Serum Amyloid P Component and Cardiovascular Disease
Is There a Sensible Link?

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Atherosclerosis shows several features of an inflammatory process. There is ubiquitous presence of characteristic cells like monocytes/macrophages, and T cells that produce various mediators involved in local inflammation and these inflammatory molecules (cytokines, chemokines, growth factors) are found at the site of the plaque in the arterial vessel wall through all stages of the process, most pronounced during acute ischemic syndromes.

Atherosclerosis is also accompanied by a systemic low-grade inflammatory response that can be detected by sensitive assays. Because of the importance of inflammation for the initiation and progression of the atherosclerotic process, and the occurrence of deleterious clinical events, interest has focused on a large number of potential biomarkers that have been tested prospectively in clinical and epidemiological studies. Most of them are part of the acute phase reaction and indeed have been found to predict clinical atherosclerosis end points, even after controlling for a variety of traditional risk factors. A particular large database has been build up for C-reactive protein (CRP), a member of the pentraxin family, and an exquisitely sensitive acute phase reactant, documenting its association with various cardiovascular disease (CVD) end points. In addition, in vitro studies and animal experiments have suggested a direct contribution of CRP to atherogenesis. However, such evidence and the issue of an incremental value of CRP and other emerging blood biomarkers to risk prediction over and above global risk assessment by risk scores using traditional risk factors, still represent a matter of controversy.

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Serum amyloid P component (SAP) represents another member of the pentraxin family, a highly conserved group of molecules that may play a role in innate immunity. Human SAP and CRP share 66% homology, and the gene for SAP is also located on chromosome 1. Like CRP, SAP is synthesized and secreted only in hepatocytes and has a half-life of approximately 24 hours. Plasma concentrations are tightly regulated and are slightly lower in females. Unlike CRP, SAP is only mildly affected during acute or chronic inflammation and serum concentrations remain close to the normal range (10 to 50 mg/L). This would argue against a significant role of this molecule in inflammation in humans, while it is an acute-phase reactant in mice. SAP and CRP show distinct differences in ligand recognition and binding. CRP activates the classical pathway of complement activation, whereas this is discussed controversially for SAP. Physiological functions of SAP are unknown but may be important because no SAP deficiencies in man and animals have been reported. However, recently created SAP knockout mice developed normally, suggesting that blocking SAP binding in vivo may not have a major adverse effect. SAP probably is best known as a universal constituent of amyloid deposits that are characteristic of systemic amyloidosis, including cerebral amyloid in Alzheimer disease and in type 2 diabetes mellitus. SAP has also been claimed to be present in atherosclerotic plaque. However, lumping these different diseases together, solely on the basis of microscopic histological features may be inappropriate even if they share a number of vascular risk factors. Whereas in systemic amyloidosis it is unequivocally clear that the amyloid deposits cause tissue damage and organ dysfunction leading to clinical disease, the role, effects, and significance of the microscopic amyloid deposits in Alzheimer disease and type 2 diabetes are unknown and the subject of much speculation; and the presence of SAP in the microfibrils of elastic membranes throughout the body has been known for long, thus providing a plausible answer for its presence in plaque.

In the February issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Jenny and colleagues hypothesize that SAP may represent a different aspect of inflammation and innate immunity in atherosclerosis (Figure) and report for the first time on the association of SAP and CVD outcomes. In multivariable adjusted analyses in elderly subjects from the prospective Cardiovascular Health Study, using a case–cohort design, they found a 66% increased risk for angina, and a 39% increased risk for combined CVD across extreme quartiles of SAP distribution. No significant association was found for stroke and CVD death, and the association with myocardial infarction was also nonsignificant in quartile analysis, but was significant when the risk was computed for a one standard deviation increase.

How should these data be interpreted? First, associations reported are modest in nature and less strong than reported for a variety of inflammatory biomarkers, although SAP was associated with fibrinogen, CRP, and interleukin (IL)–6 in this study. Second, the lack of an association with stroke and CVD death is surprising, but could either be attributable to participant selection as suggested by the authors; alternatively it may be interpreted in line with the association seen for angina pectoris, suggesting that SAP represents a different

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aspect of the underlying inflammatory process, although this seems speculative based on its behavior in humans. CRP has not been found to be elevated in angina,20 whereas it is consistently associated with stroke and CVD death.4 Thus, in contrast to CRP, elevated SAP may indicate the presence of ischemia. However, angina must be considered a soft end point, and the underlying pathophysiology remains completely unclear. Third, the authors have suggested that SAP could possibly represent a marker of progression of atherosclerosis in contrast to CRP. But SAP as well as CRP were associated with subclinical disease except for low ankle-brachial index, a strong indicator of atherosclerotic burden, which was only statistically significantly associated with SAP, but not with CRP. Based on these unsolved, controversial issues, the conclusion of the authors that SAP may have a unique potential in monitoring atherosclerotic progression seems premature, in particular in light of the subtle changes seen, and SAP may only represent an innocent bystander of the disease process as suggested for many of the inflammatory biomarkers. The next important step obviously is the need to replicate the results of this study in diverse populations. However, and most critically, basic research has to provide us with convincing arguments regarding the potential underlying pathobiology of SAP in CVD. Until then, in the absence of sound knowledge of biological functions of SAP in health and disease, there is more room for speculations than for solid conclusions.

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Disclosures

None.

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