in wild-type controls. The higher CRP values were associated with substantially lower estradiol concentrations in the apoE-deficient animals. Thus, the in vivo animal models also provide conflicting data regarding the role of CRP in atherogenesis.

Another explanation of the conflicting results of CRP biology came from the observation made with modified CRP. Khreiss et al provided evidence suggesting that native pentameric CRP must undergo structural modification, forming monomeric subunits (mCRP), before being able to promote a proinflammatory response. They showed that mCRP was able to induce endothelial activation within 4 hours, whereas with native CRP could only exert a proinflammatory effect in 24 hours. This could be attributable to the conversion of native CRP to mCRP after 24 hour incubation. This in vitro observation, however, was contradicted by an in vivo animal experiment. Schwedler et al showed that native CRP increases whereas mCRP reduces atherosclerosis in the ApoE-deficient mice after 8 weeks of injection. VCAM, ICAM, and CD154 expression were higher in the native CRP-treated mice than in those treated with mCRP. On the other hand, mCRP-treated ApoE/ mice exhibited higher serum level of the antinflammatory cytokine interleukin-10. Thus, the studies using mCRP also provide contradictory results that are difficult to reconcile.

Perhaps the best evidence to support a biological activity for CRP comes from studies on CRP receptors and CRP signaling. In this issue of Circulation Research, Kreiss et al showed that mCRP induced interleukin-8 secretion through peroxynitrite signaling in human neutrophils. These authors have previously shown that native CRP binds to CD32, one of the Fc receptors, whereas mCRP binds to CD16, another Fc receptor isoform, on human neutrophils and exerting opposite function. Conformational alterations of CRP could provide additional insights into its biological activity, but also raise additional questions. For example, we do not know how mCRP is generated in vivo. It was suggested that native CRP dissociated into monomeric unit after binding to plasma membrane or in denaturing or oxidative environment. Identification of suitable assays that allow for direct testing of mCRP versus native CRP in serum or tissue will further clarify the biological significance of mCRP.

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References


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