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C-Reactive Proteins in Atherosclerosis: Marker or Maker or Both

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C-reactive protein (CRP) is not only a predictor of cardiovascular events but also may be a new potential risk factor for the development of atherosclerosis. More recently, a number of studies using cultured cells showed that CRP can directly induce many cellular changes including the enhancement of cytokine and matrix metalloproteinases (MMP) production, cholesterol uptake by macrophages, and inhibition of NO production, etc, suggesting that CRP itself is an active mediator that may directly modulate the pathogenesis of atherosclerosis. This hypothesis is also indicated by the finding that CRP is frequently present in the lesions of atherosclerosis. Although this new theory is potentially interesting, it has not been completely settled (1) whether CRP is only a marker or (2) atherogenic mediator ("maker") or (3) both. In fact, it has not been documented where CRP deposited in the lesions come from. In attempt to answer these questions, we have performed several experiments using both human coronary arterial specimens and hypercholesterolemic rabbits. We measured CRP levels in the plasma of hypercholesterolemic rabbits and investigated CRP expression at both the mRNA and protein levels using rabbit and human atherosclerotic specimens.

We found that CRP levels were significantly elevated in both cholesterol-fed and Watanabe heritable hyperlipidemic rabbits. CRP levels in these rabbits were clearly correlated with aortic atherosclerotic lesion size. Immunohistochemical staining coupled with Western blotting analysis revealed that CRP-immunoreactive proteins were invariably found at all stages of atherosclerosis in the early to advanced lesions. CRP tended to be present extracellularly and colocalized with apolipoprotein B but was rarely associated with the cytoplasm of macrophages and foam cells. Real-time RT-PCR analysis revealed that CRP mRNA in atherosclerotic lesions was barely detectable and isolated macrophages did not express CRP mRNA, suggesting that CRP proteins contained in the lesions were essentially derived from the circulation rather than synthesized de novo by vascular cells. These results suggest that there is a link between plasma CRP and the degree of atherosclerosis, and that the inhibition of hepatic CRP production may represent a therapeutic modality for the treatment of cardiovascular disease. We are now generating transgenic rabbits expressing human CRP and hope that these models can become an important model for investigating CRP roles.

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